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54 Título: **Método para predecir la respuesta al tratamiento con quimioterapia en pacientes de cáncer colorrectal**

57 Resumen:

Método para predecir la respuesta al tratamiento con quimioterapia en pacientes de cáncer colorrectal.

Método de obtención de datos útiles para predecir la respuesta al tratamiento con quimioterapia en pacientes con cáncer colorrectal, kit, dispositivo y microarray para llevar a cabo dicho método.

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## DESCRIPCIÓN

### Método para predecir la respuesta al tratamiento con quimioterapia en pacientes de cáncer colorrectal.

#### CAMPO DE LA INVENCION

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La presente invención se encuentra dentro del campo de la Biología Molecular y la Medicina. Específicamente se refiere a un método de obtención de datos útiles para predecir la respuesta al tratamiento con quimioterapia en pacientes con cáncer colorrectal, que permite el establecimiento de un patrón individual de reconocimiento cuantitativo específico, que se puede modificar con el tratamiento, permitiendo el establecimiento de grupos de pacientes con el mismo diagnóstico pero distinto comportamiento clínico, pudiendo seleccionar así, el tratamiento más adecuado para cada paciente. La predicción de respuesta al tratamiento se realiza mediante el análisis del perfil de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*.

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#### ANTECEDENTES DE LA INVENCION

El cáncer colorrectal (CCR) es el tercer tumor más común en el mundo, con más de 1.2 millones de nuevos casos diagnosticados cada año, y es responsable de alrededor del 8% de las muertes relacionadas con cáncer (<http://globocan.iarc.fr>). Aproximadamente dos tercios de los pacientes se diagnostican en estadios precoces de la enfermedad (I-III), potencialmente curables mediante tratamiento quirúrgico seguido o no de quimioterapia adyuvante. No obstante, un 40% de estos pacientes eventualmente recidivan tras la cirugía. El tratamiento con quimioterapia adyuvante postquirúrgica reduce el riesgo de recidiva tumoral en un 10-20%. Globalmente, por lo tanto, se estima que aproximadamente un 80% de los pacientes no se benefician de un tratamiento quimioterápico complementario a la cirugía, bien por estar curados con tratamiento quirúrgico únicamente, bien por ser refractarios al tratamiento quimioterápico. Los tumores no subsidiarios de resección quirúrgica completa se consideran incurables. La quimioterapia en este contexto ha demostrado mejorar de manera modesta aunque significativa la calidad y esperanza de vida de los pacientes, si bien a expensas de un considerable coste económico y de una no desdeñable toxicidad. El tratamiento estándar en el cáncer colorrectal avanzado consiste en distintas combinaciones de fluoropirimidinas con oxaliplatino o irinotecan. Estos esquemas terapéuticos inducen respuestas tumorales objetivas en un 40-60% de los pacientes con

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medianas de supervivencia en torno a los 20 meses. A lo largo de la última década, diversos fármacos, entre los que se encuentran fármacos dirigidos frente al factor de crecimiento endotelial o VEGF (bevacizumab, aflibercept) o el receptor del factor de crecimiento epidérmico o EGFR (cetuximab, panitumumab), han sido incorporados al arsenal terapéutico con resultados prometedores. A pesar de estos avances, no obstante, la mayoría de los pacientes con enfermedad irreseccable eventualmente fallece por progresión tumoral, con una mediana de supervivencia de 20-24 meses en el mejor de los casos (Vieitz *et al.*, 2011. *Clin. Transl. Oncol.* 13(11), 798–804; García-Carbonero *et al.* 2010. *Clin. Transl. Oncol.*, 12(11), 729–734).

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Los factores pronósticos tradicionales empleados en los sistemas de estadiaje convencionales como el TNM, fundamentalmente basados en las características histopatológicas del tumor y en su grado de extensión en el organismo, clasifican a los pacientes con carcinoma colorrectal en cuatro grandes grupos o estadios de la enfermedad: tumores limitados a la mucosa colorrectal o estadio I, tumores que infiltran toda la pared intestinal o estadio II, tumores que invaden los ganglios linfáticos regionales o estadio III, y tumores con metástasis en órganos a distancia o estadio IV. Si bien estas clasificaciones tradicionales permiten diferenciar de una manera grosera subgrupos de pacientes con distinto pronóstico a largo plazo, existe una enorme heterogeneidad biológica dentro de dichos subgrupos tanto en términos de supervivencia como en términos de potencial respuesta tumoral al tratamiento con quimioterapia. En este contexto resulta fundamental el desarrollo de nuevos marcadores biológicos que nos permitan mejorar nuestra habilidad de clasificar a los pacientes en subgrupos pronósticos/predictivos.

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La elaboración de perfiles de expresión génica usando la tecnología microarray muestra un alto potencial en la investigación del cáncer, ya que permite el análisis simultáneo y comparado de miles de genes en diversas muestras biológicas (p.ej. muestras tumorales) de pacientes afectados de la misma enfermedad pero con distinto comportamiento clínico (Nannini *et al.* 2009. *Cancer Treat. Rev.* 35(3), 201-209). El análisis del patrón de expresión génica ha demostrado mejorar el diagnóstico, pronóstico y la precisión predictiva en diferentes tipos de cáncer (Liang *et al.* 2003. *Nat. Rev. Cancer*, 3, 869-876). Por ejemplo, varios estudios han mostrando como los perfiles de expresión génica discriminan entre cáncer de mama con o sin receptores de estrógenos, o entre cáncer de mama familiar o esporádico. Además, de esta manera han sido descritos subgrupos moleculares antes desconocidos, como el subgrupo de células basales o luminales de cáncer de mama, y han dado lugar a nuevas propuestas de clasificación en tumores del sistema nervioso central o

en sarcomas de partes blandas. Pero la aplicación más atractiva desde el punto de visto clínico, es la posibilidad de diferenciación entre subgrupos de pacientes con diferentes probabilidades de recurrencia o muerte por cáncer (Rosenwald *et al.*, 2002. *N. Engl. J. Med.* 246, 1937-1947; van de Vijver He Y.D. *et al.*, 2002. *N. Engl. J. Med.* 247, 1999-2009; Beer D.G. *et al.*, 2002. *Nat. Med.* 8, 816-824), o con diferentes probabilidades de responder a un determinado agente antineoplásico (Staunton J.E. *et al.*, 2001. *Proc. Natl. Acad. Sci* 98,10787-10792; Puzstai L. *et al.*, 2003. *The Oncologist*, 8, 252-258).

En las 2 últimas décadas, se ha demostrado que el perfil de expresión génica puede diferenciar entre tejido colónico normal, adenomas benignos y adenocarcinomas en distintos estadios de extensión de la enfermedad, y se puede determinar también el riesgo de desarrollar CCR dependiente del análisis de tejido colónico normal, así como la probabilidad de recurrencia después de la resección quirúrgica de un CCR (Bertucci *et al.*, 2004. *Oncogene* 23, 1377-1391; Bandrés *et al.*, 2007. *Oncology Reports* 17, 1089-1094). Sin embargo, el valor de esta tecnología como un predictor de la respuesta del cáncer de colon a la quimioterapia, ha sido poco investigado.

Los tratamientos para el CCR avanzado tienen una eficacia limitada, son costosos y no están exentos de riesgos para el paciente. Por todo ello, resulta fundamental desarrollar biomarcadores que permitan predecir prospectivamente qué pacientes van a responder al tratamiento. Por un lado, el disponer de herramientas que permitan identificar *a priori* aquellos pacientes que no se van a beneficiar de un determinado tratamiento médico evitaría al paciente la toxicidad, el gasto y el tiempo que conlleva recibir dicho tratamiento, a la vez que le posibilitaría recibir un tratamiento alternativo con mayores posibilidades de éxito. Por otro lado, la identificación de marcadores biológicos predictivos de respuesta tumoral puede aportar información fundamental acerca de los mecanismos moleculares que determinan y regulan dicha respuesta y facilitar el descubrimiento de vías de manipulación de la misma que permitan maximizar el efecto terapéutico. En este contexto, el estudio mediante microarrays del patrón de expresión génica en pacientes con CCR avanzado tratados con quimioterapia, en función de su respuesta a la misma, podría facilitar el desarrollo de una firma genética de una incuestionable utilidad clínica.

## BREVE DESCRIPCIÓN DE LA INVENCION

Un primer aspecto de la invención se refiere al uso de cualquiera de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*,

*VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, o cualquiera de sus combinaciones, para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal.

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Otro aspecto de la invención se refiere a un método de obtención de datos útiles para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, que comprende:

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a) obtener una muestra biológica aislada que comprende células tumorales del individuo, y

b) detectar la cantidad de producto de expresión de cualquiera de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, o cualquiera de sus combinaciones en la muestra aislada de (a).

20 En una realización preferida el primer método de la invención comprende además:

c) comparar los niveles de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, en la muestra obtenida en (a), con la cantidad de expresión detectada para dichos genes en una población de individuos de referencia de respuesta patológica conocida.

Otro aspecto de la invención se refiere a un método para predecir o pronosticar la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, que comprende los pasos (a)-(c) del primer método de la invención, y además comprende:

d) incluir al individuo que presentan un nivel de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2,*

*VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* significativamente superior a los niveles de expresión de los mismos genes en una población de referencia, en el grupo de individuos respondedores a la terapia del cáncer colorrectal.

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En una realización preferida de este aspecto de la invención la muestra biológica aislada de un individuo del paso (a) empleada para la determinación de los niveles de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFB3,*  
 10 *TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se obtiene del tejido tumoral colorrectal del paciente.

En otra realización preferida de la invención la determinación del nivel de expresión de los genes no necesita limitarse de manera particular y se puede seleccionar a partir de un  
 15 procedimiento de perfilado génico, tal como una micromatriz y/o un procedimiento que comprenda la PCR (reacción en cadena de la polimerasa), tal como la PCR en tiempo real; y/o la transferencia Northern.

Más preferentemente, la detección del producto de expresión de los genes *AQP, CLEC3B,*  
 20 *DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFB3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se realiza mediante PCR cuantitativa a tiempo real.

En otra realización aun mas preferida de este aspecto de la invención la detección del producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFB3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se realiza mediante microarrays.  
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En una realización preferida de este aspecto de la invención el tratamiento quimioterápico comprende el uso de compuestos basados en platino, compuestos inhibidores de la topoisomerasa I, compuestos análogos de las pirimidinas, o cualquiera de sus combinaciones. Más preferiblemente el compuesto basado en platino es el oxaliplatino, el  
 35 inhibidor de la topoisomerasa I es el irinotecan, y el análogo de pirimidina es el 5-fluorouracilo.

Una realización preferida de este aspecto de la invención, comprende realizar al menos dos veces la secuencia de pasos (a) – (b) del método de la invención, en muestras biológicas procedentes de un mismo individuo, y aisladas en momentos diferentes. Más preferiblemente, las muestras se obtienen antes y después del tratamiento, o de un ciclo de tratamiento con quimioterapia.

Otro aspecto de la presente invención se refiere a un kit o dispositivo, de ahora en adelante kit o dispositivo de la invención, que comprende los elementos necesarios para analizar la cantidad del producto de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*.

Otro aspecto de la invención se refiere a un microarray, de ahora en adelante microarray de la invención, que comprende oligonucleótidos o microarreglos de canal único diseñados a partir de una secuencia conocida o un ARNm de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*.

Más preferiblemente, la secuencia de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* es la secuencia nucleotídica correspondiente que se selecciona de la SEQ ID NO: 1 a la SEQ ID NO: 82.

Otro aspecto de la invención se refiere al uso del kit o dispositivo de la invención, o del microarray para la obtención de datos útiles para predecir o pronosticar la respuesta al tratamiento en pacientes con cáncer colorrectal.

## DESCRIPCIÓN DE LA INVENCION

La presente invención proporciona un método de obtención de datos útiles para predecir la respuesta de un sujeto humano con cáncer colorrectal al tratamiento de quimioterapia, permitiendo el establecimiento de grupos de pacientes afectados de la misma enfermedad

pero con distinto comportamiento clínico. Se trata de un procedimiento fácil y fiable *in vitro* y herramientas útiles para este objetivo, tales como kits, dispositivos o sistemas de detección que puedan emplearse para llevar a cabo los métodos de la invención. Un objetivo adicional de la presente invención, radica en proporcionar la medicación apropiada para un paciente individual que padezca de cáncer colorrectal basándose en la predicción del éxito del tratamiento.

El tratamiento de quimioterapia del cáncer colorrectal puede consistir, pero no está restringido, a la administración combinada o no de medicamentos como son capecitabina, floxuridina, fluorouracilo, oxaliplatino, irinotecán, etc.

Por tanto, un primer aspecto de la invención se refiere al uso de cualquiera de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*, o cualquiera de sus combinaciones, para predecir o pronosticar la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal.

Otro aspecto de la invención se refiere al uso simultáneo de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal. Sin embargo, el uso independiente de cualquiera de ellos o cualquiera de sus combinaciones podrían ser suficientes para evaluar la respuesta y/o el seguimiento de dicha enfermedad.

En una realización preferida de este aspecto de la invención, la respuesta al tratamiento es una respuesta a la reducción de la carga tumoral. En una realización alternativa, la respuesta al tratamiento es una mejora o ausencia de deterioro del estado del tumor. En otra realización, la respuesta al tratamiento es un resultado clínico, tal como la supervivencia exenta de progresión o la supervivencia global.

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MÉTODO DE OBTENCIÓN DE DATOS ÚTILES Y MÉTODO PARA PREDECIR LA RESPUESTA AL TRATAMIENTO DEL CÁNCER COLORRECTAL

Otro aspecto de la invención se refiere a un método de obtención de datos útiles, de ahora en adelante primer método de la invención, para predecir o pronosticar la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, que comprende:

5 a) obtener una muestra biológica aislada que comprende células tumorales del individuo, y

10 b) detectar la cantidad de producto de expresión de cualquiera de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*,  
15 *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*, o cualquiera de sus combinaciones en la muestra aislada de (a).

Aunque la detección de la cantidad de producto de expresión de cualquiera de los genes, o de cualquiera de sus combinaciones, puede servir para predecir o pronosticar la respuesta al tratamiento con quimioterapia, en una realización preferida, la detección de la cantidad de producto de expresión de los genes del paso (b) se hace de manera simultánea.

En otra realización preferida el primer método de la invención además comprende:

25 c) comparar los niveles de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*, en la muestra obtenida en (a), con la cantidad de expresión detectada para dichos genes en una población de individuos de referencia de respuesta patológica conocida.

30 Otro aspecto de la invención se refiere a un método para predecir o pronosticar la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal, de ahora en adelante segundo método de la invención, que comprende los pasos (a)-(c) del primer método de la invención, y además comprende:

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d) incluir al individuo que presentan un nivel de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* significativamente superior a los niveles de expresión de los mismos genes en una población de referencia, en el grupo de individuos respondedores a la quimioterapia del cáncer colorrectal.

La Tabla1 muestra los niveles de expresión obtenidos para dichos genes:

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**Tabla 1.** Niveles de expresión en células tumorales de pacientes respondedores con cáncer colorrectal.

Nombre del Gen	Veces de cambio en su nivel de expresión (Fold change)	Descripción	Gene ID	Secuencias nucleotídicas	Secuencias aminoacídicas
AQP1	2,30	aquaporin 1	358	SEQ ID NO:1 - SEQ ID NO:4	SEQ ID NO:83 - SEQ ID NO:86
CLEC3B	3,06	C-type lectin domain family 3, member B	7123	SEQ ID NO:5	SEQ ID NO:87
DCK	1,85	deoxycytidine kinase	1633	SEQ ID NO:6 - SEQ ID NO:7	SEQ ID NO:88 - SEQ ID NO:89
DEFA5	3,03	defensin, alpha 5, Paneth cell-specific	1670	SEQ ID NO:49	SEQ ID NO:131
DNAJC3	2,68	DnaJ (Hsp40) homolog, subfamily C, member 3	5611	SEQ ID NO:50	SEQ ID NO:132
FBLIM1	1,93	filamin binding LIM protein 1	54751	SEQ ID NO:13 - SEQ ID NO:15	SEQ ID NO:95 - SEQ ID NO:97
GAS7	2,00	growth arrest-specific 7	8522	SEQ ID NO:16 - SEQ ID NO:19	SEQ ID NO:98 - SEQ ID NO:101
IGFBP4	1,74	insulin-like growth factor binding protein 4	3487	SEQ ID NO:20	SEQ ID NO:102
KSR1	2,00	kinase suppressor of ras 1	8844	SEQ ID NO:51	SEQ ID NO:133

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<b>Nombre del Gen</b>	<b>Veces de cambio en su nivel de expresión (Fold change)</b>	<b>Descripción</b>	<b>Gene ID</b>	<b>Secuencias nucleotídicas</b>	<b>Secuencias aminoacídicas</b>
LONP1	1,74	lon peptidase 1, mitochondrial	9361	SEQ ID NO:52	SEQ ID NO:134
MTHFD1L	1,89	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	25902	SEQ ID NO:53 - SEQ ID NO:56	SEQ ID NO:135 - SEQ ID NO:138
NAV1	1,84	neuron navigator 1	89796	SEQ ID NO:21 - SEQ ID NO:22	SEQ ID NO:103 - SEQ ID NO:104
NIPBL	2,07	Nipped-B homolog	25836	SEQ ID NO:57 - SEQ ID NO:58	SEQ ID NO:139 - SEQ ID NO:140
PALM2	2,30	PALM2-AKAP2 readthrough	445815	SEQ ID NO:59 - SEQ ID NO:60	SEQ ID NO:141 - SEQ ID NO:142
PCDHGC3	1,99	protocadherin gamma subfamily C, 3	5098	SEQ ID NO:23 - SEQ ID NO:39	SEQ ID NO:105 - SEQ ID NO:121
PROS1	2,09	protein S (alpha)	5627	SEQ ID NO:8	SEQ ID NO:90
RARA	1,95	retinoic acid receptor, alpha	5914	SEQ ID NO:40 - SEQ ID NO:43	SEQ ID NO:122 - SEQ ID NO:125
RSF1	1,74	remodeling and spacing factor 1	51773	SEQ ID NO:44	SEQ ID NO:126
TENC1	1,92	tensin like C1 domain containing phosphatase (tensin 2)	23371	SEQ ID NO:45 - SEQ ID NO:47	SEQ ID NO:127 - SEQ ID NO:129
TGFBR3	2,22	transforming growth factor, beta receptor III	7049	SEQ ID NO:10 - SEQ ID NO:12	SEQ ID NO:92 - SEQ ID NO:94
TRAK2	2,33	trafficking protein, kinesin binding 2	66008	SEQ ID NO:48	SEQ ID NO:130
VSNL1	1,95	visinin-like 1	7447	SEQ ID NO:61	SEQ ID NO:143
WHSC1L1	2,17	Wolf-Hirschhorn syndrome candidate 1-like 1	54904	SEQ ID NO:9	SEQ ID NO:91
WWC2	1,91	WW and C2 domain	80014	SEQ ID NO:62	SEQ ID NO:144

Nombre del Gen	Veces de cambio en su nivel de expresión (Fold change)	Descripción	Gene ID	Secuencias nucleotídicas	Secuencias aminoacídicas
		containing 2			
FAF1	-1,01	Fas (TNFRSF6) associated factor	11124	SEQ ID NO:63	SEQ ID NO:145
FBXO9	-1,08	F-box protein 9	26268	SEQ ID NO:64 - SEQ ID NO:66	SEQ ID NO:146 - SEQ ID NO:148
KIAA1033	-1,11	WASH complex subunit 7	23325	SEQ ID NO:67	SEQ ID NO:149
N4BP2L1	-1,02	NEDD4 binding protein 2-like 1	90634	SEQ ID NO:68 - SEQ ID NO:69	SEQ ID NO:150 - SEQ ID NO:151
SLC12A	-1,03	Solute carrier family 12 (sodium/potassium/chloride transporters), member 2	6558	SEQ ID NO:70 - SEQ ID NO:74	SEQ ID NO:152 - SEQ ID NO:156
STARD13	-1,72	StAR-related lipid transfer (START) domain containing 13	90627	SEQ ID NO:75 - SEQ ID NO:80	SEQ ID NO:157 - SEQ ID NO:162
RB1CC1	-1,04	RB1-inducible coiled-coil 1	9821	SEQ ID NO:81 - SEQ ID NO:82	SEQ ID NO:162 - SEQ ID NO:164

En el contexto de la presente invención, los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* se definen también por una

5 secuencia de nucleótidos o polinucleótido, que constituye la secuencia codificante de las proteínas recogidas respectivamente en las SEQ ID recogidas en la Tabla 1, y que comprendería a diversas variantes procedentes de:

a) moléculas de ácido nucleico que codifican un polipéptido que comprende la

10 secuencia aminoacídica de la SEQ ID recogidas en la Tabla 1,

b) moléculas de ácido nucleico cuya cadena complementaria híbrida con la secuencia polinucleotídica de a),

c) moléculas de ácido nucleico cuya secuencia difiere de a) y/o b) debido a la degeneración del código genético,

5 d) moléculas de ácido nucleico que codifican un polipéptido que comprende la secuencia aminoacídica con una identidad de al menos un 80%, un 90%, un 95%, un 98% o un 99% con las SEQ ID recogidas en la Tabla 1, respectivamente, y en las que el polipéptido codificado por dichos ácidos nucleicos posee la actividad y las características estructurales de las proteínas *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*,  
10 *SLC12A*, *STARD13* y *RB1CC1*. Entre dichas moléculas de ácido nucleico se encuentra la recogida en las SEQ ID indicada en la Tabla1.

Los sujetos cuya respuesta se predice son sujetos humanos que se sospecha que padecen y/o que preferiblemente han sido diagnosticados con cáncer colorrectal preferentemente  
15 pero no limitado a estadios avanzados de la enfermedad (estadio IV de la clasificación TNM). Los términos “individuo”, “sujeto humano”, “sujeto” y “paciente” se usan por tanto de manera indistinta en esta memoria descriptiva. El término “individuo”, tal y como se utiliza en la descripción, se refiere a animales, preferiblemente mamíferos, y más preferiblemente, humanos. El término “individuo” no pretende ser limitativo en ningún aspecto, pudiendo ser  
20 éste de cualquier edad, sexo y condición física.

“Uno o más” tal como se usa también en la presente memoria descriptiva incluye uno y la especificación individualizada de cualquier número que sea más de uno, tal como dos, tres, cuatro, cinco, seis, etc. “Más de uno” o “algunos” tal como se usa en la presente memoria  
25 descriptiva incluye la especificación individualizada de cualquier número que sea más de uno, tal como dos, tres, cuatro, cinco, seis, etc.

Los pasos (b) y/o (c) de los métodos descritos anteriormente pueden ser total o parcialmente automatizados, por ejemplo, por medio de un equipo robótico sensor para la detección de la  
30 cantidad de producto de la expresión de los genes en el paso (b) o la comparación computarizada en el paso (c). Además de los pasos especificados anteriormente puede comprender otros pasos adicionales, por ejemplo relacionados con el pre-tratamiento de la muestra o la evaluación de los resultados obtenidos mediante estos métodos. Por ejemplo, el método para predecir la respuesta al tratamiento de un paciente con cáncer colorrectal,  
35 puede incluir un paso adicional consistente en la generación de un informe sobre los

resultados del perfil génico del paciente, que incluya la probabilidad de respuesta al tratamiento de dicho paciente diagnosticado de cáncer colorrectal.

5 En una realización preferida de este aspecto de la invención la muestra biológica aislada de un individuo del paso (a) empleada para la determinación de los niveles de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* se obtiene del tejido tumoral colorrectal del paciente.

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Los estudios de los autores de la presente invención han permitido obtener información sobre los patrones de expresión de genes en pacientes afectados de cáncer colorrectal respondedores al tratamiento frente a sujetos no respondedores. Esto ha permitido obtener un modelo de las modificaciones significativas que definen la sensibilidad al tratamiento de

15 quimioterapia en este tipo de patología.

La detección de la cantidad del producto de expresión de los genes puede realizarse por cualquier medio conocido en el estado de la técnica. Los autores de la presente invención han demostrado que la detección de la cantidad o la concentración de estos productos de

20 expresión de manera semicuantitativa o cuantitativa permiten diferenciar entre el individuo con cáncer colorrectal respondedor y el individuo no respondedor. La cantidad del producto de expresión de los genes detectada podría establecer un perfil diferencial en individuos afectados por cáncer de colorrectal, que permite subclasificarlos en función de su sensibilidad a la quimioterapia.

25

La medida de la cantidad o la concentración, preferiblemente de manera semicuantitativa o cuantitativa, puede ser llevada a cabo de manera directa o indirecta. La medida directa se refiere a la medida de la cantidad o la concentración del producto de expresión de los genes, basada en una señal que se obtiene directamente de los transcritos de dichos genes, o de

30 las proteínas a las que se traducen, y que está correlacionada directamente con el número de moléculas de RNA o de proteínas producidas por los genes. Dicha señal a la que también podemos referirnos como señal de intensidad – puede obtenerse, por ejemplo, midiendo un valor de intensidad de una propiedad química o física de dichos productos. La medida indirecta incluye la medida obtenida de un componente secundario o un sistema de

35 medida biológica (por ejemplo la medida de respuestas celulares, ligandos, “etiquetas” o productos de reacción enzimática).

- El término “cantidad”, tal y como se utiliza en la descripción, se refiere pero no se limita, a la cantidad absoluta o relativa de los productos de expresión de los genes, así como a cualquier otro valor o parámetro relacionado con los mismos o que pueda derivarse de éstos. Dichos valores o parámetros comprenden valores de intensidad de la señal obtenidos a partir de cualquiera de las propiedades físicas o químicas de dichos productos de expresión obtenidos mediante medida directa. Adicionalmente, dichos valores o parámetros incluyen todos aquellos obtenidos mediante medida indirecta, por ejemplo, cualquiera de los sistemas de medida descritos en otra parte del presente documento.
- El término “comparación”, tal y como se utiliza en la descripción, se refiere pero no se limita, a la comparación de la cantidad de los productos de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* de la muestra biológica a analizar, también llamada muestra biológica problema, con una cantidad de los productos de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* de una o varias muestras de referencia deseable descrita en otra parte de la presente descripción. La muestra de referencia puede ser analizada, por ejemplo, simultánea o consecutivamente, junto con la muestra biológica problema. La comparación descrita en el apartado (c) del método de la presente invención puede ser realizada manualmente o asistida por ordenador.
- Los productos de expresión de los genes van a dar un determinado perfil de expresión génica. Se entiende por “perfil de expresión génica” el perfil génico obtenido tras la cuantificación del ARNm y/o de proteína producida por los genes de interés o biomarcadores, es decir, por los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*, en una muestra biológica aislada. El perfil de expresión de los genes se realiza, preferiblemente, determinando el nivel de ARNm derivado de su transcripción, previa extracción del ARN total presente en la muestra biológica aislada, lo cual puede realizarse mediante protocolos conocidos en el estado de la técnica. La determinación del nivel de ARNm derivado de la transcripción de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*,

*NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, puede realizarse, por ejemplo, aunque sin limitarnos, mediante amplificación por reacción en cadena de la polimerasa (PCR), retrotranscripción en combinación con la
   
 5 reacción en cadena de la polimerasa (RT-PCR), RT-PCR cuantitativa, retrotranscripción en combinación con la reacción en cadena de la ligasa (RT-LCR), o cualquier otro método de amplificación de ácidos nucleicos; análisis en serie de la expresión génica (SAGE, SuperSAGE); chips de ADN elaborados con oligonucleótidos depositados por cualquier mecanismo; microarrays de ADN elaborados con oligonucleótidos sintetizados *in situ*
  
 10 mediante fotolitografía o por cualquier otro mecanismo; hibridación *in situ* utilizando sondas específicas marcadas con cualquier método de marcaje; mediante geles de electroforesis; mediante transferencia a membrana e hibridación con una sonda específica; mediante resonancia magnética nuclear o cualquier otra técnica de diagnóstico por imagen utilizando nanopartículas paramagnéticas o cualquier otro tipo de nanopartículas detectables
   
 15 funcionalizadas con anticuerpos o por cualquier otro medio. El perfil de expresión génica también podría obtenerse mediante la detección y/o cuantificación de las proteínas producto de la traducción del ARNm derivado de la transcripción de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1,*
  
 20 *WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1*, mediante por ejemplo, pero sin limitarnos, inmunodetección por western blot. La detección cuantitativa de la expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033,*
  
 25 *N4BP2L1, SLC12A, STARD13 y RB1CC1* y puede realizarse más preferiblemente mediante PCR en tiempo real (RT-PCR ó RTqPCR). La detección en tiempo real de los productos amplificados puede llevarse a cabo mediante la utilización de moléculas fluorescentes que se intercalan en el ADN de cadena doble o mediante hibridación con diferentes tipos de sondas.

30

Por tanto, en otra realización preferida de la invención la determinación del nivel de expresión de los genes no necesita limitarse de manera particular y se puede seleccionar a partir de un procedimiento de perfilado génico, tal como una micromatriz y/o un procedimiento que comprenda la PCR (reacción en cadena de la polimerasa), tal como la
   
 35 PCR en tiempo real; y/o la transferencia Northern.



Más preferentemente, la detección del producto de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* se realiza mediante PCR cuantitativa a tiempo real y se expresa como  $-\Delta\Delta Ct$ . La PCR cuantitativa en tiempo real (RQ-PCR) es una técnica de cuantificación de la expresión génica sensible y reproducible que se puede usar de manera particular para la expresión del perfil génico en células y tejidos. Se puede usar cualquier procedimiento para la evaluación de los resultados de la RT-PCR y se puede preferir el procedimiento  $\Delta\Delta Ct$ . El procedimiento  $\Delta\Delta Ct$  se describe en detalle en Livak y col. (*Methods* 2001, 25, 402-408). (Ct = Valores umbral del ciclo). Cuando se lleva la presente invención a la práctica, se deberá usar preferiblemente el procedimiento  $\Delta\Delta Ct$  tal como describen Livak y col. (*Methods* 2001, 25:402-408). El procedimiento  $\Delta\Delta Ct$  implicará una "muestra del control" y una "muestra del sujeto". La "muestra del sujeto" es una muestra procedente del sujeto que se va a analizar. Por cada muestra, se incluyen un gen diana (aquí: el gen de interés) y un gen endógeno del control (tal como se describe a continuación) para la amplificación de la PCR a partir de alícuotas (normalmente diluciones en serie). Normalmente se usan varias réplicas de cada concentración diluida para derivar la eficacia de la amplificación. La eficacia de la amplificación de la PCR se puede definir como el porcentaje de amplificación (de 0 a 1). Durante la reacción de la qPCR, un software mide normalmente el número de ciclos de cada muestra en el cual la fluorescencia cruza una línea arbitraria (indicadora de la amplificación de la PCR), el umbral. Este punto de cruce es el valor Ct. Muestras más diluidas cruzarán a valores Ct posteriores. Para cuantificar la expresión génica de un gen particular, se resta el Ct de un ácido nucleico procedente del gen de interés al Ct del ácido nucleico procedente del control endógeno en la misma muestra para normalizar la variación en la cantidad y calidad del ARN entre diferentes muestras y obtener la expresión relativa (con respecto al control endógeno) de cada una de las muestras, la "muestra del sujeto" y la "muestra del control". Opcionalmente, esto se lleva a cabo por duplicado, triplicado, cuadruplicado y de manera similar, respectivamente. Se puede obtener de manera adecuada un valor  $\Delta Ct$  del control calculando el promedio de los valores  $\Delta Ct$  obtenidos a partir de muestras de un grupo del control de varios individuos con los cuales se van a comparar los valores de la "muestra del sujeto". El grupo del control (del cual se calcula el valor promedio) consiste en los individuos adecuados a los respectivos fines (de comparación). La persona experta aprenderá de esta divulgación que un grupo de control adecuado es para un fin concreto. En una realización particular, la presente invención se puede llevar a la práctica omitiendo la determinación del valor  $\Delta Ct$  del grupo del control, es decir, determinar (solo) el valor  $\Delta Ct$  de

la "muestra del sujeto" y a continuación comparando posteriormente este con el respectivo valor  $\Delta Ct$  promedio del control indicado en los ejemplos.

5 En otra realización aun mas preferida de este aspecto de la invención la detección del producto de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* se realiza mediante microarrays.

10 La cantidad de referencia se obtiene a partir de los valores de expresión constitutiva de los genes, en un grupo de individuos sanos, o de la expresión de los genes en el grupo de individuos antes de ser sometidos al tratamiento.

15 La cantidad de referencia será, por ejemplo, en el caso de la diferenciación entre los pacientes afectados por cáncer colorrectal respondedores al tratamiento, la expresión constitutiva del gen en un grupo control de individuos no respondedores.

20 Por otro lado, la muestra o muestras de referencia pueden ser, por ejemplo, obtenidas a partir de tejido tumoral de un paciente con cáncer colorrectal que no respondió al tratamiento.

25 En otra realización preferida de este aspecto de la presente invención, la cantidad de referencia se obtiene a partir de una muestra de referencia. La cantidad de referencia puede obtenerse también, por ejemplo, de los límites de distribución normal de una cantidad encontrada en muestras obtenidas de una población de individuos con cáncer colorrectal no respondedores, mediante técnicas estadísticas bien conocidas. En otra realización preferida, la muestra de referencia se obtiene de los pacientes antes y después del tratamiento. Por tanto, una realización preferida de este aspecto de la invención, comprende realizar al menos dos veces la secuencia de pasos (a) – (b) del método de la invención, en  
30 muestras biológicas procedentes de un mismo individuo, y aisladas en momentos diferentes. Más preferiblemente, las muestras se obtienen antes y después del tratamiento.

35 Los inventores han demostrado que los niveles de expresión de uno o más de estos genes pueden ser indicativos de la respuesta de un sujeto al tratamiento. En una realización preferida de este aspecto de la invención, la respuesta es una reducción significativa de la carga tumoral evaluada por criterios radiológicos objetivos estándar universales (criterios

RECIST). En una realización alternativa, la respuesta es un resultado clínico, tal como la supervivencia exenta de progresión tumoral.

La evaluación de la respuesta completa y/o la respuesta parcial es un factor importante para determinar el estado de un paciente individual. De esta manera, es necesario estimar la carga total del tumor en el valor inicial y usar ésta como elemento comparador para las posteriores medidas que se llevan a cabo normalmente de acuerdo a los criterios RECIST (versión 1.1), Eisenhauer *et al.*, 2009. *Eur. J. Cancer*, 45 (228–247), definidos de la siguiente manera:

1. Respuesta Completa (RC): Desaparición de todas las evidencias medibles y evaluables de la enfermedad

2. Respuesta Parcial (RP): Al menos una disminución del 30% en la suma de diámetros de las lesiones diana, tomando como referencia el valor inicial de la suma de diámetros.

3. Enfermedad Progresiva (EP): Al menos un aumento del 20% en la suma de diámetros de las lesiones diana, tomando como referencia la suma más pequeña en el estudio (esto incluye el valor inicial de la suma si este es el más pequeño del estudio). Además del aumento relativo del 20%, la suma debe también demostrar un aumento absoluto de al menos 5 mm. (Nota: la aparición de una o más nuevas lesiones se considera también progresión).

4. Enfermedad Estable (EE): Ni una disminución suficiente para calificarla como RP ni un aumento suficiente para calificarla como EP.

A lo largo de la presente invención, los términos RC, RP, EP y EE se definen de acuerdo con las definiciones 1 a 4 anteriores tomadas de las Directrices RECIST revisadas de Eisenhauer *et al.*, 2009. *Eur. J. Cancer*, 45 228–247.

En otra realización preferida, el tratamiento neoadyuvante comprende el uso de radioterapia. En otra realización aun más preferida, dicho tratamiento comprende la administración de quimioterapia con compuestos de tipo fluoropirimidina y un agente adicional.

La quimioterapia, la respuesta a la cual se va a prever, comprende esquemas de quimioterapia estándar en el tratamiento del cáncer colorrectal, esquemas basados en fluoropirimidinas. Se entiende la quimioterapia como el tratamiento del cáncer con un fármaco antineoplásico o con una combinación de dichos fármacos. Sin pretender estar vinculado a ninguna teoría particular, se entiende que la quimioterapia actúa normalmente

eliminando células que se dividen rápidamente, lo que es una de las propiedades principales de la mayor parte de células cancerosas. Para el tratamiento de los pacientes de cáncer colorrectal, la quimioterapia comprende preferiblemente la administración de fluoropirimidinas, que se piensa que actúan como antimetabolitos. Los ejemplos de compuestos de fluoropirimidina son la capecitabina, la floxuridina, y el fluorouracilo (5-FU), que es el más preferido en la presente invención. Dicha fluoropirimidina se puede administrar sola o en combinación con un agente adicional, siendo la poliquimioterapia en general más eficaz aunque también más tóxica. El agente adicional puede ser una molécula capaz de interactuar con el ADN, tal como en la inhibición de la síntesis de ADN y/o en prevenir el desenrollado del ADN. En una realización preferida de la presente invención, la quimioterapia puede comprender la administración de oxaliplatino y fluoropirimidina, o de irinotecán y fluoropirimidina. Se piensa que la citotoxicidad del oxaliplatino (documento US 4.169.846) da como resultado la inhibición de la síntesis del ADN en células cancerosas. Los estudios *in vivo* han mostrado que oxaliplatino presenta actividad antitumoral frente al carcinoma de colon por su efecto citotóxico (no dirigidos). Irinotecán por otra parte es un análogo semisintético del alcaloide natural camptotecina, que se piensa que actúa evitando el desenrollado del ADN mediante la inhibición de la topoisomerasa 1. De esta manera, oxaliplatino e irinotecán se piensa que ejercen su función interviniendo con el ADN.

Por lo tanto, en una realización aún mas preferida, la quimioterapia es una terapia que comprende la administración de compuestos basados en platino, compuestos inhibidores de la topoisomerasa I, un compuesto análogo de pirimidina, o cualquiera de sus combinaciones. Más preferiblemente, el compuesto basado en platino es el oxaliplatino, el inhibidor de la topoisomerasa I es el irinotecan, y el análogo de pirimidina es el 5-fluorouracilo.

Otro aspecto de la invención se refiere a un método para el seguimiento de la evolución del cáncer colorrectal en un individuo, de ahora en adelante tercer método de la invención, que comprende realizar al menos dos veces la secuencia de pasos (a) – (b) según el primer o el segundo método de la invención, en muestras biológicas procedentes de un mismo individuo, y aisladas en momentos diferentes.

#### KIT DE LA INVENCION

Otro aspecto de la presente invención se refiere a un kit o dispositivo, de aquí en adelante kit o dispositivo de la invención, que comprende los elementos necesarios para analizar la

cantidad del producto de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*.

5

El kit se basa en el poder predictivo del procedimiento de la presente invención. Tal como se ha mencionado anteriormente, el valor indicador de referencia para la falta de respuesta de cada gen concreto se puede determinar antes de llevar a cabo el procedimiento de la presente invención. En el caso particular del kit, se pueden proporcionar con el valor  
10 indicador de referencia para la falta de respuesta (y/o un valor de referencia indicador para la respuesta). Con la ayuda del kit, se puede calcular la expresión de cada gen, es decir, con respecto a las muestras de control ejemplificadas anteriormente. El control puede de esta manera estar comprendido también en el kit.

15 El kit de la invención más preferiblemente comprende los medios necesarios para comparar la cantidad detectada en el paso (b) con una cantidad de referencia. Dicho kit puede contener todos aquellos reactivos necesarios para analizar la cantidad del producto de expresión de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*,  
20 *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* por medio de cualquiera de los métodos descritos anteriormente en este documento. El kit además puede incluir, sin ningún tipo de limitación, tampones, agentes para prevenir la contaminación, inhibidores de la degradación de las proteínas, etc. Por otro lado el kit puede incluir todos los soportes y recipientes necesarios  
25 para su puesta en marcha y optimización. Preferiblemente, el kit comprende además las instrucciones para llevar a cabo cualquiera de los métodos de la invención.

Más preferiblemente, el kit o dispositivo de la invención comprende los cebadores y sondas obtenidos de las secuencias de los genes de la invención, tal y como también se encuentran en la Tabla 1. Puesto que un solo gen puede ser útil para predecir o pronosticar la respuesta  
30 al tratamiento en pacientes con cáncer colorrectal, el kit puede contener la/s sonda/s y cebadores útiles para cuantificar la expresión de dicho gen, o cualquiera de las combinaciones de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*,  
35 *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*.

En realizaciones particulares, el kit se selecciona entre (a) un kit adecuado para la PCR, (b) un kit adecuado para la Transferencia Northern Blot y (c) un kit adecuado para los análisis de micromatriz. Se pueden combinar cualquiera de dos o más de estas realizaciones, de tal manera que el kit puede comprender, por ejemplo, ambos de (a) y (c).

5

En el caso de (a) un kit adecuado para la PCR, esta PCR es normalmente la PCR cuantitativa en tiempo real PCR (RQ-PCR), una técnica de cuantificación de la expresión génica sensible y reproducible. En este caso se desea que el kit comprenda adicionalmente cebadores y sondas y oligonucleótido(s) del kit. Estos reactivos pueden estar comprendidos

10 opcionalmente en el kit.

Una Transferencia Northern implica el uso de electroforesis para separar las muestras de ARN por tamaño y la posterior detección con un(os) oligonucleótido(s) (sonda de hibridación) complementaria con (parte de) la secuencia diana del ARN de interés.

15

Es también posible que el(los) oligonucleótido(s) estén inmovilizados en manchas sobre una superficie (preferiblemente sólida). En una de sus realizaciones, el kit comprende una micromatriz. Una micromatriz de ARN es una matriz sobre un sustrato sólido (normalmente un porta de vidrio o una celda de una película fina de silicio) que evalúa grandes cantidades

20 de diferentes ARN que son detectables mediante sondas específicas inmovilizadas sobre manchas sobre un sustrato sólido. Cada mancha contiene una secuencia específica de ácido nucleico, normalmente una secuencia de ADN, como sondas (o indicadores). Aunque el número de manchas no está limitado de manera alguna, existe una realización preferida en la que la micromatriz se personaliza para los procedimientos de la invención. En una

25 realización, dicha matriz personalizada comprende cincuenta manchas o menos, tal como treinta manchas o menos, incluyendo veinte manchas o menos.

MICROARRAY DE LA INVENCION

Por tanto, otro aspecto de la invención se refiere a un microarray, de ahora en adelante

30 microarray de la invención, que comprende oligonucleótidos o microarreglos de canal único diseñados a partir de una secuencia conocida o un ARNm de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*. Más

35 preferiblemente, la secuencia de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*,

*RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* es la secuencia nucleotídica indicada para cada uno de ellos en la Tabla 1, respectivamente.

5 El uso del kit no está particularmente limitado, aunque se prefiere su uso en cualquiera de los métodos de la invención o en cualquiera de sus realizaciones. Así pues, otro aspecto de la invención se refiere al uso del kit o dispositivo de la invención para la obtención de datos útiles para el pronóstico o la predicción de la respuesta a la quimioterapia neoadyuvante en individuos con cáncer colorrectal.

10 Otro aspecto de la invención se refiere a un medio de almacenamiento legible por un ordenador que comprende instrucciones de programa capaces de hacer que un ordenador lleve a cabo los pasos de cualquiera de los métodos de la invención (del primer, el segundo o el tercer método de la invención).

15 Otro aspecto de la invención se refiere a una señal transmisible que comprende instrucciones de programa capaces de hacer que un ordenador lleve a cabo los pasos de cualquiera de los métodos de la invención.

20 Los términos "polinucleótido" y "ácido nucleico" se usan aquí de manera intercambiable, refiriéndose a formas poliméricas de nucleótidos de cualquier longitud, tanto ribonucleótidos (ARN ó RNA) como desoxiribonucleótidos (ADN ó DNA). Los términos "secuencia aminoacídica", "péptido", "oligopéptido", "polipéptido" y "proteína" se usan aquí de manera intercambiable, y se refieren a una forma polimérica de aminoácidos de cualquier longitud, que pueden ser codificantes o no codificantes, química o bioquímicamente modificados.

25 A lo largo de la descripción y las reivindicaciones la palabra "comprende" y sus variantes no pretenden excluir otras características técnicas, aditivos, componentes o pasos. Para los expertos en la materia, otros objetos, ventajas y características de la invención se desprenderán en parte de la descripción y en parte de la práctica de la invención. Los siguientes ejemplos y dibujos se proporcionan a modo de ilustración, y no se pretende que  
30 sean limitativos de la presente invención.

## **BREVE DESCRIPCIÓN DE LAS FIGURAS**

35 Con objeto de ayudar a una mejor comprensión de las características del invento de acuerdo con un ejemplo preferente de realización práctica del mismo y para complementar esta

descripción, se acompaña como parte integrante de la misma un juego de dibujos, cuyo carácter es ilustrativo y no limitativo. En estas figuras:

**Figura 1.** Análisis cluster jerárquico supervisado que muestra los genes diferencialmente expresados en pacientes que lograron una respuesta objetiva a la quimioterapia (Si: RC y RP; azul) frente a pacientes que no responden a la quimioterapia (No: EE o EP; rojo). Los genes en rojo indican sobreexpresión, verde indica infraexpresión.

**Figura 2.** Análisis cluster jerárquico supervisado que muestra los genes expresados diferencialmente en paciente que lograron una supervivencia libre de progresión (SLP) mayor que la media de tiempo de SLP (Si; azul) frente a pacientes SLP menor que la media (No; rojo). Los genes en rojo indican sobreexpresión, verde indica infraexpresión.

**Figura 3.** Valores medios  $\Delta Ct$  de genes validados en pacientes con respuesta objetiva a la quimioterapia (si) frente a no respondedores (No). \*valor de  $p < 0.05$ . \*\*valor de  $p < 0.01$ . \*\*\*valor de  $p < 0.001$ . Los datos derivados de RT-qPCR son presentados como valores  $\Delta Ct$  con valores más altos para la menor expresión de ARN.

**Figura 4.** El resultado clínico considerando la supervivencia libre de progresión (SLP) de pacientes por los niveles de expresión génica. La línea negra sólida representa a los pacientes con mayor nivel de expresión génica (sobre la media). La línea negra discontinua representa a los pacientes con menos niveles de expresión génica.

**Figura 5.** Los valores medios  $\Delta Ct$  de genes validados en pacientes con supervivencia libre de progresión (SLP) mayor que la media (11.53 meses) [Si] comparados con los pacientes con menor SLP [No]. \*valor- $p < 0.05$ ; \*\*valor  $p < 0.01$ ; \*\*\*valor- $p < 0.001$ . Los datos derivados de la RT-qPCR están representados como valores  $\Delta Ct$ , con mayores valores para menos expresión de ARN.

### 30 EJEMPLOS DE LA INVENCION

A continuación se ilustrará la invención mediante unos ensayos realizados por los inventores, que pone de manifiesto la especificidad y efectividad de los métodos de la invención para obtener datos útiles en la predicción de la respuesta al tratamiento de dicha enfermedad.



## Materiales y métodos

El protocolo del estudio ha sido aprobado por los comités éticos de los centros participantes y con un formulario de consentimiento por escrito de todos los pacientes. Se utilizaron un total de 159 tumores de pacientes diagnosticados con CCR avanzado, como *training* (formación) (n=40) y validación (n=119). Las muestras que cumplían los siguientes criterios fueron incluidas en el estudio: (1) diagnóstico primario confirmado de CCR; (2) los pacientes fueron tratados con al menos una línea de quimioterapia para la enfermedad avanzada y la respuesta fue evaluada; (3) tejidos adecuados congelados disponibles para ensayos moleculares (se requiere una proporción de células tumorales >50%). El conjunto de formación consistía en 40 muestras de CCR procedentes del Hospital Marqués de Valdecilla, Santander, España. El conjunto de validación consistía en 119 muestras procedentes de 4 hospitales diferentes (Hospital Virgen del Rocío de Sevilla (España), Hospital Virgen de la Victoria de Málaga (España), Hospital Virgen de la Merced de Osuna (España) y Hospital Marqués de Valdecilla de Santander (España), y se incluyeron 86 muestra tumorales (40 procedentes del conjunto de formación y 46 de pacientes de CCR recién tratados) y 33 muestras de tejido normal de pacientes con CCR fueron usadas como controles. La distribución de las características demográficas y clínico-patológicas de las cohortes iniciales y de validación se presenta en la Tabla 2, y las características histológicas de las muestras tumorales están esbozadas en la Tabla 3. No se encontraron diferencias significativas entre ambos grupos.

**Tabla 2.** Datos demográficos, características clínicas y tratamiento en los conjuntos de formación y validación.

	<b>Conjunto de Formación (n=40)</b>	<b>Conjunto de Validación (n=86)</b>	
<b>Características</b>	<b>N (%)</b>	<b>N (%)</b>	<b>P</b>
Edad (años)			0,417
• Mediana (rango)	61 (47-79)	65 (42-80)	
Sexo			1,00
• Femenino	16 (40)	33 (38,4)	
• Masculino	24 (60)	53 (61,6)	
Metástasis en el diagnóstico			0,625
• Sí	34 (85)	69 (80,3)	
• No	6 (15)	17 (19,7)	
<b><u>Metástasis / enfermedad avanzada</u></b>			
Estado funcional			0,306
• 0-1	40 (100)	82 (95,3)	
• 2	0 (0)	4 (4,7)	
Parámetros de laboratorio (Mediana (rango))			
• CEA (ng/mL)	62,5 (1-4007)	28 (1-1448)	
• Hemoglobina (g/dL)	12 (2-15)	12 (2-15)	
• Alcalinofosfatasa (UI/L)	107 (48-620)	96 (43-16189)	
• Lactatodehidrogenasa (UI/L)	441 (273-2692)	355 (109-2692)	
<b><u>Regímenes de quimioterapia (CT) iniciales</u></b>			
Quimioterapia basada en Oxaliplatino			
• Oxaliplatino+FP	18 (45)	39 (45,4)	
• Oxaliplatino+FP+AntiEGFR	8 (20)	14 (16,3)	
• Oxaliplatino+FP+AntiEGFR/AntiVEGFR	9 (22,5)	14 (16,3)	
Quimioterapia basada en Irinotecan			
• Irinotecan+FP	0 (0)	9 (10,5)	
• Irinotecan+FP+AntiEGFR	0 (0)	1 (1,2)	

	<b>Conjunto de Formación (n=40)</b>	<b>Conjunto de Validación (n=86)</b>	
<ul style="list-style-type: none"> <li>Irinotecan+FP+AntiEGFR+AntiEGFR/AntiVEGFR</li> </ul>	0 (0)	1 (1,2)	
Triple (Oxaliplatino+ Irinotecan+FP)	5 (12,5)	4 (4,6)	
Sólo FP	0 (0)	3 (3,4)	
<b><u>Respuesta</u></b>			
Respuesta del tumor a la CT inicial			0,441
<ul style="list-style-type: none"> <li>Sí (CR+PR)</li> </ul>	25 (62,5)	46 (53,5)	
<ul style="list-style-type: none"> <li>No (SD+PD)</li> </ul>	15 (37,5)	40 (46,5)	
Progresión del tumor después de la CT inicial			0,068
<ul style="list-style-type: none"> <li>Sí</li> </ul>	27 (67,5)	71 (82,6)	
<ul style="list-style-type: none"> <li>No</li> </ul>	13 (32,5)	15 (17,4)	
Tratamiento quirúrgico de la recidiva o metástasis con resección completa			0,378
<ul style="list-style-type: none"> <li>Sí</li> </ul>	12 (30)	19 (22,1)	
<ul style="list-style-type: none"> <li>No</li> </ul>	28 (70)	67 (77,9)	
<b><u>Resultado</u></b>			
Seguimiento de los pacientes vivo (meses)			0,586
<ul style="list-style-type: none"> <li>Mediana (rango)</li> </ul>	31.9 (12.9-77-57)	30.8 (5.50-77.57)	
Estado del paciente en el último contacto			
<ul style="list-style-type: none"> <li>Muerto</li> </ul>	17 (42,5)	49 (57)	
<ul style="list-style-type: none"> <li>Vivo con tumor</li> </ul>	22 (55)	31 (36)	
<ul style="list-style-type: none"> <li>Vivo sin tumor</li> </ul>	1 (2,5)	6 (7)	
<p><i>CEA: antígeno carcinoembrionario; EGFR: receptor del factor de crecimiento epidermal; VEGF: factor de crecimiento endotelial vascular; VEGFR: receptor del factor de crecimiento endotelial vascular; FP: fluoropirimidinas; CR: respuesta completa; PR: respuesta parcial; SD: estabilidad de la enfermedad; PD: progresión de la enfermedad.</i></p>			

**Tabla 3.** Características de los tumores en los conjuntos de formación y validación.

	<b>Conjunto de Formación (n=40)</b>	<b>Conjunto de Validación (n=86)</b>	
<b>Características</b>	<b>N (%)</b>	<b>N (%)</b>	<b>P</b>
<b><u>Tipo de muestra</u></b>			
• Pieza quirúrgica	38 (95)	85 (98,8)	
• Biopsia endoscópica	1 (2,5)	1 (1,2)	
• Otros	1 (2,5)	0 (0)	
<b><u>Localización del tumor</u></b>			
Ubicación del tumor primario			0,834
• Colon	28 (70)	62 (72,1)	
• Recto	12 (30)	24 (27,9)	
Ubicación de la metástasis			
• Hígado	33 (82,5)	57 (66,3)	0,062
• Pulmón	12 (30)	22 (25,6)	0,668
• Carcinomatosis peritoneal	6 (15)	16 (18,6)	0,802
• Otros	1 (2,5)	24 (27,9)	
<b><u>Características histológicas</u></b>			
Histología			0,306
• Adenocarcinoma	40 (100)	82 (95,3)	
• Mucino carcinoma		4 (4,7)	
Diferenciación del tumor			
• Bien diferenciado	14 (35)	38 (44,2)	
• Moderadamente diferenciado	8 (20)	28 (32,6)	
• Poco diferenciado	15 (37,5)	15 (17,4)	
• Desconocido	3 (7,5)	5 (5,8)	
Invasión Linfovascular			
• Sí	23 (57,5)	30 (34,9)	
• No	3 (7,5)	15 (17,4)	
• Desonocida	14 (35)	41 (47,7)	
Estado de K-ras			0,338
• Silvestre	25 (62,5)	45 (52,3)	
• Mutado	15 (37,5)	41 (47,7)	

## Muestras de ARN

Las muestras de tejido tumoral fueron molidas hasta un polvo fino bajo nitrógeno líquido usando un mortero. La homogenización fue lograda usando homogeneizadores  
5 QIAashredder y el ARN total fue extraído usando el mini kit RNeasy (ambos kits de QiagenInc; Valencia, CA, USA). La cantidad y calidad del ARN fueron estimadas mediante gel de agarosa y medidas espectrofotométricas. Cuando no fue posible debido a la escasa cantidad de ARN, fueron estimados usando el Bioanalyzer 2100 (Eukaryote total RNA Nano o Pico kit: Agilent Technologies; Santa Clara, CA, USA). De las 40 muestras iniciales,  
10 podríamos obtener ARN adecuado en calidad y cantidad en 37 casos (93%).

## Microarray de perfiles de expresión génica

Los experimentos de microarray fueron desarrollados usando el *Human Whole Genome*  
15 U133 Plus 2.0 array (Affymetrix; Santa Clara, CA, USA), que contiene 54675 sondas de genes humanos. El AND de doble hebra fue sintetizado usando One-Cycle cDNA Synthesis kit (Affymetrix), de acuerdo a las recomendaciones del fabricante. El ARN total (2 µg) fue primero transcrito a la inversa usando un promotor de cebador T-7 Oligo (dT) para obtener ADNc de primera hebra y después ADNc de segunda hebra que fue purificado con  
20 GeneChip Cleanup Module (Affymetrix) y usado como una plantilla en la posterior reacción de transcripción *in vitro*. El ARNc marcado fue purificado también con GeneChip Cleanup Module y cuantificado espectrofotométricamente. El ARNc purificado fue fragmentado in buffer de fragmentación (5x buffer: 200 mMTris-acetate (pH 8.1) + 500 mMKOAc + 150 mM MgOAc) e hibridizado al microarray en 200 µl de solución de hibridación que contiene  
25 µg de diana marcada en 1x Mes buffer (0.1 M Mes + 1.0 M NaCl + 20mM ETA + 0.01% Tween 20) y 0.1 mg/ml de ADN de esperma de arenque, 10% DMSO, 0.5 mg/ml BSA, 50 pM del oligonucleótido control B2 y 1x controles de hibridación eucariota (nioB, bioC, bioD, cre). Tanto el oligonucleótido control B2 como los controles de hibridación eucariota fueron obtenidos de Affymetrix. La mezcla de hibridación fue aplicada a Human Genome U133 Plus  
30 2.0 array (Affymetrix), el cual incluye el total del genoma humano con 54613 conjuntos de sondas. Los arrays se situaron en el horno de hibridación 640 (Affymetrix) a 45 °C durante 16 horas, girando a 60 rpm. Tras la hibridación, los arrays fueron lavados con 6x SSPE-T (0.9 M NaCl + 60 mM NaH<sub>2</sub>PO<sub>4</sub> + 6 mM AEDT + 0.01 % Tween 20) a 30 °C sobre una superficie fluida (FS400 Affymetrix) en 10 ciclos de 2 mezclas por ciclo, y posteriormente con  
35 0.1 M Mes + 0.1 M NaCl + 0.01% Tween 20 a 50°C en 6 ciclos de 15 mezclas por ciclo. Los

arrays fueron teñidos después durante 5 minutos a 35°C con un conjugado Estreptavidina-Phycoeritrina (sondas moleculares), seguido de 10 ciclos de lavado de 4 mezclas por ciclo con 6x SSPE-T. Para aumentar las señales, los arrays fueron teñidos complementariamente con una solución de anticuerpos anti-estreptavidina durante 5 minutos, seguido por 5 minutos de tinción con un conjugado de estreptavidina-phycoeritrina. Después de 15 ciclos de lavado de 4 mezclas por ciclo, los arrays fueron escaneados usando GC300 laser confocal scanner (Affymetrix).

### **Validación de los genes expresados diferencialmente en CCR.**

10

El ARN total fue extraído de las muestras de tejidos tumorales con mirVanaRNA isolation kit (Ambion, Austin, TX, USA), de acuerdo a las instrucciones del fabricante. El ARN total recogido, fue determinado usando el Nanodrop ND-100025 spectrophotometer (Nanodrop Tech, DE, USA). Los arrays de baja densidad Taqman® de diseño personalizado (TLDA) 7900 HT con tarjetas de microfluidos que cuentan con 161 ensayos individuales fueron ordenados a partir de Applied Biosystems (Applied Biosystems; Carlsbad, CA, USA) (\*utilizar los términos correctos en castellano).

Los TLDA fueron desarrollados en un proceso de 2 pasos: brevemente durante el primer paso, 800 ng (50 ng/16 µl) del ARN total fueron transcritos a la inversa usando Megaplex RT primers y TaqManRNA reverse transcription kit en un volumen total de 20 µl. Las reacciones fueron incubadas en un GStormThermal Cyclor (Gene Technologies, Essex, UK) durante 5 minutos a 25°C, 30 minutos a 42°C, y un minuto a 50°C durante 40 ciclos, mantenido durante 5 minutos a 85°C y después a 4°C. En el segundo paso, 450 µL de la muestra de ADNc y 450 µL de la Taqman Universal PCR master mix, fueron cargados en puertos llenos, sobre la tarjeta microfluidica TLDA. La tarjeta fue brevemente centrifugada durante 1 minutos a (280 gramos \*utilizar el término correcto) para distribuir las muestras en los múltiples pozos conectados a los puertos llenos y después sellados para prevenir la contaminación entre pozos. Las tarjetas TLDA fueron manejadas y analizadas por el ABI PRISM® 7900HT sequence detection protocol (Applied Biosystems). Las reacciones fueron incubadas a 95°C durante 10 minutos, seguido de 40 ciclos de 15 segundos a 95°C y un minuto a 60°C.

## Análisis estadístico

VARIABLES DE RESULTADO CLÍNICO. Las estadísticas fueron usadas para caracterizar los parámetros clínicos más relevantes. La asociación de las variables categóricas, fue explorada por el test del chi-cuadrado, o la prueba exacta de Fisher. Para evaluar la distribución de las variables continuas entre los grupos de estudio, fueron usados los tests paramétricos (t-test) y no-paramétrico (Kruskal-Wallis) cuando era apropiado.

La respuesta tumoral fue evaluada por métodos convencionales de acuerdo a los criterios estándar RECIST 1.0: Una respuesta completa (RC) fue definida como la desaparición de todas las evidencias medibles y evaluables de la enfermedad; una respuesta parcial (RP) fue definida como una disminución igual o mayor al 30% en la suma de los diámetros más largos de las lesiones diana; la enfermedad estable (EE) fue considerada cuando la carga tumoral disminuyó menos del 30% o aumentó menos del 20%; y enfermedad progresiva (EP) fue señalada por un incremento mayor del 20% en la suma de los diámetros más largos de las lesiones diana o la aparición de una nueva lesión. Los pacientes fueron clasificados de acuerdo a la mejor respuesta a la quimioterapia, en 2 grupos: aquellos que lograron una respuesta objetiva (respondedores [R]: RC + RP) y aquellos que no lo hicieron (no respondedores [NR]: EE + EP). La supervivencia libre de progresión (SLP) fue definida como el tiempo transcurrido desde el inicio de la quimioterapia de primera línea hasta la primera evidencia de la progresión de la enfermedad. La supervivencia general (SG) fue calculada desde el inicio de la terapia para enfermedad avanzada hasta la fecha de la muerte por cualquier causa. El método de Kaplan-Meier del límite de producto, fue usado para estimar las variables tiempo dependientes (SLP y SG), y las diferencias observadas entre los subgrupos de pacientes fueron evaluadas por el test de log-rank.  $P < 0.05$  fue considerado significativo. Todos los análisis fueron desarrollados usando el paquete estadístico para Social Sciences software (SPSS 15.0 for Windows, SPSS Inc, Chicago, IL).

## Microarrays

Los datos de imagen de microarray fueron analizados usando el GeneChip Operating Software (GCOS 1.4 Affymetrix). El partek genomics suite v7.3.1 (Partek Inc.; St. Louis, MO, USA) fue usado para el análisis estadístico. La calidad de los arrays fue evaluado usando los parámetros P llamado %, array outlier y el error estándar normalizado sin escala. Posteriormente, los datos fueron procesados a través del RMA (robusto promedio multichip), método para obtener los valores de intensidad individuales en cada array, después

normalizados y filtrados para eliminar secuencias no informativas (incluyendo secuencias control, aquellas que presentan un señal de hibridación cerca del fondo y a aquellos sin cambios en la expresión en todas las muestras). Finalmente, 9619 secuencias fueron seleccionadas para generar la lista de trabajo. Un modelo de regresión lineal usando la tasa de falso descubrimiento (siglas en inglés FDR), análisis de componentes principales (ACP) y técnicas de agrupamiento fueron usadas para comparar el perfil de expresión génica entre pacientes R y NR después de la quimioterapia metastásica de primera línea, y considerando la SLP después.

## 10 **Análisis de reacción en cadena de la polimerasa cuantitativa en tiempo real (RT-qPCR).**

La expresión de los genes diana, fue normalizada en relación a la expresión de GAPDH. Los valores de ciclo umbral (siglas en inglés Ct) fueron calculados usando el software SDS v.2.3 (Applied Biosystems) usando condiciones automáticas basales y un umbral de 0.2. La expresión de cada gen diana fue calculada relativa a un control endógeno GAPDH. Los datos se presentan como diana de expresión génica =  $2^{\Delta Ct}$ , con  $\Delta Ct = (\text{gen diana Ct} - \text{GAPDH Ct})$ . Este método es una manera conveniente para analizar los cambios relativos en la expresión génica de los experimentos PCR cuantitativos en tiempo real. (Applied Biosystems user Bulletin no.2 (P/N 4303859)). La expresión génica fue calculada usando el software Real-Time Statminer® v.4.2 (Integromics, Inc). Este software realiza un moderado t-test entre los grupos (R y NR) y los corrige usando el algoritmo Benjamini-Hochberg (Benjamini Y, et al 1995) con FDR establecido en el valor del 5%. Para el propósito de este estudio, la expresión génica significativa fue considerada cuando el gen había sido detectado al menos en el 50% de los pacientes en cada grupo comparado. Además, en situaciones en las que el gen es indetectable y los valores Ct están más allá del máximo Ct32, el software Statminer® establece un valor igual al máximo.

## 30 **RESULTADOS**

La comparativa de los niveles de expresión génica relativa entre respondedores (23 pacientes; 62%) frente a no respondedores (14 pacientes; 38%) a la quimioterapia están representados en la figura 1.

35 Se encontraron diferencias de expresión ( $p < 0.05$ ) en 595 genes (6.2%) de las 9619 secuencias finales seleccionadas después del análisis. Usando el test FDR, el 5% de ellos



(480 genes) son considerados como hallazgos de falsos positivos. En un cluster supervisado, se observó la expresión génica desregulada y SLP como un marcador de respuesta, detectando perfiles de expresión asociados diferenciales (figura 2).

5 Basado en ambos análisis, seleccionados aquellos genes (n=161) con los valores p más significativos y su desregulación fue consistente en respuesta a la quimioterapia y en el análisis de supervivencia para ser validado usando qRT-PCR en una cohorte independiente de pacientes con CCR y muestras control no-tumorales.

10 **Identificación del patrón de expresión génica pacientes con CCR de acuerdo a la respuesta a la quimioterapia.**

Se confirmaron 24 de los 161 como genes diferencialmente expresados entre pacientes que lograron una respuesta objetivo a la quimioterapia (R: RC + RP) frente a aquellos que no lo hicieron (NR: EE + EP) (p<0.05) después qRT-PCR usando el software Statminer®: *AQP1*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1* y *WWC2*.

20 **Tabla 4.** Genes expresados diferencialmente en respuesta a la quimioterapia en pacientes con carcinoma colorrectal metastásico, según el análisis de PCR en tiempo real.

Gen	Gen ID	R vs NR (- $\Delta\Delta$ Ct)	p-valor* ajustados
<i>AQP1</i>	358	1,200	<b>0,025</b>
<i>CLEC3B</i>	7123	1,614	<b>0,006</b>
<i>DCK</i>	1633	0,888	<b>0,044</b>
<i>DEFA5</i>	1670	1,599	<b>0,017</b>
<i>DNAJC3</i>	5611	1,421	<b>0,006</b>
<i>FBLIM1</i>	54751	0,947	<b>0,038</b>
<i>GAS7</i>	8522	1,000	<b>0,034</b>
<i>IGFBP4</i>	3487	0,803	<b>0,025</b>
<i>KSR1</i>	8844	0,997	<b>0,034</b>
<i>LONP1</i>	9361	0,800	<b>0,034</b>
<i>MTHFD1L</i>	25902	0,915	<b>0,044</b>
<i>NAV1</i>	89796	0,881	<b>0,038</b>

<b>Gen</b>	<b>Gen ID</b>	<b>R vs NR (-<math>\Delta\Delta</math>Ct)</b>	<b>p-valor* ajustados</b>
<i>NIPBL</i>	25836	1,049	<b>0,026</b>
<i>PALM2</i>	445815	1,203	<b>0,024</b>
<i>PCDHGC3</i>	5098	0,991	<b>0,038</b>
<i>PROS1</i>	5627	1,064	<b>0,026</b>
<i>RARA</i>	5914	0,960	<b>0,034</b>
<i>RSF1</i>	51773	0,796	<b>0,044</b>
<i>TENC1</i>	23371	0,942	<b>0,038</b>
<i>TGFBR3</i>	7049	1,150	<b>0,023</b>
<i>TRAK2</i>	66008	1,220	<b>0,017</b>
<i>VSNL1</i>	7447	0,966	<b>0,034</b>
<i>WHSC1L1</i>	54904	1,116	<b>0,026</b>
<i>WWC2</i>	80014	0,932	<b>0,044</b>

*Gen ID: número de acceso GenBank. \* Los p-valores obtenidos se ajustaron para pruebas múltiples por el ajuste de Benjamini-Hochberg.*

Los pacientes se estratificaron en dos grupos, es decir, respondedores a quimioterapia (R),  
 5 incluyendo pacientes con respuesta completa o respuesta parcial, y no respondedores (NR),  
 incluyendo pacientes con enfermedad estable o progresión de la enfermedad sobre la base  
 en el cambio en el tamaño de la lesión.

Para evaluar aún más las diferencias en la expresión génica potencialmente predictiva de la  
 10 respuesta a la quimioterapia, se compararon los niveles de expresión génica entre muestras  
 de pacientes R, NR y controles no-tumorales.

Los resultados se representan en la figura 3. Las diferencias significativas ( $p < 0.05$ ) fueron  
 encontrados en 15/24 genes: *AQP*, *CLECL3B*, *DCK*, *PROS1*, *WHSC1L1*, *TGFBR3*, *FBLIM1*,  
 15 *GAS7*, *IGFBP4*, *NAV1*, *PCDHGC3*, *RARA*, *RSF1*, *TENC1* y *TRAK2*. Y adicionalmente, el  
 gen *DNAJC3* mostró una significancia en el límite ( $p = 0,076$ ).

**La identificación de patrones de expresión génica en pacientes con cáncer de colon, de acuerdo a la supervivencia libre de progresión (SLP).**

5 El estimador Kaplan-Meier estima para la SLP de acuerdo a los niveles de expresión génica en pacientes agrupados como por arriba o por debajo de la media del tiempo (11,53 meses) mostró 4 genes con perfil de expresión diferencial ( $p < 0.05$ ); FAF1, KIAA1033, N4BP2L1 y SLC12A2. Otros 4 genes mostraron significancia límite, y fueron consideradas también por más análisis: DIDO1 ( $p = 0.076$ ), FBXO9 ( $p = 0.054$ ), RB1CC1 ( $p = 0.065$ ) y STARD13 ( $p = 0.051$ )

10

**Tabla 5.** Genes expresados diferencialmente por supervivencia libre de progresión en pacientes con carcinoma colorrectal metastásico, según análisis de PCR en tiempo real.

Gen	Gen ID	PFS_LM vs PFS_HM ( $-\Delta\Delta Ct$ )	p-valor* (95%CI)
<i>DIDO1</i>	11083	-0.020	<b>0.076</b>
<i>FAF1</i>	11124	-0.021	<b>0.022</b>
<i>FBXO9</i>	26268	-0.116	<b>0.054</b>
<i>KIAA1033</i>	23325	-0.148	<b>0.026</b>
<i>N4BP2L1</i>	90634	-0.025	<b>0.001</b>
<i>SLC12A2</i>	6558	-0.047	<b>0.033</b>
<i>STARD13</i>	90627	-0.784	<b>0.051</b>
<i>RB1CC1</i>	9821	-0.052	<b>0.065</b>

15 Los pacientes fueron estratificados en dos grupos. En pacientes con tiempo de supervivencia más baja que la progresión de la mediana (PFS\_LM) o superior a la mediana (PFS\_HM). \* PFS se estimó mediante el método de Kaplan-Meier y los valores de  $p$  fueron evaluados mediante la prueba de log-rank. Gene ID: número de acceso GenBank, IC: intervalo de confianza.

20 Luego, se compararon estos niveles de expresión génica entre pacientes agrupados por encima o por debajo de la media de tiempo de SLP y muestras control no-tumorales. Las diferencias significativas se mostraban en 5/8 genes: *N4BP2L1*, *STARD13*, *FAF1*, *FBXO9* y *SLC12A2*. (Figura 4).

**REIVINDICACIONES**

1. El uso simultáneo de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*,  
5 *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*,  
*PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*,  
*FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*, para predecir la  
respuesta al tratamiento con quimioterapia en un individuo que se sospecha que  
padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal.
- 10 2. Un método de obtención de datos útiles para predecir la respuesta al tratamiento con  
quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que  
ha sido diagnosticado de cáncer colorrectal, que comprende:
- a. Obtener una muestra biológica aislada que comprende células del individuo, y  
b. Detectar la cantidad de producto de expresión de los genes *AQP*, *CLEC3B*,  
15 *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*,  
*NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*,  
*TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*,  
*SLC12A*, *STARD13* y *RB1CC1* en la muestra aislada de (a).
- 20 3. El método según la reivindicación 2, que además comprende:
- c. Comparar los niveles de expresión de los genes *AQP*, *CLEC3B*, *DCK*,  
*DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*,  
*NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*,  
25 *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*,  
*SLC12A*, *STARD13* y *RB1CC1* en la muestra obtenida en (a), con la cantidad  
de expresión detectada para dichos genes en una población de individuos de  
referencia de respuesta patológica conocida.
- 30 4. Un método para predecir la respuesta al tratamiento con quimioterapia en un  
individuo que se sospecha que padece cáncer colorrectal, o que ha sido  
diagnosticado de cáncer colorrectal, que comprende los pasos (a)-(c) según  
cualquiera de las reivindicaciones 2-3, y además comprende:
- d. incluir al individuo que presenta una cantidad de expresión de los genes *AQP*,  
35 *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*,  
*MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*,  
*TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*,

*KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* significativamente superior a los niveles de expresión de los mismos genes en una población de referencia, en el grupo de individuos respondedores a la quimioterapia del cáncer colorrectal.

5

5. El método según cualquiera de las reivindicaciones 2-4, donde la muestra se obtiene de un tumor colorrectal.

10

6. El método según cualquiera de las reivindicaciones 2-5 en el que la cantidad de producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se obtiene mediante:

15

- a. Un procedimiento de perfilado génico, tal y como una micromatriz y/o
- b. Un procedimiento que comprende la PCR, tal como la PCR en tiempo real; y/o
- c. Transferencia Northern

20

7. El método según la reivindicación anterior, donde la cantidad de producto de expresión de los genes *AQP, CLEC3B, DCK, DEFA5, DNAJC3, FBLIM1, GAS7, IGFBP4, KSR1, LONP1, MTHFD1L, NAV1, NIPBL, PALM2, PCDHGC3, PROS1, RARA, RSF1, TENC1, TGFBR3, TRAK2, VSNL1, WHSC1L1, WWC2, FAF1, FBXO9, KIAA1033, N4BP2L1, SLC12A, STARD13 y RB1CC1* se obtiene mediante PCR cuantitativa a tiempo real.

25

8. El método según la reivindicación 7, donde la detección del producto de expresión se realiza mediante microarrays.

30

9. El método para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal según cualquiera de las reivindicaciones 2-8, donde el tratamiento quimioterápico comprende el uso de compuestos basados en platino, compuestos inhibidores de la topoisomerasa I, compuestos análogos de las pirimidinas, o cualquiera de sus combinaciones.

35

- 5 10. El método para predecir la respuesta al tratamiento con quimioterapia en un individuo que se sospecha que padece cáncer colorrectal, o que ha sido diagnosticado de cáncer colorrectal según la reivindicación anterior, donde el compuesto basado en platino es el oxaliplatino, el inhibidor de la topoisomerasa I es el Irinotecan, y el análogo de pirimidina es el 5-fluorouracilo.
- 10 11. Un método de seguimiento de la evolución del cáncer colorrectal que comprende realizar al menos dos veces la secuencia de pasos (a) y (c) según cualquiera de las reivindicaciones 3-10, en muestras biológicas procedentes de un mismo individuo, y aisladas en momentos diferentes.
12. Un kit o dispositivo que comprende los cebadores y sondas diseñados a partir de las secuencias nucleotídicas de la Tabla 1.
- 15 13. Un microarray que comprende oligonucleótidos o microarreglos de canal único diseñados a partir de una secuencia conocida o de un ARNm de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1*.
- 20 14. El microarray según la reivindicación anterior, donde la secuencia de los genes *AQP*, *CLEC3B*, *DCK*, *DEFA5*, *DNAJC3*, *FBLIM1*, *GAS7*, *IGFBP4*, *KSR1*, *LONP1*, *MTHFD1L*, *NAV1*, *NIPBL*, *PALM2*, *PCDHGC3*, *PROS1*, *RARA*, *RSF1*, *TENC1*, *TGFBR3*, *TRAK2*, *VSNL1*, *WHSC1L1*, *WWC2*, *FAF1*, *FBXO9*, *KIAA1033*, *N4BP2L1*, *SLC12A*, *STARD13* y *RB1CC1* es la secuencia nucleotídica SEQ ID recogida en la Tabla 1, respectivamente.
- 25 15. El uso del kit o dispositivo según la reivindicación 12, o del microarray según cualquiera de las reivindicaciones 13-14, para la obtención de datos útiles para predecir la respuesta al tratamiento en pacientes con cáncer de colorrectal.
- 30

FIG.1

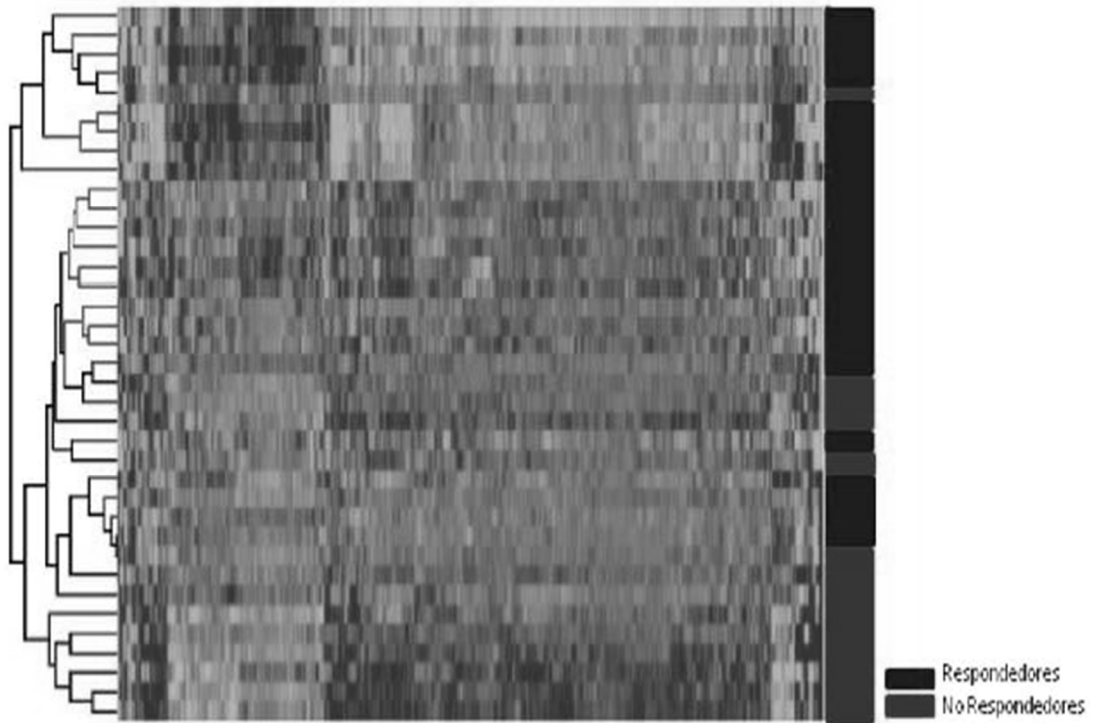


FIG.2

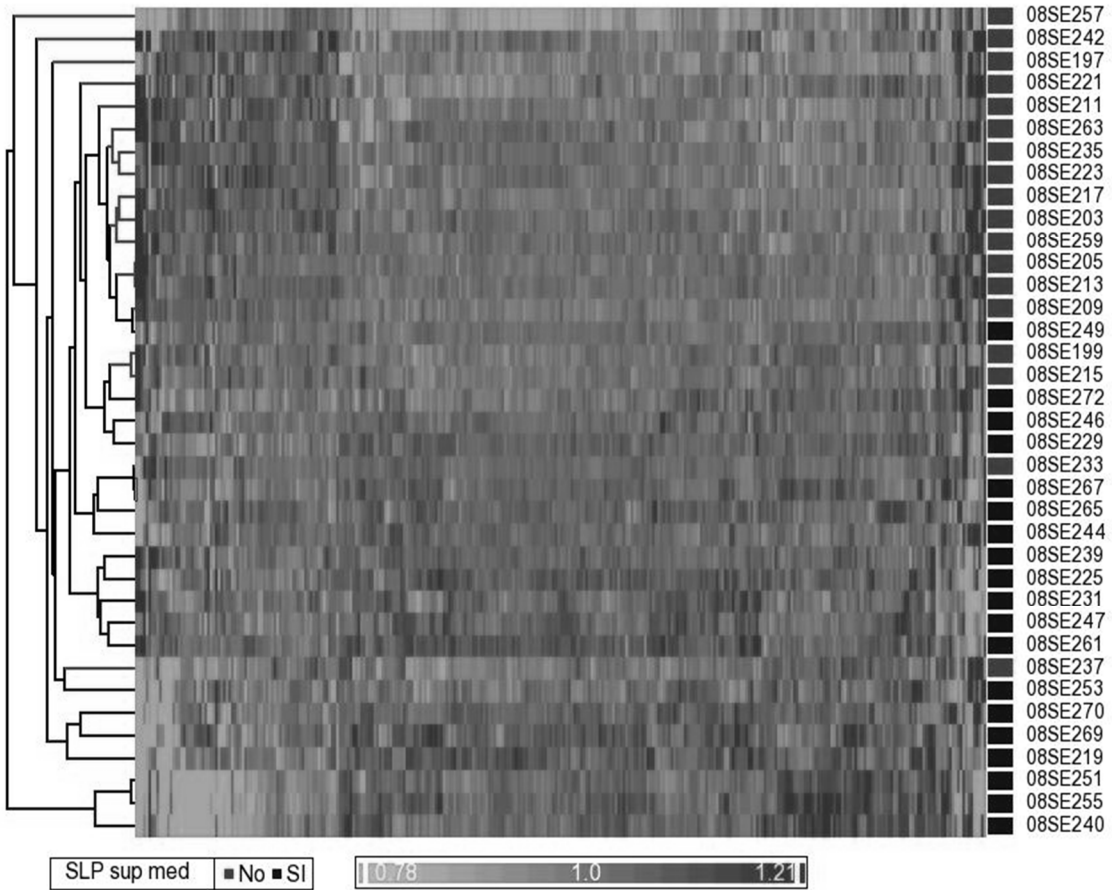




FIG.3

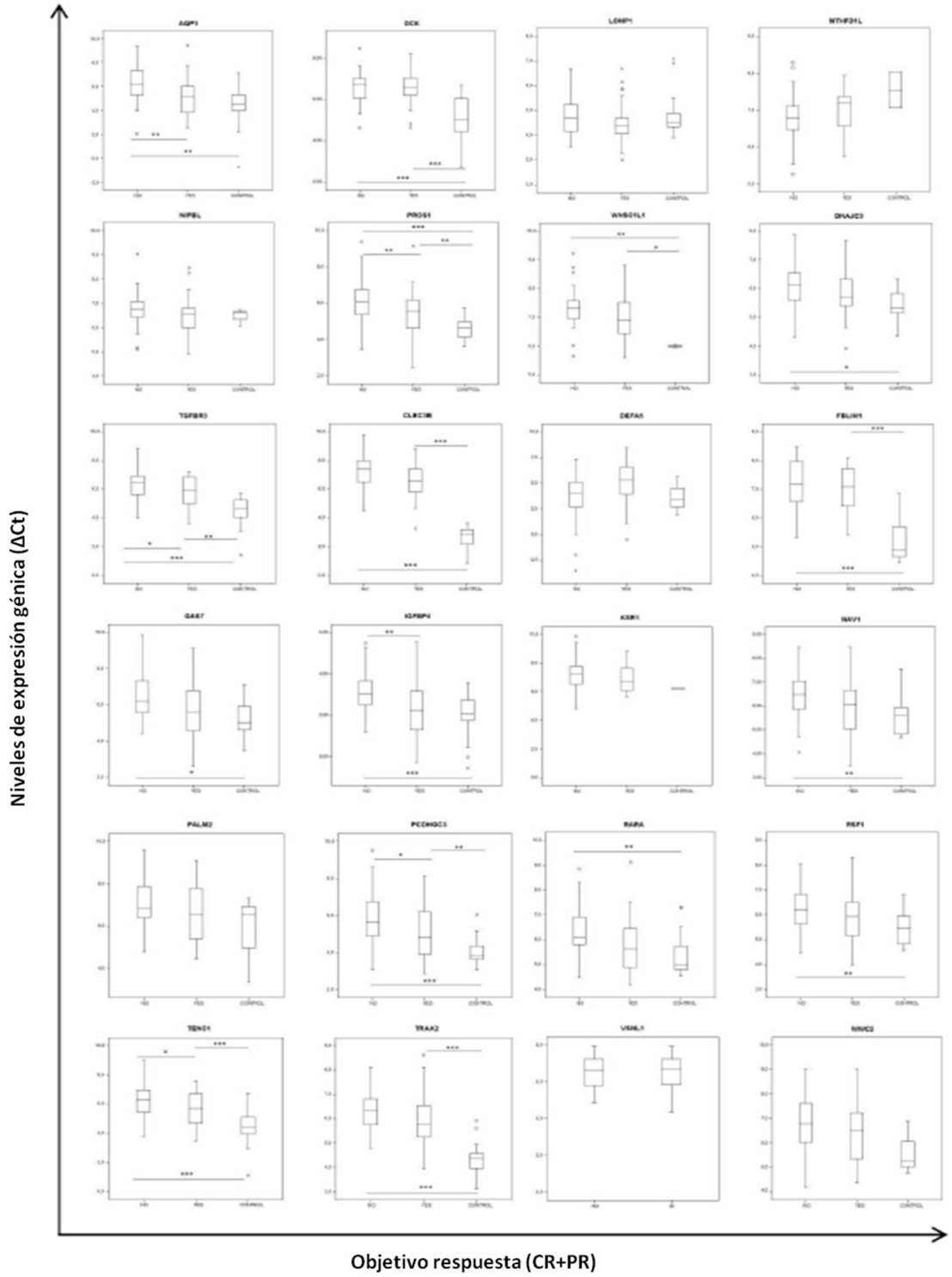


FIG.4

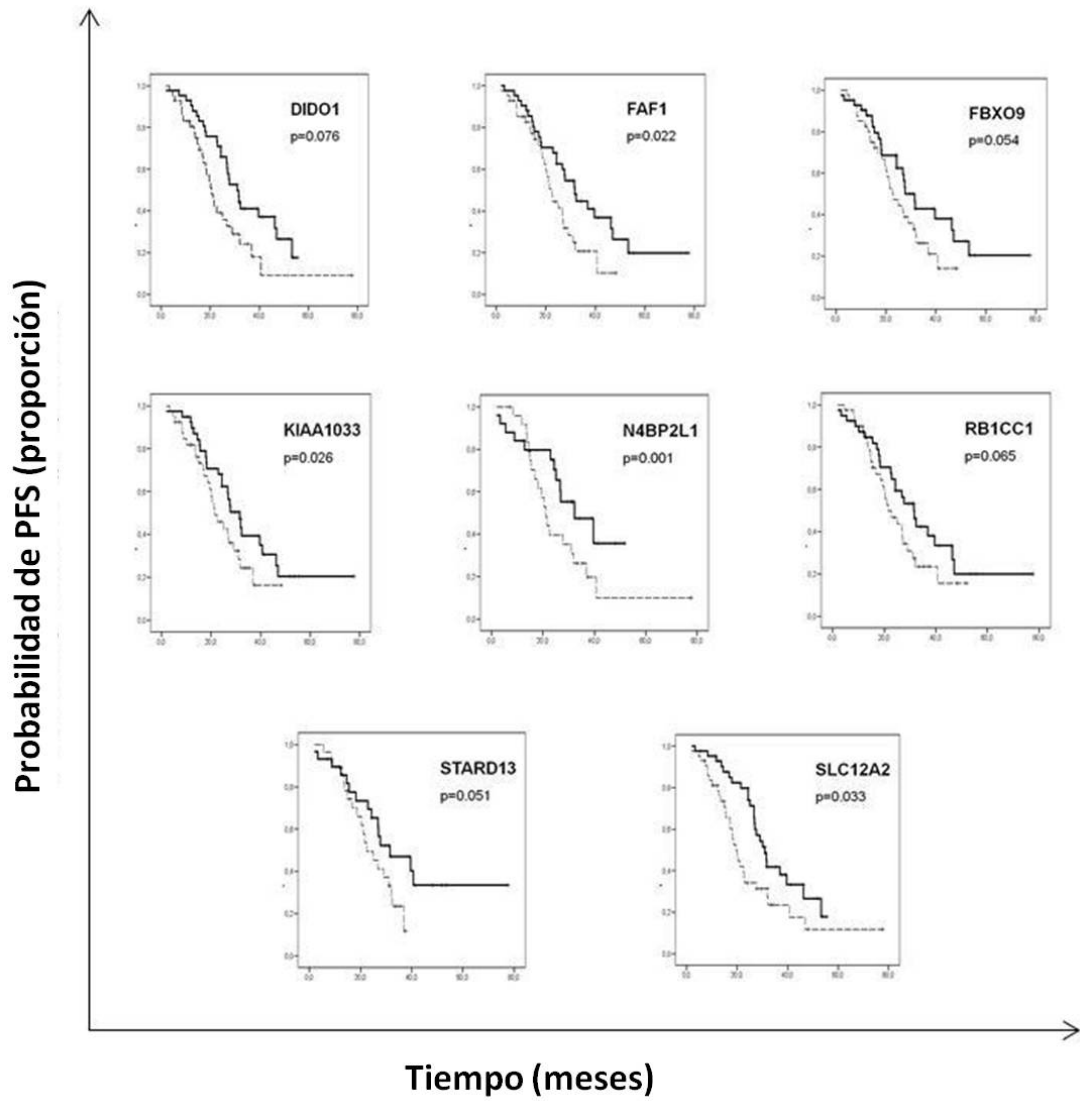
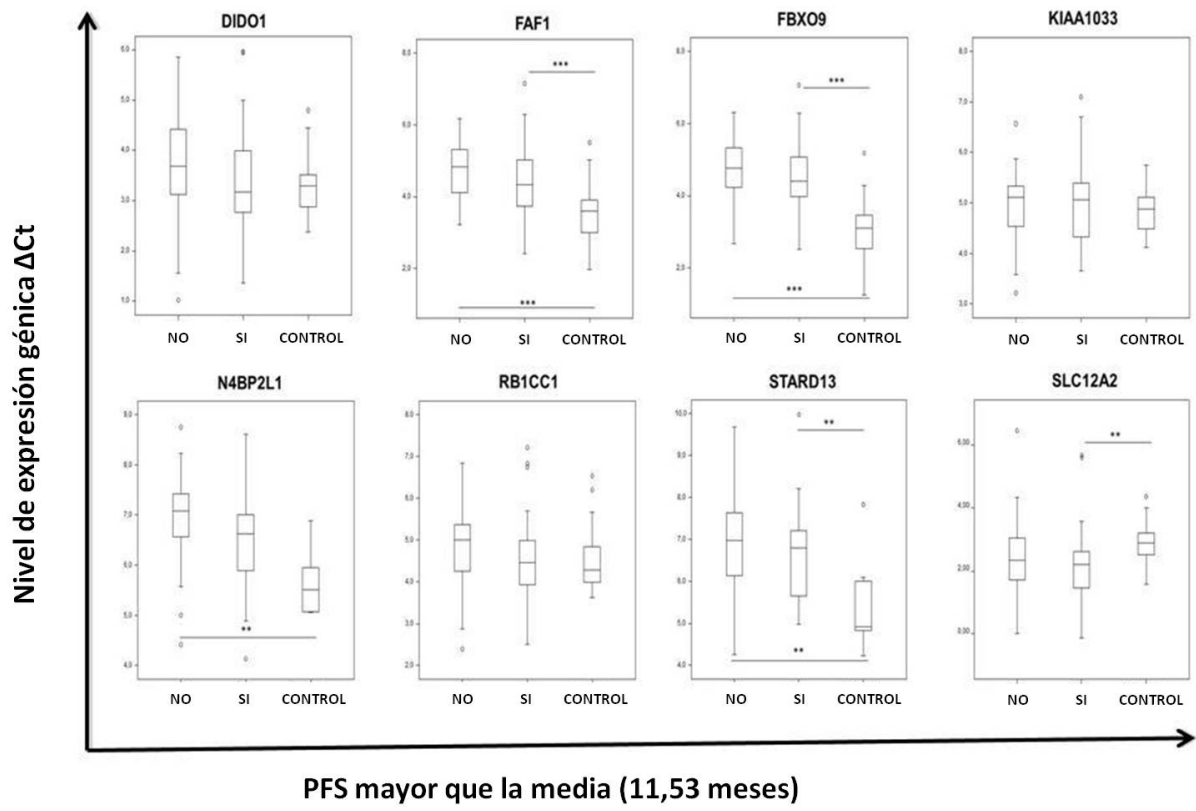


FIG.5



# ES 2 534 734 A1

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SALUD EN SEVILLA  
UNIVERSIDAD DE SEVILLA

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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# ES 2 534 734 A1

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<212> DNA
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cctgagaacc agccgtcccg cgccatgggc acgcgtctgc cgctcgtcct gcgccagctc      180
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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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## ES 2 534 734 A1

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# ES 2 534 734 A1

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<212> PRT
<213> Homo sapiens

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<400> 83
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```

```
Glu Phe Leu Ala Thr Thr Leu Phe Val Phe Ile Ser Ile Gly Ser Ala
          20           25           30
```

```
Leu Gly Phe Lys Tyr Pro Val Gly Asn Asn Gln Thr Ala Val Gln Asp
          35           40           45
```

```
Asn Val Lys Val Ser Leu Ala Phe Gly Leu Ser Ile Ala Thr Leu Ala
          50           55           60
```

```
Gln Ser Val Gly His Ile Ser Gly Ala His Leu Asn Pro Ala Val Thr
65           70           75           80
```

```
Leu Gly Leu Leu Leu Ser Cys Gln Ile Ser Ile Phe Arg Ala Leu Met
          85           90           95
```

```
Tyr Ile Ile Ala Gln Cys Val Gly Ala Ile Val Ala Thr Ala Ile Leu
          100          105          110
```

```
Ser Gly Ile Thr Ser Ser Leu Thr Gly Asn Ser Leu Gly Arg Asn Asp
          115          120          125
```

```
Leu Ala Asp Gly Val Asn Ser Gly Gln Gly Leu Gly Ile Glu Ile Ile
          130          135          140
```

# ES 2 534 734 A1

Gly Thr Leu Gln Leu Val Leu Cys Val Leu Ala Thr Thr Asp Arg Arg  
 145 150 155 160

Arg Arg Asp Leu Gly Gly Ser Ala Pro Leu Ala Ile Gly Leu Ser Val  
 165 170 175

Ala Leu Gly His Leu Leu Ala Ile Asp Tyr Thr Gly Cys Gly Ile Asn  
 180 185 190

Pro Ala Arg Ser Phe Gly Ser Ala Val Ile Thr His Asn Phe Ser Asn  
 195 200 205

His Trp Ile Phe Trp Val Gly Pro Phe Ile Gly Gly Ala Leu Ala Val  
 210 215 220

Leu Ile Tyr Asp Phe Ile Leu Ala Pro Arg Ser Ser Asp Leu Thr Asp  
 225 230 235 240

Arg Val Lys Val Trp Thr Ser Gly Gln Val Glu Glu Tyr Asp Leu Asp  
 245 250 255

Ala Asp Asp Ile Asn Ser Arg Val Glu Met Lys Pro Lys  
 260 265

<210> 84  
 <211> 186  
 <212> PRT  
 <213> Homo sapiens

<400> 84

Met Pro Gly Ala Arg Pro Leu Pro Leu Val Leu Val Pro Gln Asn Thr  
 1 5 10 15

Leu Ala Trp Met Gln Leu Asp Ala Lys Ala Pro Ala His Pro Arg Pro  
 20 25 30

Leu Gln Leu Leu Gly Arg Val Gly Pro Gly Ser Arg Gln Leu Ala Asp  
 35 40 45

Gly Val Asn Ser Gly Gln Gly Leu Gly Ile Glu Ile Ile Gly Thr Leu  
 50 55 60

Gln Leu Val Leu Cys Val Leu Ala Thr Thr Asp Arg Arg Arg Arg Asp  
 65 70 75 80

# ES 2 534 734 A1

Leu Gly Gly Ser Ala Pro Leu Ala Ile Gly Leu Ser Val Ala Leu Gly  
                                   85                                  90                                  95

His Leu Leu Ala Ile Asp Tyr Thr Gly Cys Gly Ile Asn Pro Ala Arg  
                                   100                                  105                                  110

Ser Phe Gly Ser Ala Val Ile Thr His Asn Phe Ser Asn His Trp Ile  
                                   115                                  120                                  125

Phe Trp Val Gly Pro Phe Ile Gly Gly Ala Leu Ala Val Leu Ile Tyr  
                                   130                                  135                                  140

Asp Phe Ile Leu Ala Pro Arg Ser Ser Asp Leu Thr Asp Arg Val Lys  
                                   145                                  150                                  155                                  160

Val Trp Thr Ser Gly Gln Val Glu Glu Tyr Asp Leu Asp Ala Asp Asp  
                                   165                                  170                                  175

Ile Asn Ser Arg Val Glu Met Lys Pro Lys  
                                   180                                  185

<210> 85  
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 <212> PRT  
 <213> Homo sapiens

<400> 85

Met Phe Trp Thr Phe Gly Tyr Glu Ala Val Ser Pro Ala Gly Pro Ser  
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His Leu Phe Ala Ser Leu Leu Leu Gly Val Leu Leu Thr Ile Thr Phe  
                                   20                                  25                                  30

Met Pro Gly Ala Arg Pro Leu Pro Leu Val Leu Val Pro Gln Asn Thr  
                                   35                                  40                                  45

Leu Ala Trp Met Gln Leu Asp Ala Lys Ala Pro Ala His Pro Arg Pro  
                                   50                                  55                                  60

Leu Gln Leu Leu Gly Arg Val Gly Pro Gly Ser Arg Gln Leu Ala Asp  
   65                                  70                                  75                                  80

Gly Val Asn Ser Gly Gln Gly Leu Gly Ile Glu Ile Ile Gly Thr Leu  
                                   85                                  90                                  95

# ES 2 534 734 A1

Gln Leu Val Leu Cys Val Leu Ala Thr Thr Asp Arg Arg Arg Arg Asp  
 100 105 110

Leu Gly Gly Ser Ala Pro Leu Ala Ile Gly Leu Ser Val Ala Leu Gly  
 115 120 125

His Leu Leu Ala Ile Asp Tyr Thr Gly Cys Gly Ile Asn Pro Ala Arg  
 130 135 140

Ser Phe Gly Ser Ala Val Ile Thr His Asn Phe Ser Asn His Trp Ile  
 145 150 155 160

Phe Trp Val Gly Pro Phe Ile Gly Gly Ala Leu Ala Val Leu Ile Tyr  
 165 170 175

Asp Phe Ile Leu Ala Pro Arg Ser Ser Asp Leu Thr Asp Arg Val Lys  
 180 185 190

Val Trp Thr Ser Gly Gln Val Glu Glu Tyr Asp Leu Asp Ala Asp Asp  
 195 200 205

Ile Asn Ser Arg Val Glu Met Lys Pro Lys  
 210 215

<210> 86  
 <211> 154  
 <212> PRT  
 <213> Homo sapiens

<400> 86

Met Gln Ser Gly Met Gly Trp Asn Val Leu Asp Phe Trp Leu Ala Asp  
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Gly Val Asn Ser Gly Gln Gly Leu Gly Ile Glu Ile Ile Gly Thr Leu  
 20 25 30

Gln Leu Val Leu Cys Val Leu Ala Thr Thr Asp Arg Arg Arg Arg Asp  
 35 40 45

Leu Gly Gly Ser Ala Pro Leu Ala Ile Gly Leu Ser Val Ala Leu Gly  
 50 55 60

His Leu Leu Ala Ile Asp Tyr Thr Gly Cys Gly Ile Asn Pro Ala Arg  
 65 70 75 80



# ES 2 534 734 A1

Ser Phe Gly Ser Ala Val Ile Thr His Asn Phe Ser Asn His Trp Ile  
85 90 95

Phe Trp Val Gly Pro Phe Ile Gly Gly Ala Leu Ala Val Leu Ile Tyr  
100 105 110

Asp Phe Ile Leu Ala Pro Arg Ser Ser Asp Leu Thr Asp Arg Val Lys  
115 120 125

Val Trp Thr Ser Gly Gln Val Glu Glu Tyr Asp Leu Asp Ala Asp Asp  
130 135 140

Ile Asn Ser Arg Val Glu Met Lys Pro Lys  
145 150

<210> 87  
<211> 202  
<212> PRT  
<213> Homo sapiens

<400> 87

Met Glu Leu Trp Gly Ala Tyr Leu Leu Leu Cys Leu Phe Ser Leu Leu  
1 5 10 15

Thr Gln Val Thr Thr Glu Pro Pro Thr Gln Lys Pro Lys Lys Ile Val  
20 25 30

Asn Ala Lys Lys Asp Val Val Asn Thr Lys Met Phe Glu Glu Leu Lys  
35 40 45

Ser Arg Leu Asp Thr Leu Ala Gln Glu Val Ala Leu Leu Lys Glu Gln  
50 55 60

Gln Ala Leu Gln Thr Val Cys Leu Lys Gly Thr Lys Val His Met Lys  
65 70 75 80

Cys Phe Leu Ala Phe Thr Gln Thr Lys Thr Phe His Glu Ala Ser Glu  
85 90 95

Asp Cys Ile Ser Arg Gly Gly Thr Leu Gly Thr Pro Gln Thr Gly Ser  
100 105 110

Glu Asn Asp Ala Leu Tyr Glu Tyr Leu Arg Gln Ser Val Gly Asn Glu  
115 120 125

# ES 2 534 734 A1

Ala Glu Ile Trp Leu Gly Leu Asn Asp Met Ala Ala Glu Gly Thr Trp  
 130 135 140

Val Asp Met Thr Gly Ala Arg Ile Ala Tyr Lys Asn Trp Glu Thr Glu  
 145 150 155 160

Ile Thr Ala Gln Pro Asp Gly Gly Lys Thr Glu Asn Cys Ala Val Leu  
 165 170 175

Ser Gly Ala Ala Asn Gly Lys Trp Phe Asp Lys Arg Cys Arg Asp Gln  
 180 185 190

Leu Pro Tyr Ile Cys Gln Phe Gly Ile Val  
 195 200

<210> 88  
 <211> 514  
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 <213> Homo sapiens

<400> 88

Met Ala Asp Ala Glu Val Ile Ile Leu Pro Lys Lys His Lys Lys Lys  
 1 5 10 15

Lys Glu Arg Lys Ser Leu Pro Glu Glu Asp Val Ala Glu Ile Gln His  
 20 25 30

Ala Glu Glu Phe Leu Ile Lys Pro Glu Ser Lys Val Ala Lys Leu Asp  
 35 40 45

Thr Ser Gln Trp Pro Leu Leu Leu Lys Asn Phe Asp Lys Leu Asn Val  
 50 55 60

Arg Thr Thr His Tyr Thr Pro Leu Ala Cys Gly Ser Asn Pro Leu Lys  
 65 70 75 80

Arg Glu Ile Gly Asp Tyr Ile Arg Thr Gly Phe Ile Asn Leu Asp Lys  
 85 90 95

Pro Ser Asn Pro Ser Ser His Glu Val Val Ala Trp Ile Arg Arg Ile  
 100 105 110

Leu Arg Val Glu Lys Thr Gly His Ser Gly Thr Leu Asp Pro Lys Val  
 115 120 125

# ES 2 534 734 A1

Thr Gly Cys Leu Ile Val Cys Ile Glu Arg Ala Thr Arg Leu Val Lys  
 130 135 140

Ser Gln Gln Ser Ala Gly Lys Glu Tyr Val Gly Ile Val Arg Leu His  
 145 150 155 160

Asn Ala Ile Glu Gly Gly Thr Gln Leu Ser Arg Ala Leu Glu Thr Leu  
 165 170 175

Thr Gly Ala Leu Phe Gln Arg Pro Pro Leu Ile Ala Ala Val Lys Arg  
 180 185 190

Gln Leu Arg Val Arg Thr Ile Tyr Glu Ser Lys Met Ile Glu Tyr Asp  
 195 200 205

Pro Glu Arg Arg Leu Gly Ile Phe Trp Val Ser Cys Glu Ala Gly Thr  
 210 215 220

Tyr Ile Arg Thr Leu Cys Val His Leu Gly Leu Leu Leu Gly Val Gly  
 225 230 235 240

Gly Gln Met Gln Glu Leu Arg Arg Val Arg Ser Gly Val Met Ser Glu  
 245 250 255

Lys Asp His Met Val Thr Met His Asp Val Leu Asp Ala Gln Trp Leu  
 260 265 270

Tyr Asp Asn His Lys Asp Glu Ser Tyr Leu Arg Arg Val Val Tyr Pro  
 275 280 285

Leu Glu Lys Leu Leu Thr Ser His Lys Arg Leu Val Met Lys Asp Ser  
 290 295 300

Ala Val Asn Ala Ile Cys Tyr Gly Ala Lys Ile Met Leu Pro Gly Val  
 305 310 315 320

Leu Arg Tyr Glu Asp Gly Ile Glu Val Asn Gln Glu Ile Val Val Ile  
 325 330 335

Thr Thr Lys Gly Glu Ala Ile Cys Met Ala Ile Ala Leu Met Thr Thr  
 340 345 350

Ala Val Ile Ser Thr Cys Asp His Gly Ile Val Ala Lys Ile Lys Arg  
 355 360 365

ES 2 534 734 A1

Val Ile Met Glu Arg Asp Thr Tyr Pro Arg Lys Trp Gly Leu Gly Pro  
 370 375 380

Lys Ala Ser Gln Lys Lys Leu Met Ile Lys Gln Gly Leu Leu Asp Lys  
 385 390 395 400

His Gly Lys Pro Thr Asp Ser Thr Pro Ala Thr Trp Lys Gln Glu Tyr  
 405 410 415

Val Asp Tyr Ser Glu Ser Ala Lys Lys Glu Val Val Ala Glu Val Val  
 420 425 430

Lys Ala Pro Gln Val Val Ala Glu Ala Ala Lys Thr Ala Lys Arg Lys  
 435 440 445

Arg Glu Ser Glu Ser Glu Ser Asp Glu Thr Pro Pro Ala Ala Pro Gln  
 450 455 460

Leu Ile Lys Lys Glu Lys Lys Lys Ser Lys Lys Asp Lys Lys Ala Lys  
 465 470 475 480

Ala Gly Leu Glu Ser Gly Ala Glu Pro Gly Asp Gly Asp Ser Asp Thr  
 485 490 495

Thr Lys Lys Lys Lys Lys Lys Lys Lys Ala Lys Glu Val Glu Leu Val  
 500 505 510

Ser Glu

<210> 89  
 <211> 509  
 <212> PRT  
 <213> Homo sapiens

<400> 89

Met Ala Asp Ala Glu Val Ile Ile Leu Pro Lys Lys His Lys Lys Lys  
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Lys Glu Arg Lys Ser Leu Pro Glu Glu Asp Val Ala Glu Ile Gln His  
 20 25 30

Ala Glu Glu Phe Leu Ile Lys Pro Glu Ser Lys Val Ala Lys Leu Asp  
 35 40 45

# ES 2 534 734 A1

Thr Ser Gln Trp Pro Leu Leu Leu Lys Asn Phe Asp Lys Leu Asn Val  
 50 55 60

Arg Thr Thr His Tyr Thr Pro Leu Ala Cys Gly Ser Asn Pro Leu Lys  
 65 70 75 80

Arg Glu Ile Gly Asp Tyr Ile Arg Thr Gly Phe Ile Asn Leu Asp Lys  
 85 90 95

Pro Ser Asn Pro Ser Ser His Glu Val Val Ala Trp Ile Arg Arg Ile  
 100 105 110

Leu Arg Val Glu Lys Thr Gly His Ser Gly Thr Leu Asp Pro Lys Val  
 115 120 125

Thr Gly Cys Leu Ile Val Cys Ile Glu Arg Ala Thr Arg Leu Val Lys  
 130 135 140

Ser Gln Gln Ser Ala Gly Lys Glu Tyr Val Gly Ile Val Arg Leu His  
 145 150 155 160

Asn Ala Ile Glu Gly Gly Thr Gln Leu Ser Arg Ala Leu Glu Thr Leu  
 165 170 175

Thr Gly Ala Leu Phe Gln Arg Pro Pro Leu Ile Ala Ala Val Lys Arg  
 180 185 190

Gln Leu Arg Val Arg Thr Ile Tyr Glu Ser Lys Met Ile Glu Tyr Asp  
 195 200 205

Pro Glu Arg Arg Leu Gly Ile Phe Trp Val Ser Cys Glu Ala Gly Thr  
 210 215 220

Tyr Ile Arg Thr Leu Cys Val His Leu Gly Leu Leu Gly Val Gly  
 225 230 235 240

Gly Gln Met Gln Glu Leu Arg Arg Val Arg Ser Gly Val Met Ser Glu  
 245 250 255

Lys Asp His Met Val Thr Met His Asp Val Leu Asp Ala Gln Trp Leu  
 260 265 270

# ES 2 534 734 A1

Tyr Asp Asn His Lys Asp Glu Ser Tyr Leu Arg Arg Val Val Tyr Pro  
 275 280 285

Leu Glu Lys Leu Leu Thr Ser His Lys Arg Leu Val Met Lys Asp Ser  
 290 295 300

Ala Val Asn Ala Ile Cys Tyr Gly Ala Lys Ile Met Leu Pro Gly Val  
 305 310 315 320

Leu Arg Tyr Glu Asp Gly Ile Glu Val Asn Gln Glu Ile Val Val Ile  
 325 330 335

Thr Thr Lys Gly Glu Ala Ile Cys Met Ala Ile Ala Leu Met Thr Thr  
 340 345 350

Ala Val Ile Ser Thr Cys Asp His Gly Ile Val Ala Lys Ile Lys Arg  
 355 360 365

Val Ile Met Glu Arg Asp Thr Tyr Pro Arg Lys Trp Gly Leu Gly Pro  
 370 375 380

Lys Ala Ser Gln Lys Lys Leu Met Ile Lys Gln Gly Leu Leu Asp Lys  
 385 390 395 400

His Gly Lys Pro Thr Asp Ser Thr Pro Ala Thr Trp Lys Gln Asp Glu  
 405 410 415

Ser Ala Lys Lys Glu Val Val Ala Glu Val Val Lys Ala Pro Gln Val  
 420 425 430

Val Ala Glu Ala Ala Lys Thr Ala Lys Arg Lys Arg Glu Ser Glu Ser  
 435 440 445

Glu Ser Asp Glu Thr Pro Pro Ala Ala Pro Gln Leu Ile Lys Lys Glu  
 450 455 460

Lys Lys Lys Ser Lys Lys Asp Lys Lys Ala Lys Ala Gly Leu Glu Ser  
 465 470 475 480

Gly Ala Glu Pro Gly Asp Gly Asp Ser Asp Thr Thr Lys Lys Lys Lys  
 485 490 495

Lys Lys Lys Lys Ala Lys Glu Val Glu Leu Val Ser Glu  
 500 505

# ES 2 534 734 A1

<210> 90  
 <211> 676  
 <212> PRT  
 <213> Homo sapiens

<400> 90

Met Arg Val Leu Gly Gly Arg Cys Gly Ala Leu Leu Ala Cys Leu Leu  
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Leu Val Leu Pro Val Ser Glu Ala Asn Phe Leu Ser Lys Gln Gln Ala  
 20 25 30

Ser Gln Val Leu Val Arg Lys Arg Arg Ala Asn Ser Leu Leu Glu Glu  
 35 40 45

Thr Lys Gln Gly Asn Leu Glu Arg Glu Cys Ile Glu Glu Leu Cys Asn  
 50 55 60

Lys Glu Glu Ala Arg Glu Val Phe Glu Asn Asp Pro Glu Thr Asp Tyr  
 65 70 75 80

Phe Tyr Pro Lys Tyr Leu Val Cys Leu Arg Ser Phe Gln Thr Gly Leu  
 85 90 95

Phe Thr Ala Ala Arg Gln Ser Thr Asn Ala Tyr Pro Asp Leu Arg Ser  
 100 105 110

Cys Val Asn Ala Ile Pro Asp Gln Cys Ser Pro Leu Pro Cys Asn Glu  
 115 120 125

Asp Gly Tyr Met Ser Cys Lys Asp Gly Lys Ala Ser Phe Thr Cys Thr  
 130 135 140

Cys Lys Pro Gly Trp Gln Gly Glu Lys Cys Glu Phe Asp Ile Asn Glu  
 145 150 155 160

Cys Lys Asp Pro Ser Asn Ile Asn Gly Gly Cys Ser Gln Ile Cys Asp  
 165 170 175

Asn Thr Pro Gly Ser Tyr His Cys Ser Cys Lys Asn Gly Phe Val Met  
 180 185 190

Leu Ser Asn Lys Lys Asp Cys Lys Asp Val Asp Glu Cys Ser Leu Lys  
 195 200 205

# ES 2 534 734 A1

Pro Ser Ile Cys Gly Thr Ala Val Cys Lys Asn Ile Pro Gly Asp Phe  
 210 215 220

Glu Cys Glu Cys Pro Glu Gly Tyr Arg Tyr Asn Leu Lys Ser Lys Ser  
 225 230 235 240

Cys Glu Asp Ile Asp Glu Cys Ser Glu Asn Met Cys Ala Gln Leu Cys  
 245 250 255

Val Asn Tyr Pro Gly Gly Tyr Thr Cys Tyr Cys Asp Gly Lys Lys Gly  
 260 265 270

Phe Lys Leu Ala Gln Asp Gln Lys Ser Cys Glu Val Val Ser Val Cys  
 275 280 285

Leu Pro Leu Asn Leu Asp Thr Lys Tyr Glu Leu Leu Tyr Leu Ala Glu  
 290 295 300

Gln Phe Ala Gly Val Val Leu Tyr Leu Lys Phe Arg Leu Pro Glu Ile  
 305 310 315 320

Ser Arg Phe Ser Ala Glu Phe Asp Phe Arg Thr Tyr Asp Ser Glu Gly  
 325 330 335

Val Ile Leu Tyr Ala Glu Ser Ile Asp His Ser Ala Trp Leu Leu Ile  
 340 345 350

Ala Leu Arg Gly Gly Lys Ile Glu Val Gln Leu Lys Asn Glu His Thr  
 355 360 365

Ser Lys Ile Thr Thr Gly Gly Asp Val Ile Asn Asn Gly Leu Trp Asn  
 370 375 380

Met Val Ser Val Glu Glu Leu Glu His Ser Ile Ser Ile Lys Ile Ala  
 385 390 395 400

Lys Glu Ala Val Met Asp Ile Asn Lys Pro Gly Pro Leu Phe Lys Pro  
 405 410 415

Glu Asn Gly Leu Leu Glu Thr Lys Val Tyr Phe Ala Gly Phe Pro Arg  
 420 425 430

Lys Val Glu Ser Glu Leu Ile Lys Pro Ile Asn Pro Arg Leu Asp Gly  
 435 440 445



# ES 2 534 734 A1

Cys Ile Arg Ser Trp Asn Leu Met Lys Gln Gly Ala Ser Gly Ile Lys  
 450 455 460

Glu Ile Ile Gln Glu Lys Gln Asn Lys His Cys Leu Val Thr Val Glu  
 465 470 475 480

Lys Gly Ser Tyr Tyr Pro Gly Ser Gly Ile Ala Gln Phe His Ile Asp  
 485 490 495

Tyr Asn Asn Val Ser Ser Ala Glu Gly Trp His Val Asn Val Thr Leu  
 500 505 510

Asn Ile Arg Pro Ser Thr Gly Thr Gly Val Met Leu Ala Leu Val Ser  
 515 520 525

Gly Asn Asn Thr Val Pro Phe Ala Val Ser Leu Val Asp Ser Thr Ser  
 530 535 540

Glu Lys Ser Gln Asp Ile Leu Leu Ser Val Glu Asn Thr Val Ile Tyr  
 545 550 555 560

Arg Ile Gln Ala Leu Ser Leu Cys Ser Asp Gln Gln Ser His Leu Glu  
 565 570 575

Phe Arg Val Asn Arg Asn Asn Leu Glu Leu Ser Thr Pro Leu Lys Ile  
 580 585 590

Glu Thr Ile Ser His Glu Asp Leu Gln Arg Gln Leu Ala Val Leu Asp  
 595 600 605

Lys Ala Met Lys Ala Lys Val Ala Thr Tyr Leu Gly Gly Leu Pro Asp  
 610 615 620

Val Pro Phe Ser Ala Thr Pro Val Asn Ala Phe Tyr Asn Gly Cys Met  
 625 630 635 640

Glu Val Asn Ile Asn Gly Val Gln Leu Asp Leu Asp Glu Ala Ile Ser  
 645 650 655

Lys His Asn Asp Ile Arg Ala His Ser Cys Pro Ser Val Trp Lys Lys  
 660 665 670

Thr Lys Asn Ser  
 675

# ES 2 534 734 A1

<210> 91  
 <211> 1437  
 <212> PRT  
 <213> Homo sapiens

<400> 91

Met Asp Phe Ser Phe Ser Phe Met Gln Gly Ile Met Gly Asn Thr Ile  
 1 5 10 15

Gln Gln Pro Pro Gln Leu Ile Asp Ser Ala Asn Ile Arg Gln Glu Asp  
 20 25 30

Ala Phe Asp Asn Asn Ser Asp Ile Ala Glu Asp Gly Gly Gln Thr Pro  
 35 40 45

Tyr Glu Ala Thr Leu Gln Gln Gly Phe Gln Tyr Pro Ala Thr Thr Glu  
 50 55 60

Asp Leu Pro Pro Leu Thr Asn Gly Tyr Pro Ser Ser Ile Ser Val Tyr  
 65 70 75 80

Glu Thr Gln Thr Lys Tyr Gln Ser Tyr Asn Gln Tyr Pro Asn Gly Ser  
 85 90 95

Ala Asn Gly Phe Gly Ala Val Arg Asn Phe Ser Pro Thr Asp Tyr Tyr  
 100 105 110

His Ser Glu Ile Pro Asn Thr Arg Pro His Glu Ile Leu Glu Lys Pro  
 115 120 125

Ser Pro Pro Gln Pro Pro Pro Pro Pro Ser Val Pro Gln Thr Val Ile  
 130 135 140

Pro Lys Lys Thr Gly Ser Pro Glu Ile Lys Leu Lys Ile Thr Lys Thr  
 145 150 155 160

Ile Gln Asn Gly Arg Glu Leu Phe Glu Ser Ser Leu Cys Gly Asp Leu  
 165 170 175

Leu Asn Glu Val Gln Ala Ser Glu His Thr Lys Ser Lys His Glu Ser  
 180 185 190

Arg Lys Glu Lys Arg Lys Lys Ser Asn Lys His Asp Ser Ser Arg Ser  
 195 200 205

# ES 2 534 734 A1

Glu Glu Arg Lys Ser His Lys Ile Pro Lys Leu Glu Pro Glu Glu Gln  
 210 215 220

Asn Arg Pro Asn Glu Arg Val Asp Thr Val Ser Glu Lys Pro Arg Glu  
 225 230 235 240

Glu Pro Val Leu Lys Glu Glu Ala Pro Val Gln Pro Ile Leu Ser Ser  
 245 250 255

Val Pro Thr Thr Glu Val Ser Thr Gly Val Lys Phe Gln Val Gly Asp  
 260 265 270

Leu Val Trp Ser Lys Val Gly Thr Tyr Pro Trp Trp Pro Cys Met Val  
 275 280 285

Ser Ser Asp Pro Gln Leu Glu Val His Thr Lys Ile Asn Thr Arg Gly  
 290 295 300

Ala Arg Glu Tyr His Val Gln Phe Phe Ser Asn Gln Pro Glu Arg Ala  
 305 310 315 320

Trp Val His Glu Lys Arg Val Arg Glu Tyr Lys Gly His Lys Gln Tyr  
 325 330 335

Glu Glu Leu Leu Ala Glu Ala Thr Lys Gln Ala Ser Asn His Ser Glu  
 340 345 350

Lys Gln Lys Ile Arg Lys Pro Arg Pro Gln Arg Glu Arg Ala Gln Trp  
 355 360 365

Asp Ile Gly Ile Ala His Ala Glu Lys Ala Leu Lys Met Thr Arg Glu  
 370 375 380

Glu Arg Ile Glu Gln Tyr Thr Phe Ile Tyr Ile Asp Lys Gln Pro Glu  
 385 390 395 400

Glu Ala Leu Ser Gln Ala Lys Lys Ser Val Ala Ser Lys Thr Glu Val  
 405 410 415

Lys Lys Thr Arg Arg Pro Arg Ser Val Leu Asn Thr Gln Pro Glu Gln  
 420 425 430

Thr Asn Ala Gly Glu Val Ala Ser Ser Leu Ser Ser Thr Glu Ile Arg  
 435 440 445

# ES 2 534 734 A1

Arg His Ser Gln Arg Arg His Thr Ser Ala Glu Glu Glu Glu Pro Pro  
 450 455 460

Pro Val Lys Ile Ala Trp Lys Thr Ala Ala Ala Arg Lys Ser Leu Pro  
 465 470 475 480

Ala Ser Ile Thr Met His Lys Gly Ser Leu Asp Leu Gln Lys Cys Asn  
 485 490 495

Met Ser Pro Val Val Lys Ile Glu Gln Val Phe Ala Leu Gln Asn Ala  
 500 505 510

Thr Gly Asp Gly Lys Phe Ile Asp Gln Phe Val Tyr Ser Thr Lys Gly  
 515 520 525

Ile Gly Asn Lys Thr Glu Ile Ser Val Arg Gly Gln Asp Arg Leu Ile  
 530 535 540

Ile Ser Thr Pro Asn Gln Arg Asn Glu Lys Pro Thr Gln Ser Val Ser  
 545 550 555 560

Ser Pro Glu Ala Thr Ser Gly Ser Thr Gly Ser Val Glu Lys Lys Gln  
 565 570 575

Gln Arg Arg Ser Ile Arg Thr Arg Ser Glu Ser Glu Lys Ser Thr Glu  
 580 585 590

Val Val Pro Lys Lys Lys Ile Lys Lys Glu Gln Val Glu Thr Val Pro  
 595 600 605

Gln Ala Thr Val Lys Thr Gly Leu Gln Lys Gly Ala Ser Glu Ile Ser  
 610 615 620

Asp Ser Cys Lys Pro Leu Lys Lys Arg Ser Arg Ala Ser Thr Asp Val  
 625 630 635 640

Glu Met Thr Ser Ser Ala Tyr Arg Asp Thr Ser Asp Ser Asp Ser Arg  
 645 650 655

Gly Leu Ser Asp Leu Gln Val Gly Phe Gly Lys Gln Val Asp Ser Pro  
 660 665 670

Ser Ala Thr Ala Asp Ala Asp Val Ser Asp Val Gln Ser Met Asp Ser  
 675 680 685

# ES 2 534 734 A1

Ser Leu Ser Arg Arg Gly Thr Gly Met Ser Lys Lys Asp Thr Val Cys  
 690 695 700

Gln Ile Cys Glu Ser Ser Gly Asp Ser Leu Ile Pro Cys Glu Gly Glu  
 705 710 715 720

Cys Cys Lys His Phe His Leu Glu Cys Leu Gly Leu Ala Ser Leu Pro  
 725 730 735

Asp Ser Lys Phe Ile Cys Met Glu Cys Lys Thr Gly Gln His Pro Cys  
 740 745 750

Phe Ser Cys Lys Val Ser Gly Lys Asp Val Lys Arg Cys Ser Val Gly  
 755 760 765

Ala Cys Gly Lys Phe Tyr His Glu Ala Cys Val Arg Lys Phe Pro Thr  
 770 775 780

Ala Ile Phe Glu Ser Lys Gly Phe Arg Cys Pro Gln His Cys Cys Ser  
 785 790 795 800

Ala Cys Ser Met Glu Lys Asp Ile His Lys Ala Ser Lys Gly Arg Met  
 805 810 815

Met Arg Cys Leu Arg Cys Pro Val Ala Tyr His Ser Gly Asp Ala Cys  
 820 825 830

Ile Ala Ala Gly Ser Met Leu Val Ser Ser Tyr Ile Leu Ile Cys Ser  
 835 840 845

Asn His Ser Lys Arg Ser Ser Asn Ser Ser Ala Val Asn Val Gly Phe  
 850 855 860

Cys Phe Val Cys Ala Arg Gly Leu Ile Val Gln Asp His Ser Asp Pro  
 865 870 875 880

Met Phe Ser Ser Tyr Ala Tyr Lys Ser His Tyr Leu Leu Asn Glu Ser  
 885 890 895

Asn Arg Ala Glu Leu Met Lys Leu Pro Met Ile Pro Ser Ser Ser Ala  
 900 905 910

Ser Lys Lys Lys Cys Glu Lys Gly Gly Arg Leu Leu Cys Cys Glu Ser  
 915 920 925

# ES 2 534 734 A1

Cys Pro Ala Ser Phe His Pro Glu Cys Leu Ser Ile Glu Met Pro Glu  
 930 935 940

Gly Cys Trp Asn Cys Asn Asp Cys Lys Ala Gly Lys Lys Leu His Tyr  
 945 950 955 960

Lys Gln Ile Val Trp Val Lys Leu Gly Asn Tyr Arg Trp Trp Pro Ala  
 965 970 975

Glu Ile Cys Asn Pro Arg Ser Val Pro Leu Asn Ile Gln Gly Leu Lys  
 980 985 990

His Asp Leu Gly Asp Phe Pro Val Phe Phe Phe Gly Ser His Asp Tyr  
 995 1000 1005

Tyr Trp Val His Gln Gly Arg Val Phe Pro Tyr Val Glu Gly Asp  
 1010 1015 1020

Lys Ser Phe Ala Glu Gly Gln Thr Ser Ile Asn Lys Thr Phe Lys  
 1025 1030 1035

Lys Ala Leu Glu Glu Ala Ala Lys Arg Phe Gln Glu Leu Lys Ala  
 1040 1045 1050

Gln Arg Glu Ser Lys Glu Ala Leu Glu Ile Glu Lys Asn Ser Arg  
 1055 1060 1065

Lys Pro Pro Pro Tyr Lys His Ile Lys Ala Asn Lys Val Ile Gly  
 1070 1075 1080

Lys Val Gln Ile Gln Val Ala Asp Leu Ser Glu Ile Pro Arg Cys  
 1085 1090 1095

Asn Cys Lys Pro Ala Asp Glu Asn Pro Cys Gly Leu Glu Ser Glu  
 1100 1105 1110

Cys Leu Asn Arg Met Leu Gln Tyr Glu Cys His Pro Gln Val Cys  
 1115 1120 1125

Pro Ala Gly Asp Arg Cys Gln Asn Gln Cys Phe Thr Lys Arg Leu  
 1130 1135 1140

Tyr Pro Asp Ala Glu Ile Ile Lys Thr Glu Arg Arg Gly Trp Gly  
 1145 1150 1155

## ES 2 534 734 A1

Leu	Arg	Thr	Lys	Arg	Ser	Ile	Lys	Lys	Gly	Glu	Phe	Val	Asn	Glu
1160						1165					1170			
Tyr	Val	Gly	Glu	Leu	Ile	Asp	Glu	Glu	Glu	Cys	Arg	Leu	Arg	Ile
1175						1180					1185			
Lys	Arg	Ala	His	Glu	Asn	Ser	Val	Thr	Asn	Phe	Tyr	Met	Leu	Thr
1190						1195					1200			
Val	Thr	Lys	Asp	Arg	Ile	Ile	Asp	Ala	Gly	Pro	Lys	Gly	Asn	Tyr
1205						1210					1215			
Ser	Arg	Phe	Met	Asn	His	Ser	Cys	Asn	Pro	Asn	Cys	Glu	Thr	Gln
1220						1225					1230			
Lys	Trp	Thr	Val	Asn	Gly	Asp	Val	Arg	Val	Gly	Leu	Phe	Ala	Leu
1235						1240					1245			
Cys	Asp	Ile	Pro	Ala	Gly	Met	Glu	Leu	Thr	Phe	Asn	Tyr	Asn	Leu
1250						1255					1260			
Asp	Cys	Leu	Gly	Asn	Gly	Arg	Thr	Glu	Cys	His	Cys	Gly	Ala	Asp
1265						1270					1275			
Asn	Cys	Ser	Gly	Phe	Leu	Gly	Val	Arg	Pro	Lys	Ser	Ala	Cys	Ala
1280						1285					1290			
Ser	Thr	Asn	Glu	Glu	Lys	Ala	Lys	Asn	Ala	Lys	Leu	Lys	Gln	Lys
1295						1300					1305			
Arg	Arg	Lys	Ile	Lys	Thr	Glu	Pro	Lys	Gln	Met	His	Glu	Asp	Tyr
1310						1315					1320			
Cys	Phe	Gln	Cys	Gly	Asp	Gly	Gly	Glu	Leu	Val	Met	Cys	Asp	Lys
1325						1330					1335			
Lys	Asp	Cys	Pro	Lys	Ala	Tyr	His	Leu	Leu	Cys	Leu	Asn	Leu	Thr
1340						1345					1350			
Gln	Pro	Pro	Tyr	Gly	Lys	Trp	Glu	Cys	Pro	Trp	His	Gln	Cys	Asp
1355						1360					1365			
Glu	Cys	Ser	Ser	Ala	Ala	Val	Ser	Phe	Cys	Glu	Phe	Cys	Pro	His
1370						1375					1380			

# ES 2 534 734 A1

Ser Phe Cys Lys Asp His Glu Lys Gly Ala Leu Val Pro Ser Ala  
 1385 1390 1395

Leu Glu Gly Arg Leu Cys Cys Ser Glu His Asp Pro Met Ala Pro  
 1400 1405 1410

Val Ser Pro Glu Tyr Trp Ser Lys Ile Lys Cys Lys Trp Glu Ser  
 1415 1420 1425

Gln Asp His Gly Glu Glu Val Lys Glu  
 1430 1435

<210> 92  
 <211> 850  
 <212> PRT  
 <213> Homo sapiens

<400> 92

Met Thr Ser His Tyr Val Ile Ala Ile Phe Ala Leu Met Ser Ser Cys  
 1 5 10 15

Leu Ala Thr Ala Gly Pro Glu Pro Gly Ala Leu Cys Glu Leu Ser Pro  
 20 25 30

Val Ser Ala Ser His Pro Val Gln Ala Leu Met Glu Ser Phe Thr Val  
 35 40 45

Leu Ser Gly Cys Ala Ser Arg Gly Thr Thr Gly Leu Pro Gln Glu Val  
 50 55 60

His Val Leu Asn Leu Arg Thr Ala Gly Gln Gly Pro Gly Gln Leu Gln  
 65 70 75 80

Arg Glu Val Thr Leu His Leu Asn Pro Ile Ser Ser Val His Ile His  
 85 90 95

His Lys Ser Val Val Phe Leu Leu Asn Ser Pro His Pro Leu Val Trp  
 100 105 110

His Leu Lys Thr Glu Arg Leu Ala Thr Gly Val Ser Arg Leu Phe Leu  
 115 120 125

Val Ser Glu Gly Ser Val Val Gln Phe Ser Ser Ala Asn Phe Ser Leu  
 130 135 140



# ES 2 534 734 A1

Thr Ala Glu Thr Glu Glu Arg Asn Phe Pro His Gly Asn Glu His Leu  
 145 150 155 160

Leu Asn Trp Ala Arg Lys Glu Tyr Gly Ala Val Thr Ser Phe Thr Glu  
 165 170 175

Leu Lys Ile Ala Arg Asn Ile Tyr Ile Lys Val Gly Glu Asp Gln Val  
 180 185 190

Phe Pro Pro Lys Cys Asn Ile Gly Lys Asn Phe Leu Ser Leu Asn Tyr  
 195 200 205

Leu Ala Glu Tyr Leu Gln Pro Lys Ala Ala Glu Gly Cys Val Met Ser  
 210 215 220

Ser Gln Pro Gln Asn Glu Glu Val His Ile Ile Glu Leu Ile Thr Pro  
 225 230 235 240

Asn Ser Asn Pro Tyr Ser Ala Phe Gln Val Asp Ile Thr Ile Asp Ile  
 245 250 255

Arg Pro Ser Gln Glu Asp Leu Glu Val Val Lys Asn Leu Ile Leu Ile  
 260 265 270

Leu Lys Cys Lys Lys Ser Val Asn Trp Val Ile Lys Ser Phe Asp Val  
 275 280 285

Lys Gly Ser Leu Lys Ile Ile Ala Pro Asn Ser Ile Gly Phe Gly Lys  
 290 295 300

Glu Ser Glu Arg Ser Met Thr Met Thr Lys Ser Ile Arg Asp Asp Ile  
 305 310 315 320

Pro Ser Thr Gln Gly Asn Leu Val Lys Trp Ala Leu Asp Asn Gly Tyr  
 325 330 335

Ser Pro Ile Thr Ser Tyr Thr Met Ala Pro Val Ala Asn Arg Phe His  
 340 345 350

Leu Arg Leu Glu Asn Asn Glu Glu Met Gly Asp Glu Glu Val His Thr  
 355 360 365

Ile Pro Pro Glu Leu Arg Ile Leu Leu Asp Pro Gly Ala Leu Pro Ala  
 370 375 380

# ES 2 534 734 A1

Leu Gln Asn Pro Pro Ile Arg Gly Gly Glu Gly Gln Asn Gly Gly Leu  
 385 390 395 400

Pro Phe Pro Phe Pro Asp Ile Ser Arg Arg Val Trp Asn Glu Glu Gly  
 405 410 415

Glu Asp Gly Leu Pro Arg Pro Lys Asp Pro Val Ile Pro Ser Ile Gln  
 420 425 430

Leu Phe Pro Gly Leu Arg Glu Pro Glu Glu Val Gln Gly Ser Val Asp  
 435 440 445

Ile Ala Leu Ser Val Lys Cys Asp Asn Glu Lys Met Ile Val Ala Val  
 450 455 460

Glu Lys Asp Ser Phe Gln Ala Ser Gly Tyr Ser Gly Met Asp Val Thr  
 465 470 475 480

Leu Leu Asp Pro Thr Cys Lys Ala Lys Met Asn Gly Thr His Phe Val  
 485 490 495

Leu Glu Ser Pro Leu Asn Gly Cys Gly Thr Arg Pro Arg Trp Ser Ala  
 500 505 510

Leu Asp Gly Val Val Tyr Tyr Asn Ser Ile Val Ile Gln Val Pro Ala  
 515 520 525

Leu Gly Asp Ser Ser Gly Trp Pro Asp Gly Tyr Glu Asp Leu Glu Ser  
 530 535 540

Gly Asp Asn Gly Phe Pro Gly Asp Met Asp Glu Gly Asp Ala Ser Leu  
 545 550 555 560

Phe Thr Arg Pro Glu Ile Val Val Phe Asn Cys Ser Leu Gln Gln Val  
 565 570 575

Arg Asn Pro Ser Ser Phe Gln Glu Gln Pro His Gly Asn Ile Thr Phe  
 580 585 590

Asn Met Glu Leu Tyr Asn Thr Asp Leu Phe Leu Val Pro Ser Gln Gly  
 595 600 605

Val Phe Ser Val Pro Glu Asn Gly His Val Tyr Val Glu Val Ser Val  
 610 615 620

# ES 2 534 734 A1

Thr Lys Ala Glu Gln Glu Leu Gly Phe Ala Ile Gln Thr Cys Phe Ile  
 625 630 635 640

Ser Pro Tyr Ser Asn Pro Asp Arg Met Ser His Tyr Thr Ile Ile Glu  
 645 650 655

Asn Ile Cys Pro Lys Asp Glu Ser Val Lys Phe Tyr Ser Pro Lys Arg  
 660 665 670

Val His Phe Pro Ile Pro Gln Ala Asp Met Asp Lys Lys Arg Phe Ser  
 675 680 685

Phe Val Phe Lys Pro Val Phe Asn Thr Ser Leu Leu Phe Leu Gln Cys  
 690 695 700

Glu Leu Thr Leu Cys Thr Lys Met Glu Lys His Pro Gln Lys Leu Pro  
 705 710 715 720

Lys Cys Val Pro Pro Asp Glu Ala Cys Thr Ser Leu Asp Ala Ser Ile  
 725 730 735

Ile Trp Ala Met Met Gln Asn Lys Lys Thr Phe Thr Lys Pro Leu Ala  
 740 745 750

Val Ile His His Glu Ala Glu Ser Lys Glu Lys Gly Pro Ser Met Lys  
 755 760 765

Glu Pro Asn Pro Ile Ser Pro Pro Ile Phe His Gly Leu Asp Thr Leu  
 770 775 780

Thr Val Met Gly Ile Ala Phe Ala Ala Phe Val Ile Gly Ala Leu Leu  
 785 790 795 800

Thr Gly Ala Leu Trp Tyr Ile Tyr Ser His Thr Gly Glu Thr Ala Gly  
 805 810 815

Arg Gln Gln Val Pro Thr Ser Pro Pro Ala Ser Glu Asn Ser Ser Ala  
 820 825 830

Ala His Ser Ile Gly Ser Thr Gln Ser Thr Pro Cys Ser Ser Ser Ser  
 835 840 845

Thr Ala  
 850

# ES 2 534 734 A1

<210> 93  
 <211> 850  
 <212> PRT  
 <213> Homo sapiens

<400> 93

Met Thr Ser His Tyr Val Ile Ala Ile Phe Ala Leu Met Ser Ser Cys  
 1 5 10 15

Leu Ala Thr Ala Gly Pro Glu Pro Gly Ala Leu Cys Glu Leu Ser Pro  
 20 25 30

Val Ser Ala Ser His Pro Val Gln Ala Leu Met Glu Ser Phe Thr Val  
 35 40 45

Leu Ser Gly Cys Ala Ser Arg Gly Thr Thr Gly Leu Pro Gln Glu Val  
 50 55 60

His Val Leu Asn Leu Arg Thr Ala Gly Gln Gly Pro Gly Gln Leu Gln  
 65 70 75 80

Arg Glu Val Thr Leu His Leu Asn Pro Ile Ser Ser Val His Ile His  
 85 90 95

His Lys Ser Val Val Phe Leu Leu Asn Ser Pro His Pro Leu Val Trp  
 100 105 110

His Leu Lys Thr Glu Arg Leu Ala Thr Gly Val Ser Arg Leu Phe Leu  
 115 120 125

Val Ser Glu Gly Ser Val Val Gln Phe Ser Ser Ala Asn Phe Ser Leu  
 130 135 140

Thr Ala Glu Thr Glu Glu Arg Asn Phe Pro His Gly Asn Glu His Leu  
 145 150 155 160

Leu Asn Trp Ala Arg Lys Glu Tyr Gly Ala Val Thr Ser Phe Thr Glu  
 165 170 175

Leu Lys Ile Ala Arg Asn Ile Tyr Ile Lys Val Gly Glu Asp Gln Val  
 180 185 190

Phe Pro Pro Lys Cys Asn Ile Gly Lys Asn Phe Leu Ser Leu Asn Tyr  
 195 200 205

# ES 2 534 734 A1

Leu Ala Glu Tyr Leu Gln Pro Lys Ala Ala Glu Gly Cys Val Met Ser  
 210 215 220

Ser Gln Pro Gln Asn Glu Glu Val His Ile Ile Glu Leu Ile Thr Pro  
 225 230 235 240

Asn Ser Asn Pro Tyr Ser Ala Phe Gln Val Asp Ile Thr Ile Asp Ile  
 245 250 255

Arg Pro Ser Gln Glu Asp Leu Glu Val Val Lys Asn Leu Ile Leu Ile  
 260 265 270

Leu Lys Cys Lys Lys Ser Val Asn Trp Val Ile Lys Ser Phe Asp Val  
 275 280 285

Lys Gly Ser Leu Lys Ile Ile Ala Pro Asn Ser Ile Gly Phe Gly Lys  
 290 295 300

Glu Ser Glu Arg Ser Met Thr Met Thr Lys Ser Ile Arg Asp Asp Ile  
 305 310 315 320

Pro Ser Thr Gln Gly Asn Leu Val Lys Trp Ala Leu Asp Asn Gly Tyr  
 325 330 335

Ser Pro Ile Thr Ser Tyr Thr Met Ala Pro Val Ala Asn Arg Phe His  
 340 345 350

Leu Arg Leu Glu Asn Asn Glu Glu Met Gly Asp Glu Glu Val His Thr  
 355 360 365

Ile Pro Pro Glu Leu Arg Ile Leu Leu Asp Pro Gly Ala Leu Pro Ala  
 370 375 380

Leu Gln Asn Pro Pro Ile Arg Gly Gly Glu Gly Gln Asn Gly Gly Leu  
 385 390 395 400

Pro Phe Pro Phe Pro Asp Ile Ser Arg Arg Val Trp Asn Glu Glu Gly  
 405 410 415

Glu Asp Gly Leu Pro Arg Pro Lys Asp Pro Val Ile Pro Ser Ile Gln  
 420 425 430

Leu Phe Pro Gly Leu Arg Glu Pro Glu Glu Val Gln Gly Ser Val Asp  
 435 440 445

# ES 2 534 734 A1

Ile Ala Leu Ser Val Lys Cys Asp Asn Glu Lys Met Ile Val Ala Val  
 450 455 460

Glu Lys Asp Ser Phe Gln Ala Ser Gly Tyr Ser Gly Met Asp Val Thr  
 465 470 475 480

Leu Leu Asp Pro Thr Cys Lys Ala Lys Met Asn Gly Thr His Phe Val  
 485 490 495

Leu Glu Ser Pro Leu Asn Gly Cys Gly Thr Arg Pro Arg Trp Ser Ala  
 500 505 510

Leu Asp Gly Val Val Tyr Tyr Asn Ser Ile Val Ile Gln Val Pro Ala  
 515 520 525

Leu Gly Asp Ser Ser Gly Trp Pro Asp Gly Tyr Glu Asp Leu Glu Ser  
 530 535 540

Gly Asp Asn Gly Phe Pro Gly Asp Met Asp Glu Gly Asp Ala Ser Leu  
 545 550 555

Phe Thr Arg Pro Glu Ile Val Val Phe Asn Cys Ser Leu Gln Gln Val  
 565 570 575

Arg Asn Pro Ser Ser Phe Gln Glu Gln Pro His Gly Asn Ile Thr Phe  
 580 585 590

Asn Met Glu Leu Tyr Asn Thr Asp Leu Phe Leu Val Pro Ser Gln Gly  
 595 600 605

Val Phe Ser Val Pro Glu Asn Gly His Val Tyr Val Glu Val Ser Val  
 610 615 620

Thr Lys Ala Glu Gln Glu Leu Gly Phe Ala Ile Gln Thr Cys Phe Ile  
 625 630 635 640

Ser Pro Tyr Ser Asn Pro Asp Arg Met Ser His Tyr Thr Ile Ile Glu  
 645 650 655

Asn Ile Cys Pro Lys Asp Glu Ser Val Lys Phe Tyr Ser Pro Lys Arg  
 660 665 670

Val His Phe Pro Ile Pro Gln Ala Asp Met Asp Lys Lys Arg Phe Ser  
 675 680 685

ES 2 534 734 A1

Phe Val Phe Lys Pro Val Phe Asn Thr Ser Leu Leu Phe Leu Gln Cys  
 690 695 700

Glu Leu Thr Leu Cys Thr Lys Met Glu Lys His Pro Gln Lys Leu Pro  
 705 710 715 720

Lys Cys Val Pro Pro Asp Glu Ala Cys Thr Ser Leu Asp Ala Ser Ile  
 725 730 735

Ile Trp Ala Met Met Gln Asn Lys Lys Thr Phe Thr Lys Pro Leu Ala  
 740 745 750

Val Ile His His Glu Ala Glu Ser Lys Glu Lys Gly Pro Ser Met Lys  
 755 760 765

Glu Pro Asn Pro Ile Ser Pro Pro Ile Phe His Gly Leu Asp Thr Leu  
 770 775 780

Thr Val Met Gly Ile Ala Phe Ala Ala Phe Val Ile Gly Ala Leu Leu  
 785 790 795 800

Thr Gly Ala Leu Trp Tyr Ile Tyr Ser His Thr Gly Glu Thr Ala Gly  
 805 810 815

Arg Gln Gln Val Pro Thr Ser Pro Pro Ala Ser Glu Asn Ser Ser Ala  
 820 825 830

Ala His Ser Ile Gly Ser Thr Gln Ser Thr Pro Cys Ser Ser Ser Ser  
 835 840 845

Thr Ala  
 850

<210> 94  
 <211> 851  
 <212> PRT  
 <213> Homo sapiens

<400> 94

Met Thr Ser His Tyr Val Ile Ala Ile Phe Ala Leu Met Ser Ser Cys  
 1 5 10 15

Leu Ala Thr Ala Gly Pro Glu Pro Gly Ala Leu Cys Glu Leu Ser Pro  
 20 25 30

# ES 2 534 734 A1

Val Ser Ala Ser His Pro Val Gln Ala Leu Met Glu Ser Phe Thr Val  
 35 40 45

Leu Ser Gly Cys Ala Ser Arg Gly Thr Thr Gly Leu Pro Gln Glu Val  
 50 55 60

His Val Leu Asn Leu Arg Thr Ala Gly Gln Gly Pro Gly Gln Leu Gln  
 65 70 75 80

Arg Glu Val Thr Leu His Leu Asn Pro Ile Ser Ser Val His Ile His  
 85 90 95

His Lys Ser Val Val Phe Leu Leu Asn Ser Pro His Pro Leu Val Trp  
 100 105 110

His Leu Lys Thr Glu Arg Leu Ala Thr Gly Val Ser Arg Leu Phe Leu  
 115 120 125

Val Ser Glu Gly Ser Val Val Gln Phe Ser Ser Ala Asn Phe Ser Leu  
 130 135 140

Thr Ala Glu Thr Glu Glu Arg Asn Phe Pro His Gly Asn Glu His Leu  
 145 150 155 160

Leu Asn Trp Ala Arg Lys Glu Tyr Gly Ala Val Thr Ser Phe Thr Glu  
 165 170 175

Leu Lys Ile Ala Arg Asn Ile Tyr Ile Lys Val Gly Glu Asp Gln Val  
 180 185 190

Phe Pro Pro Lys Cys Asn Ile Gly Lys Asn Phe Leu Ser Leu Asn Tyr  
 195 200 205

Leu Ala Glu Tyr Leu Gln Pro Lys Ala Ala Glu Gly Cys Val Met Ser  
 210 215 220

Ser Gln Pro Gln Asn Glu Glu Val His Ile Ile Glu Leu Ile Thr Pro  
 225 230 235 240

Asn Ser Asn Pro Tyr Ser Ala Phe Gln Val Asp Ile Thr Ile Asp Ile  
 245 250 255

Arg Pro Ser Gln Glu Asp Leu Glu Val Val Lys Asn Leu Ile Leu Ile  
 260 265 270



# ES 2 534 734 A1

Leu Lys Cys Lys Lys Ser Val Asn Trp Val Ile Lys Ser Phe Asp Val  
 275 280 285

Lys Gly Ser Leu Lys Ile Ile Ala Pro Asn Ser Ile Gly Phe Gly Lys  
 290 295 300

Glu Ser Glu Arg Ser Met Thr Met Thr Lys Ser Ile Arg Asp Asp Ile  
 305 310 315 320

Pro Ser Thr Gln Gly Asn Leu Val Lys Trp Ala Leu Asp Asn Gly Tyr  
 325 330 335

Ser Pro Ile Thr Ser Tyr Thr Met Ala Pro Val Ala Asn Arg Phe His  
 340 345 350

Leu Arg Leu Glu Asn Asn Ala Glu Glu Met Gly Asp Glu Glu Val His  
 355 360 365

Thr Ile Pro Pro Glu Leu Arg Ile Leu Leu Asp Pro Gly Ala Leu Pro  
 370 375 380

Ala Leu Gln Asn Pro Pro Ile Arg Gly Gly Glu Gly Gln Asn Gly Gly  
 385 390 395 400

Leu Pro Phe Pro Phe Pro Asp Ile Ser Arg Arg Val Trp Asn Glu Glu  
 405 410 415

Gly Glu Asp Gly Leu Pro Arg Pro Lys Asp Pro Val Ile Pro Ser Ile  
 420 425 430

Gln Leu Phe Pro Gly Leu Arg Glu Pro Glu Glu Val Gln Gly Ser Val  
 435 440 445

Asp Ile Ala Leu Ser Val Lys Cys Asp Asn Glu Lys Met Ile Val Ala  
 450 455 460

Val Glu Lys Asp Ser Phe Gln Ala Ser Gly Tyr Ser Gly Met Asp Val  
 465 470 475 480

Thr Leu Leu Asp Pro Thr Cys Lys Ala Lys Met Asn Gly Thr His Phe  
 485 490 495

Val Leu Glu Ser Pro Leu Asn Gly Cys Gly Thr Arg Pro Arg Trp Ser  
 500 505 510

# ES 2 534 734 A1

Ala Leu Asp Gly Val Val Tyr Tyr Asn Ser Ile Val Ile Gln Val Pro  
515 520 525

Ala Leu Gly Asp Ser Ser Gly Trp Pro Asp Gly Tyr Glu Asp Leu Glu  
530 535 540

Ser Gly Asp Asn Gly Phe Pro Gly Asp Met Asp Glu Gly Asp Ala Ser  
545 550 555 560

Leu Phe Thr Arg Pro Glu Ile Val Val Phe Asn Cys Ser Leu Gln Gln  
565 570 575

Val Arg Asn Pro Ser Ser Phe Gln Glu Gln Pro His Gly Asn Ile Thr  
580 585 590

Phe Asn Met Glu Leu Tyr Asn Thr Asp Leu Phe Leu Val Pro Ser Gln  
595 600 605

Gly Val Phe Ser Val Pro Glu Asn Gly His Val Tyr Val Glu Val Ser  
610 615 620

Val Thr Lys Ala Glu Gln Glu Leu Gly Phe Ala Ile Gln Thr Cys Phe  
625 630 635 640

Ile Ser Pro Tyr Ser Asn Pro Asp Arg Met Ser His Tyr Thr Ile Ile  
645 650 655

Glu Asn Ile Cys Pro Lys Asp Glu Ser Val Lys Phe Tyr Ser Pro Lys  
660 665 670

Arg Val His Phe Pro Ile Pro Gln Ala Asp Met Asp Lys Lys Arg Phe  
675 680 685

Ser Phe Val Phe Lys Pro Val Phe Asn Thr Ser Leu Leu Phe Leu Gln  
690 695 700

Cys Glu Leu Thr Leu Cys Thr Lys Met Glu Lys His Pro Gln Lys Leu  
705 710 715 720

Pro Lys Cys Val Pro Pro Asp Glu Ala Cys Thr Ser Leu Asp Ala Ser  
725 730 735

Ile Ile Trp Ala Met Met Gln Asn Lys Lys Thr Phe Thr Lys Pro Leu  
740 745 750

# ES 2 534 734 A1

Ala Val Ile His His Glu Ala Glu Ser Lys Glu Lys Gly Pro Ser Met  
 755 760 765

Lys Glu Pro Asn Pro Ile Ser Pro Pro Ile Phe His Gly Leu Asp Thr  
 770 775 780

Leu Thr Val Met Gly Ile Ala Phe Ala Ala Phe Val Ile Gly Ala Leu  
 785 790 795 800

Leu Thr Gly Ala Leu Trp Tyr Ile Tyr Ser His Thr Gly Glu Thr Ala  
 805 810 815

Gly Arg Gln Gln Val Pro Thr Ser Pro Pro Ala Ser Glu Asn Ser Ser  
 820 825 830

Ala Ala His Ser Ile Gly Ser Thr Gln Ser Thr Pro Cys Ser Ser Ser  
 835 840 845

Ser Thr Ala  
 850

<210> 95  
 <211> 373  
 <212> PRT  
 <213> Homo sapiens

<400> 95

Met Ala Ser Lys Pro Glu Lys Arg Val Ala Ser Ser Val Phe Ile Thr  
 1 5 10 15

Leu Ala Pro Pro Arg Arg Asp Val Ala Val Ala Glu Glu Val Arg Gln  
 20 25 30

Ala Val Cys Glu Ala Arg Arg Gly Arg Pro Trp Glu Ala Pro Ala Pro  
 35 40 45

Met Lys Thr Pro Glu Ala Gly Leu Ala Gly Arg Pro Ser Pro Trp Thr  
 50 55 60

Thr Pro Gly Arg Ala Ala Ala Thr Val Pro Ala Ala Pro Met Gln Leu  
 65 70 75 80

Phe Asn Gly Gly Cys Pro Pro Pro Pro Pro Val Leu Asp Gly Glu Asp  
 85 90 95

# ES 2 534 734 A1

Val Leu Pro Asp Leu Asp Leu Leu Pro Pro Pro Pro Pro Pro Pro Pro  
 100 105 110

Val Leu Leu Pro Ser Glu Glu Glu Ala Pro Ala Pro Met Gly Ala Ser  
 115 120 125

Leu Ile Ala Asp Leu Glu Gln Leu His Leu Ser Pro Pro Pro Pro Pro  
 130 135 140

Pro Gln Ala Pro Ala Glu Gly Pro Ser Val Gln Pro Gly Pro Leu Arg  
 145 150 155 160

Pro Met Glu Glu Glu Leu Pro Pro Pro Pro Ala Glu Pro Val Glu Lys  
 165 170 175

Gly Ala Ser Thr Asp Ile Cys Ala Phe Cys His Lys Thr Val Ser Pro  
 180 185 190

Arg Glu Leu Ala Val Glu Ala Met Lys Arg Gln Tyr His Ala Gln Cys  
 195 200 205

Phe Thr Cys Arg Thr Cys Arg Arg Gln Leu Ala Gly Gln Ser Phe Tyr  
 210 215 220

Gln Lys Asp Gly Arg Pro Leu Cys Glu Pro Cys Tyr Gln Asp Thr Leu  
 225 230 235 240

Glu Arg Cys Gly Lys Cys Gly Glu Val Val Arg Asp His Ile Ile Arg  
 245 250 255

Ala Leu Gly Gln Ala Phe His Pro Ser Cys Phe Thr Cys Val Thr Cys  
 260 265 270

Ala Arg Cys Ile Gly Asp Glu Ser Phe Ala Leu Gly Ser Gln Asn Glu  
 275 280 285

Val Tyr Cys Leu Asp Asp Phe Tyr Arg Lys Phe Ala Pro Val Cys Ser  
 290 295 300

Ile Cys Glu Asn Pro Ile Ile Pro Arg Asp Gly Lys Asp Ala Phe Lys  
 305 310 315 320

Ile Glu Cys Met Gly Arg Asn Phe His Glu Asn Cys Tyr Arg Cys Glu  
 325 330 335

# ES 2 534 734 A1

Asp Cys Arg Ile Leu Leu Ser Val Glu Pro Thr Asp Gln Gly Cys Tyr  
 340 345 350

Pro Leu Asn Asn His Leu Phe Cys Lys Pro Cys His Val Lys Arg Ser  
 355 360 365

Ala Ala Gly Cys Cys  
 370

<210> 96  
 <211> 374  
 <212> PRT  
 <213> Homo sapiens

<400> 96

Met Ala Ser Lys Pro Glu Lys Arg Val Ala Ser Ser Val Phe Ile Thr  
 1 5 10 15

Leu Ala Pro Pro Arg Arg Asp Val Ala Val Ala Glu Glu Val Arg Gln  
 20 25 30

Ala Val Cys Glu Ala Arg Arg Gly Arg Pro Trp Glu Ala Pro Ala Pro  
 35 40 45

Met Lys Thr Pro Glu Ala Gly Leu Ala Gly Arg Pro Ser Pro Trp Thr  
 50 55 60

Thr Pro Gly Arg Ala Ala Ala Thr Val Pro Ala Ala Pro Met Gln Leu  
 65 70 75 80

Phe Asn Gly Gly Cys Pro Pro Pro Pro Pro Val Leu Asp Gly Glu Asp  
 85 90 95

Val Leu Pro Asp Leu Asp Leu Leu Pro Pro Pro Pro Pro Pro Pro  
 100 105 110

Val Leu Leu Pro Ser Glu Glu Glu Ala Pro Ala Pro Met Gly Ala Ser  
 115 120 125

Leu Ile Ala Asp Leu Glu Gln Leu His Leu Ser Pro Pro Pro Pro Pro  
 130 135 140

Pro Gln Ala Pro Ala Glu Gly Pro Ser Val Gln Pro Gly Pro Leu Arg  
 145 150 155 160

# ES 2 534 734 A1

Pro Met Glu Glu Glu Leu Pro Pro Pro Pro Ala Glu Pro Val Glu Lys  
 165 170 175

Gly Ala Ser Thr Asp Ile Cys Ala Phe Cys His Lys Thr Val Ser Pro  
 180 185 190

Arg Glu Leu Ala Val Glu Ala Met Lys Arg Gln Tyr His Ala Gln Cys  
 195 200 205

Phe Thr Cys Arg Thr Cys Arg Arg Gln Leu Ala Gly Gln Ser Phe Tyr  
 210 215 220

Gln Lys Asp Gly Arg Pro Leu Cys Glu Pro Cys Tyr Gln Asp Thr Leu  
 225 230 235 240

Glu Arg Cys Gly Lys Cys Gly Glu Val Val Arg Asp His Ile Ile Arg  
 245 250 255

Ala Leu Gly Gln Ala Phe His Pro Ser Cys Phe Thr Cys Val Thr Cys  
 260 265 270

Ala Arg Cys Ile Gly Asp Glu Ser Phe Ala Leu Gly Ser Gln Asn Glu  
 275 280 285

Val Tyr Cys Leu Asp Asp Phe Tyr Arg Tyr Glu Lys Gly Leu Cys Thr  
 290 295 300

Gly Trp Gly Ala Gly Thr Gly Arg Asp Pro Ser Arg Val Lys Glu Leu  
 305 310 315 320

Ser Leu Ser Pro Gly Cys Trp Ala Arg Val Ser Cys Leu Leu Val Tyr  
 325 330 335

Tyr Lys Glu Tyr Tyr Arg Ala Gly Leu Gly Ala Val Ala His Ala Cys  
 340 345 350

Asn Pro Ser Thr Leu Gly Gly Arg Gly Gly Trp Ile Thr Arg Ser Gly  
 355 360 365

Asp Arg Asp His Pro Gly  
 370

<210> 97  
 <211> 276

# ES 2 534 734 A1

<212> PRT

<213> Homo sapiens

<400> 97

Met Ala Ser Lys Pro Glu Lys Arg Val Ala Ser Ser Val Phe Ile Thr  
 1 5 10 15

Leu Ala Pro Pro Arg Arg Asp Val Ala Val Ala Glu Glu Val Arg Gln  
 20 25 30

Ala Val Cys Glu Ala Arg Arg Gly Arg Pro Trp Glu Ala Pro Ala Pro  
 35 40 45

Met Lys Thr Pro Glu Ala Gly Leu Ala Gly Arg Pro Ser Pro Trp Thr  
 50 55 60

Thr Pro Gly Arg Ala Ala Ala Thr Val Pro Ala Ala Pro Met Gln Leu  
 65 70 75 80

Phe Asn Gly Asp Ile Cys Ala Phe Cys His Lys Thr Val Ser Pro Arg  
 85 90 95

Glu Leu Ala Val Glu Ala Met Lys Arg Gln Tyr His Ala Gln Cys Phe  
 100 105 110

Thr Cys Arg Thr Cys Arg Arg Gln Leu Ala Gly Gln Ser Phe Tyr Gln  
 115 120 125

Lys Asp Gly Arg Pro Leu Cys Glu Pro Cys Tyr Gln Asp Thr Leu Glu  
 130 135 140

Arg Cys Gly Lys Cys Gly Glu Val Val Arg Asp His Ile Ile Arg Ala  
 145 150 155 160

Leu Gly Gln Ala Phe His Pro Ser Cys Phe Thr Cys Val Thr Cys Ala  
 165 170 175

Arg Cys Ile Gly Asp Glu Ser Phe Ala Leu Gly Ser Gln Asn Glu Val  
 180 185 190

Tyr Cys Leu Asp Asp Phe Tyr Arg Lys Phe Ala Pro Val Cys Ser Ile  
 195 200 205

# ES 2 534 734 A1

Cys Glu Asn Pro Ile Ile Pro Arg Asp Gly Lys Asp Ala Phe Lys Ile  
 210 215 220

Glu Cys Met Gly Arg Asn Phe His Glu Asn Cys Tyr Arg Cys Glu Asp  
 225 230 235 240

Cys Arg Ile Leu Leu Ser Val Glu Pro Thr Asp Gln Gly Cys Tyr Pro  
 245 250 255

Leu Asn Asn His Leu Phe Cys Lys Pro Cys His Val Lys Arg Ser Ala  
 260 265 270

Ala Gly Cys Cys  
 275

<210> 98  
 <211> 476  
 <212> PRT  
 <213> Homo sapiens

<400> 98

Met Ser Gly Ala Arg Cys Arg Thr Leu Tyr Pro Phe Ser Gly Glu Arg  
 1 5 10 15

His Gly Gln Gly Leu Arg Phe Ala Ala Gly Glu Leu Ile Thr Leu Leu  
 20 25 30

Gln Val Pro Asp Gly Gly Trp Trp Glu Gly Glu Lys Glu Asp Gly Leu  
 35 40 45

Arg Gly Trp Phe Pro Ala Ser Tyr Val Gln Leu Leu Glu Lys Pro Gly  
 50 55 60

Met Val Pro Pro Pro Pro Gly Glu Glu Ser Gln Thr Val Ile Leu Pro  
 65 70 75 80

Pro Gly Trp Gln Ser Tyr Leu Ser Pro Gln Gly Arg Arg Tyr Tyr Val  
 85 90 95

Asn Thr Thr Thr Asn Glu Thr Thr Trp Glu Arg Pro Ser Ser Ser Pro  
 100 105 110

Gly Ile Pro Ala Ser Pro Gly Ser His Arg Ser Ser Leu Pro Pro Thr  
 115 120 125



# ES 2 534 734 A1

Val	Asn	Gly	Tyr	His	Ala	Ser	Gly	Thr	Pro	Ala	His	Pro	Pro	Glu	Thr
	130					135					140				
Ala	His	Met	Ser	Val	Arg	Lys	Ser	Thr	Gly	Asp	Ser	Gln	Asn	Leu	Gly
145					150					155					160
Ser	Ser	Ser	Pro	Ser	Lys	Lys	Gln	Ser	Lys	Glu	Asn	Thr	Ile	Thr	Ile
				165					170					175	
Asn	Cys	Val	Thr	Phe	Pro	His	Pro	Asp	Thr	Met	Pro	Glu	Gln	Gln	Leu
			180					185					190		
Leu	Lys	Pro	Thr	Glu	Trp	Ser	Tyr	Cys	Asp	Tyr	Phe	Trp	Ala	Asp	Lys
		195					200					205			
Lys	Asp	Pro	Gln	Gly	Asn	Gly	Thr	Val	Ala	Gly	Phe	Glu	Leu	Leu	Leu
	210					215					220				
Gln	Lys	Gln	Leu	Lys	Gly	Lys	Gln	Met	Gln	Lys	Glu	Met	Ser	Glu	Phe
225					230					235					240
Ile	Arg	Glu	Arg	Ile	Lys	Ile	Glu	Glu	Asp	Tyr	Ala	Lys	Asn	Leu	Ala
				245					250					255	
Lys	Leu	Ser	Gln	Asn	Ser	Leu	Ala	Ser	Gln	Glu	Glu	Gly	Ser	Leu	Gly
			260					265					270		
Glu	Ala	Trp	Ala	Gln	Val	Lys	Lys	Ser	Leu	Ala	Asp	Glu	Ala	Glu	Val
		275					280					285			
His	Leu	Lys	Phe	Ser	Ala	Lys	Leu	His	Ser	Glu	Val	Glu	Lys	Pro	Leu
	290					295					300				
Met	Asn	Phe	Arg	Glu	Asn	Phe	Lys	Lys	Asp	Met	Lys	Lys	Cys	Asp	His
305					310					315					320
His	Ile	Ala	Asp	Leu	Arg	Lys	Gln	Leu	Ala	Ser	Arg	Tyr	Ala	Ser	Val
				325					330					335	
Glu	Lys	Ala	Arg	Lys	Ala	Leu	Thr	Glu	Arg	Gln	Arg	Asp	Leu	Glu	Met
			340					345					350		
Lys	Thr	Gln	Gln	Leu	Glu	Ile	Lys	Leu	Ser	Asn	Lys	Thr	Glu	Glu	Asp
		355					360					365			

# ES 2 534 734 A1

Ile Lys Lys Ala Arg Arg Lys Ser Thr Gln Ala Gly Asp Asp Leu Met  
 370 375 380

Arg Cys Val Asp Leu Tyr Asn Gln Ala Gln Ser Lys Trp Phe Glu Glu  
 385 390 395 400

Met Val Thr Thr Thr Leu Glu Leu Glu Arg Leu Glu Val Glu Arg Val  
 405 410 415

Glu Met Ile Arg Gln His Leu Cys Gln Tyr Thr Gln Leu Arg His Glu  
 420 425 430

Thr Asp Met Phe Asn Gln Ser Thr Val Glu Pro Val Asp Gln Leu Leu  
 435 440 445

Arg Lys Val Asp Pro Ala Lys Asp Arg Glu Leu Trp Val Arg Glu His  
 450 455 460

Lys Thr Gly Asn Ile Arg Pro Val Asp Met Glu Ile  
 465 470 475

<210> 99  
 <211> 416  
 <212> PRT  
 <213> Homo sapiens

<400> 99

Met Lys Pro Gly Met Val Pro Pro Pro Pro Gly Glu Glu Ser Gln Thr  
 1 5 10 15

Val Ile Leu Pro Pro Gly Trp Gln Ser Tyr Leu Ser Pro Gln Gly Arg  
 20 25 30

Arg Tyr Tyr Val Asn Thr Thr Thr Asn Glu Thr Thr Trp Glu Arg Pro  
 35 40 45

Ser Ser Ser Pro Gly Ile Pro Ala Ser Pro Gly Ser His Arg Ser Ser  
 50 55 60

Leu Pro Pro Thr Val Asn Gly Tyr His Ala Ser Gly Thr Pro Ala His  
 65 70 75 80

Pro Pro Glu Thr Ala His Met Ser Val Arg Lys Ser Thr Gly Asp Ser  
 85 90 95

# ES 2 534 734 A1

Gln Asn Leu Gly Ser Ser Ser Pro Ser Lys Lys Gln Ser Lys Glu Asn  
 100 105 110

Thr Ile Thr Ile Asn Cys Val Thr Phe Pro His Pro Asp Thr Met Pro  
 115 120 125

Glu Gln Gln Leu Leu Lys Pro Thr Glu Trp Ser Tyr Cys Asp Tyr Phe  
 130 135 140

Trp Ala Asp Lys Lys Asp Pro Gln Gly Asn Gly Thr Val Ala Gly Phe  
 145 150 155 160

Glu Leu Leu Leu Gln Lys Gln Leu Lys Gly Lys Gln Met Gln Lys Glu  
 165 170 175

Met Ser Glu Phe Ile Arg Glu Arg Ile Lys Ile Glu Glu Asp Tyr Ala  
 180 185 190

Lys Asn Leu Ala Lys Leu Ser Gln Asn Ser Leu Ala Ser Gln Glu Glu  
 195 200 205

Gly Ser Leu Gly Glu Ala Trp Ala Gln Val Lys Lys Ser Leu Ala Asp  
 210 215 220

Glu Ala Glu Val His Leu Lys Phe Ser Ala Lys Leu His Ser Glu Val  
 225 230 235 240

Glu Lys Pro Leu Met Asn Phe Arg Glu Asn Phe Lys Lys Asp Met Lys  
 245 250 255

Lys Cys Asp His His Ile Ala Asp Leu Arg Lys Gln Leu Ala Ser Arg  
 260 265 270

Tyr Ala Ser Val Glu Lys Ala Arg Lys Ala Leu Thr Glu Arg Gln Arg  
 275 280 285

Asp Leu Glu Met Lys Thr Gln Gln Leu Glu Ile Lys Leu Ser Asn Lys  
 290 295 300

Thr Glu Glu Asp Ile Lys Lys Ala Arg Arg Lys Ser Thr Gln Ala Gly  
 305 310 315 320

Asp Asp Leu Met Arg Cys Val Asp Leu Tyr Asn Gln Ala Gln Ser Lys  
 325 330 335

# ES 2 534 734 A1

Trp Phe Glu Glu Met Val Thr Thr Thr Leu Glu Leu Glu Arg Leu Glu  
 340 345 350

Val Glu Arg Val Glu Met Ile Arg Gln His Leu Cys Gln Tyr Thr Gln  
 355 360 365

Leu Arg His Glu Thr Asp Met Phe Asn Gln Ser Thr Val Glu Pro Val  
 370 375 380

Asp Gln Leu Leu Arg Lys Val Asp Pro Ala Lys Asp Arg Glu Leu Trp  
 385 390 395 400

Val Arg Glu His Lys Thr Gly Asn Ile Arg Pro Val Asp Met Glu Ile  
 405 410 415

<210> 100  
 <211> 412  
 <212> PRT  
 <213> Homo sapiens

<400> 100

Met Val Pro Pro Pro Pro Gly Glu Glu Ser Gln Thr Val Ile Leu Pro  
 1 5 10 15

Pro Gly Trp Gln Ser Tyr Leu Ser Pro Gln Gly Arg Arg Tyr Tyr Val  
 20 25 30

Asn Thr Thr Thr Asn Glu Thr Thr Trp Glu Arg Pro Ser Ser Ser Pro  
 35 40 45

Gly Ile Pro Ala Ser Pro Gly Ser His Arg Ser Ser Leu Pro Pro Thr  
 50 55 60

Val Asn Gly Tyr His Ala Ser Gly Thr Pro Ala His Pro Pro Glu Thr  
 65 70 75 80

Ala His Met Ser Val Arg Lys Ser Thr Gly Asp Ser Gln Asn Leu Gly  
 85 90 95

Ser Ser Ser Pro Ser Lys Lys Gln Ser Lys Glu Asn Thr Ile Thr Ile  
 100 105 110

Asn Cys Val Thr Phe Pro His Pro Asp Thr Met Pro Glu Gln Gln Leu  
 115 120 125

# ES 2 534 734 A1

Leu Lys Pro Thr Glu Trp Ser Tyr Cys Asp Tyr Phe Trp Ala Asp Lys  
 130 135 140

Lys Asp Pro Gln Gly Asn Gly Thr Val Ala Gly Phe Glu Leu Leu Leu  
 145 150 155 160

Gln Lys Gln Leu Lys Gly Lys Gln Met Gln Lys Glu Met Ser Glu Phe  
 165 170 175

Ile Arg Glu Arg Ile Lys Ile Glu Glu Asp Tyr Ala Lys Asn Leu Ala  
 180 185 190

Lys Leu Ser Gln Asn Ser Leu Ala Ser Gln Glu Glu Gly Ser Leu Gly  
 195 200 205

Glu Ala Trp Ala Gln Val Lys Lys Ser Leu Ala Asp Glu Ala Glu Val  
 210 215 220

His Leu Lys Phe Ser Ala Lys Leu His Ser Glu Val Glu Lys Pro Leu  
 225 230 235 240

Met Asn Phe Arg Glu Asn Phe Lys Lys Asp Met Lys Lys Cys Asp His  
 245 250 255

His Ile Ala Asp Leu Arg Lys Gln Leu Ala Ser Arg Tyr Ala Ser Val  
 260 265 270

Glu Lys Ala Arg Lys Ala Leu Thr Glu Arg Gln Arg Asp Leu Glu Met  
 275 280 285

Lys Thr Gln Gln Leu Glu Ile Lys Leu Ser Asn Lys Thr Glu Glu Asp  
 290 295 300

Ile Lys Lys Ala Arg Arg Lys Ser Thr Gln Ala Gly Asp Asp Leu Met  
 305 310 315 320

Arg Cys Val Asp Leu Tyr Asn Gln Ala Gln Ser Lys Trp Phe Glu Glu  
 325 330 335

Met Val Thr Thr Thr Leu Glu Leu Glu Arg Leu Glu Val Glu Arg Val  
 340 345 350

Glu Met Ile Arg Gln His Leu Cys Gln Tyr Thr Gln Leu Arg His Glu  
 355 360 365

# ES 2 534 734 A1

Thr Asp Met Phe Asn Gln Ser Thr Val Glu Pro Val Asp Gln Leu Leu  
 370 375 380

Arg Lys Val Asp Pro Ala Lys Asp Arg Glu Leu Trp Val Arg Glu His  
 385 390 395 400

Lys Thr Gly Asn Ile Arg Pro Val Asp Met Glu Ile  
 405 410

<210> 101  
 <211> 336  
 <212> PRT  
 <213> Homo sapiens

<400> 101

Met Ser Asn Met Glu Asn Ser Phe Asp Asp Val Ser Cys Leu Ser Pro  
 1 5 10 15

Gln Asn Leu Gly Ser Ser Ser Pro Ser Lys Lys Gln Ser Lys Glu Asn  
 20 25 30

Thr Ile Thr Ile Asn Cys Val Thr Phe Pro His Pro Asp Thr Met Pro  
 35 40 45

Glu Gln Gln Leu Leu Lys Pro Thr Glu Trp Ser Tyr Cys Asp Tyr Phe  
 50 55 60

Trp Ala Asp Lys Lys Asp Pro Gln Gly Asn Gly Thr Val Ala Gly Phe  
 65 70 75 80

Glu Leu Leu Leu Gln Lys Gln Leu Lys Gly Lys Gln Met Gln Lys Glu  
 85 90 95

Met Ser Glu Phe Ile Arg Glu Arg Ile Lys Ile Glu Glu Asp Tyr Ala  
 100 105 110

Lys Asn Leu Ala Lys Leu Ser Gln Asn Ser Leu Ala Ser Gln Glu Glu  
 115 120 125

Gly Ser Leu Gly Glu Ala Trp Ala Gln Val Lys Lys Ser Leu Ala Asp  
 130 135 140

Glu Ala Glu Val His Leu Lys Phe Ser Ala Lys Leu His Ser Glu Val  
 145 150 155 160

# ES 2 534 734 A1

Glu Lys Pro Leu Met Asn Phe Arg Glu Asn Phe Lys Lys Asp Met Lys  
                                   165                                  170                                  175

Lys Cys Asp His His Ile Ala Asp Leu Arg Lys Gln Leu Ala Ser Arg  
                                   180                                  185                                  190

Tyr Ala Ser Val Glu Lys Ala Arg Lys Ala Leu Thr Glu Arg Gln Arg  
                                   195                                  200                                  205

Asp Leu Glu Met Lys Thr Gln Gln Leu Glu Ile Lys Leu Ser Asn Lys  
                                   210                                  215                                  220

Thr Glu Glu Asp Ile Lys Lys Ala Arg Arg Lys Ser Thr Gln Ala Gly  
                                   225                                  230                                  235                                  240

Asp Asp Leu Met Arg Cys Val Asp Leu Tyr Asn Gln Ala Gln Ser Lys  
                                   245                                  250                                  255

Trp Phe Glu Glu Met Val Thr Thr Thr Leu Glu Leu Glu Arg Leu Glu  
                                   260                                  265                                  270

Val Glu Arg Val Glu Met Ile Arg Gln His Leu Cys Gln Tyr Thr Gln  
                                   275                                  280                                  285

Leu Arg His Glu Thr Asp Met Phe Asn Gln Ser Thr Val Glu Pro Val  
                                   290                                  295                                  300

Asp Gln Leu Leu Arg Lys Val Asp Pro Ala Lys Asp Arg Glu Leu Trp  
                                   305                                  310                                  315                                  320

Val Arg Glu His Lys Thr Gly Asn Ile Arg Pro Val Asp Met Glu Ile  
                                   325                                  330                                  335

<210> 102  
 <211> 258  
 <212> PRT  
 <213> Homo sapiens

<400> 102

Met Leu Pro Leu Cys Leu Val Ala Ala Leu Leu Leu Ala Ala Gly Pro  
   1                                  5                                  10                                  15

Gly Pro Ser Leu Gly Asp Glu Ala Ile His Cys Pro Pro Cys Ser Glu  
                                   20                                  25                                  30

# ES 2 534 734 A1

Glu Lys Leu Ala Arg Cys Arg Pro Pro Val Gly Cys Glu Glu Leu Val  
 35 40 45

Arg Glu Pro Gly Cys Gly Cys Cys Ala Thr Cys Ala Leu Gly Leu Gly  
 50 55 60

Met Pro Cys Gly Val Tyr Thr Pro Arg Cys Gly Ser Gly Leu Arg Cys  
 65 70 75 80

Tyr Pro Pro Arg Gly Val Glu Lys Pro Leu His Thr Leu Met His Gly  
 85 90 95

Gln Gly Val Cys Met Glu Leu Ala Glu Ile Glu Ala Ile Gln Glu Ser  
 100 105 110

Leu Gln Pro Ser Asp Lys Asp Glu Gly Asp His Pro Asn Asn Ser Phe  
 115 120 125

Ser Pro Cys Ser Ala His Asp Arg Arg Cys Leu Gln Lys His Phe Ala  
 130 135 140

Lys Ile Arg Asp Arg Ser Thr Ser Gly Gly Lys Met Lys Val Asn Gly  
 145 150 155 160

Ala Pro Arg Glu Asp Ala Arg Pro Val Pro Gln Gly Ser Cys Gln Ser  
 165 170 175

Glu Leu His Arg Ala Leu Glu Arg Leu Ala Ala Ser Gln Ser Arg Thr  
 180 185 190

His Glu Asp Leu Tyr Ile Ile Pro Ile Pro Asn Cys Asp Arg Asn Gly  
 195 200 205

Asn Phe His Pro Lys Gln Cys His Pro Ala Leu Asp Gly Gln Arg Gly  
 210 215 220

Lys Cys Trp Cys Val Asp Arg Lys Thr Gly Val Lys Leu Pro Gly Gly  
 225 230 235 240

Leu Glu Pro Lys Gly Glu Leu Asp Cys His Gln Leu Ala Asp Ser Phe  
 245 250 255

Arg Glu



# ES 2 534 734 A1

<210> 103  
 <211> 1877  
 <212> PRT  
 <213> Homo sapiens

<400> 103

Met Leu Gly Ser Ser Val Lys Ser Val Gln Pro Glu Val Glu Leu Ser  
 1 5 10 15

Ser Gly Gly Gly Asp Glu Gly Ala Asp Glu Pro Arg Gly Ala Gly Arg  
 20 25 30

Lys Ala Ala Ala Ala Asp Gly Arg Gly Met Leu Pro Lys Arg Ala Lys  
 35 40 45

Ala Pro Gly Gly Gly Gly Gly Met Ala Lys Ala Ser Ala Ala Glu Leu  
 50 55 60

Lys Val Phe Lys Ser Gly Ser Val Asp Ser Arg Val Pro Gly Gly Pro  
 65 70 75 80

Pro Ala Ser Asn Leu Arg Lys Gln Lys Ser Leu Thr Asn Leu Ser Phe  
 85 90 95

Leu Thr Asp Ser Glu Lys Lys Leu Gln Leu Tyr Glu Pro Glu Trp Ser  
 100 105 110

Asp Asp Met Ala Lys Ala Pro Lys Gly Leu Gly Lys Val Gly Ser Lys  
 115 120 125

Gly Arg Glu Ala Pro Leu Met Ser Lys Thr Leu Ser Lys Ser Glu His  
 130 135 140

Ser Leu Phe Gln Ala Lys Gly Ser Pro Ala Gly Gly Ala Lys Thr Pro  
 145 150 155 160

Leu Ala Pro Leu Ala Pro Asn Leu Gly Lys Pro Ser Arg Ile Pro Arg  
 165 170 175

Gly Pro Tyr Ala Glu Val Lys Pro Leu Ser Lys Ala Pro Glu Ala Ala  
 180 185 190

Val Ser Glu Asp Gly Lys Ser Asp Asp Glu Leu Leu Ser Ser Lys Ala  
 195 200 205

# ES 2 534 734 A1

Lys Ala Gln Lys Ser Ser Gly Pro Val Pro Ser Ala Lys Gly Gln Glu  
 210 215 220

Glu Arg Ala Phe Leu Lys Val Asp Pro Glu Leu Val Val Thr Val Leu  
 225 230 235 240

Gly Asp Leu Glu Gln Leu Leu Phe Ser Gln Met Leu Asp Pro Glu Ser  
 245 250 255

Gln Arg Lys Arg Thr Val Gln Asn Val Leu Asp Leu Arg Gln Asn Leu  
 260 265 270

Glu Glu Thr Met Ser Ser Leu Arg Gly Ser Gln Val Thr His Ser Ser  
 275 280 285

Leu Glu Met Thr Cys Tyr Asp Ser Asp Asp Ala Asn Pro Arg Ser Val  
 290 295 300

Ser Ser Leu Ser Asn Arg Ser Ser Pro Leu Ser Trp Arg Tyr Gly Gln  
 305 310 315 320

Ser Ser Pro Arg Leu Gln Ala Gly Asp Ala Pro Ser Val Gly Gly Ser  
 325 330 335

Cys Arg Ser Glu Gly Thr Pro Ala Trp Tyr Met His Gly Glu Arg Ala  
 340 345 350

His Tyr Ser His Thr Met Pro Met Arg Ser Pro Ser Lys Leu Ser His  
 355 360 365

Ile Ser Arg Leu Glu Leu Val Glu Ser Leu Asp Ser Asp Glu Val Asp  
 370 375 380

Leu Lys Ser Gly Tyr Met Ser Asp Ser Asp Leu Met Gly Lys Thr Met  
 385 390 395 400

Thr Glu Asp Asp Asp Ile Thr Thr Gly Trp Asp Glu Ser Ser Ser Ile  
 405 410 415

Ser Ser Gly Leu Ser Asp Ala Ser Asp Asn Leu Ser Ser Glu Glu Phe  
 420 425 430

Asn Ala Ser Ser Ser Leu Asn Ser Leu Pro Ser Thr Pro Thr Ala Ser  
 435 440 445

# ES 2 534 734 A1

Arg Arg Asn Ser Thr Ile Val Leu Arg Thr Asp Ser Glu Lys Arg Ser  
 450 455 460

Leu Ala Glu Ser Gly Leu Ser Trp Phe Ser Glu Ser Glu Glu Lys Ala  
 465 470 475 480

Pro Lys Lys Leu Glu Tyr Asp Ser Gly Ser Leu Lys Met Glu Pro Gly  
 485 490 495

Thr Ser Lys Trp Arg Arg Glu Arg Pro Glu Ser Cys Asp Asp Ser Ser  
 500 505 510

Lys Gly Gly Glu Leu Lys Lys Pro Ile Ser Leu Gly His Pro Gly Ser  
 515 520 525

Leu Lys Lys Gly Lys Thr Pro Pro Val Ala Val Thr Ser Pro Ile Thr  
 530 535 540

His Thr Ala Gln Ser Ala Leu Lys Val Ala Gly Lys Pro Glu Gly Lys  
 545 550 555 560

Ala Thr Asp Lys Gly Lys Leu Ala Val Lys Asn Thr Gly Leu Gln Arg  
 565 570 575

Ser Ser Ser Asp Ala Gly Arg Asp Arg Leu Ser Asp Ala Lys Lys Pro  
 580 585 590

Pro Ser Gly Ile Ala Arg Pro Ser Thr Ser Gly Ser Phe Gly Tyr Lys  
 595 600 605

Lys Pro Pro Pro Ala Thr Gly Thr Ala Thr Val Met Gln Thr Gly Gly  
 610 615 620

Ser Ala Thr Leu Ser Lys Ile Gln Lys Ser Ser Gly Ile Pro Val Lys  
 625 630 635 640

Pro Val Asn Gly Arg Lys Thr Ser Leu Asp Val Ser Asn Ser Ala Glu  
 645 650 655

Pro Gly Phe Leu Ala Pro Gly Ala Arg Ser Asn Ile Gln Tyr Arg Ser  
 660 665 670

Leu Pro Arg Pro Ala Lys Ser Ser Ser Met Ser Val Thr Gly Gly Arg  
 675 680 685

# ES 2 534 734 A1

Gly Gly Pro Arg Pro Val Ser Ser Ser Ile Asp Pro Ser Leu Leu Ser  
 690 695 700

Thr Lys Gln Gly Gly Leu Thr Pro Ser Arg Leu Lys Glu Pro Thr Lys  
 705 710 715 720

Val Ala Ser Gly Arg Thr Thr Pro Ala Pro Val Asn Gln Thr Asp Arg  
 725 730 735

Glu Lys Glu Lys Ala Lys Ala Lys Ala Val Ala Leu Asp Ser Asp Asn  
 740 745 750

Ile Ser Leu Lys Ser Ile Gly Ser Pro Glu Ser Thr Pro Lys Asn Gln  
 755 760 765

Ala Ser His Pro Thr Ala Thr Lys Leu Ala Glu Leu Pro Pro Thr Pro  
 770 775 780

Leu Arg Ala Thr Ala Lys Ser Phe Val Lys Pro Pro Ser Leu Ala Asn  
 785 790 795 800

Leu Asp Lys Val Asn Ser Asn Ser Leu Asp Leu Pro Ser Ser Ser Asp  
 805 810 815

Thr Thr His Ala Ser Lys Val Pro Asp Leu His Ala Thr Ser Ser Ala  
 820 825 830

Ser Gly Gly Pro Leu Pro Ser Cys Phe Thr Pro Ser Pro Ala Pro Ile  
 835 840 845

Leu Asn Ile Asn Ser Ala Ser Phe Ser Gln Gly Leu Glu Leu Met Ser  
 850 855 860

Gly Phe Ser Val Pro Lys Glu Thr Arg Met Tyr Pro Lys Leu Ser Gly  
 865 870 875 880

Leu His Arg Ser Met Glu Ser Leu Gln Met Pro Met Ser Leu Pro Ser  
 885 890 895

Ala Phe Pro Ser Ser Thr Pro Val Pro Thr Pro Pro Ala Pro Pro Ala  
 900 905 910

Ala Pro Thr Glu Glu Glu Thr Glu Glu Leu Thr Trp Ser Gly Ser Pro  
 915 920 925

# ES 2 534 734 A1

Arg Ala Gly Gln Leu Asp Ser Asn Gln Arg Asp Arg Asn Thr Leu Pro  
 930 935 940

Lys Lys Gly Leu Arg Tyr Gln Leu Gln Ser Gln Glu Glu Thr Lys Glu  
 945 950 955 960

Arg Arg His Ser His Thr Ile Gly Gly Leu Pro Glu Ser Asp Asp Gln  
 965 970 975

Ser Glu Leu Pro Ser Pro Pro Ala Leu Pro Met Ser Leu Ser Ala Lys  
 980 985 990

Gly Gln Leu Thr Asn Ile Val Ser Pro Thr Ala Ala Thr Thr Pro Arg  
 995 1000 1005

Ile Thr Arg Ser Asn Ser Ile Pro Thr His Glu Ala Ala Phe Glu  
 1010 1015 1020

Leu Tyr Ser Gly Ser Gln Met Gly Ser Thr Leu Ser Leu Ala Glu  
 1025 1030 1035

Arg Pro Lys Gly Met Ile Arg Ser Gly Ser Phe Arg Asp Pro Thr  
 1040 1045 1050

Asp Asp Val His Gly Ser Val Leu Ser Leu Ala Ser Ser Ala Ser  
 1055 1060 1065

Ser Thr Tyr Ser Ser Ala Glu Glu Arg Met Gln Ser Glu Gln Ile  
 1070 1075 1080

Arg Lys Leu Arg Arg Glu Leu Glu Ser Ser Gln Glu Lys Val Ala  
 1085 1090 1095

Thr Leu Thr Ser Gln Leu Ser Ala Asn Ala Asn Leu Val Ala Ala  
 1100 1105 1110

Phe Glu Gln Ser Leu Val Asn Met Thr Ser Arg Leu Arg His Leu  
 1115 1120 1125

Ala Glu Thr Ala Glu Glu Lys Asp Thr Glu Leu Leu Asp Leu Arg  
 1130 1135 1140

Glu Thr Ile Asp Phe Leu Lys Lys Lys Asn Ser Glu Ala Gln Ala  
 1145 1150 1155

# ES 2 534 734 A1

Val	Ile	Gln	Gly	Ala	Leu	Asn	Ala	Ser	Glu	Thr	Thr	Pro	Lys	Glu
1160						1165					1170			
Leu	Arg	Ile	Lys	Arg	Gln	Asn	Ser	Ser	Asp	Ser	Ile	Ser	Ser	Leu
1175						1180					1185			
Asn	Ser	Ile	Thr	Ser	His	Ser	Ser	Ile	Gly	Ser	Ser	Lys	Asp	Ala
1190						1195					1200			
Asp	Ala	Lys	Lys	Lys	Lys	Lys	Lys	Ser	Trp	Val	Tyr	Glu	Leu	Arg
1205						1210					1215			
Ser	Ser	Phe	Asn	Lys	Ala	Phe	Ser	Ile	Lys	Lys	Gly	Pro	Lys	Ser
1220						1225					1230			
Ala	Ser	Ser	Tyr	Ser	Asp	Ile	Glu	Glu	Ile	Ala	Thr	Pro	Asp	Ser
1235						1240					1245			
Ser	Ala	Pro	Ser	Ser	Pro	Lys	Leu	Gln	His	Gly	Ser	Thr	Glu	Thr
1250						1255					1260			
Ala	Ser	Pro	Ser	Ile	Lys	Ser	Ser	Thr	Ser	Ser	Ser	Val	Gly	Thr
1265						1270					1275			
Asp	Val	Thr	Glu	Gly	Pro	Ala	His	Pro	Ala	Pro	His	Thr	Arg	Leu
1280						1285					1290			
Phe	His	Ala	Asn	Glu	Glu	Glu	Glu	Pro	Glu	Lys	Lys	Glu	Val	Ser
1295						1300					1305			
Glu	Leu	Arg	Ser	Glu	Leu	Trp	Glu	Lys	Glu	Met	Lys	Leu	Thr	Asp
1310						1315					1320			
Ile	Arg	Leu	Glu	Ala	Leu	Asn	Ser	Ala	His	Gln	Leu	Asp	Gln	Leu
1325						1330					1335			
Arg	Glu	Thr	Met	His	Asn	Met	Gln	Leu	Glu	Val	Asp	Leu	Leu	Lys
1340						1345					1350			
Ala	Glu	Asn	Asp	Arg	Leu	Lys	Val	Ala	Pro	Gly	Pro	Ser	Ser	Gly
1355						1360					1365			
Ser	Thr	Pro	Gly	Gln	Val	Pro	Gly	Ser	Ser	Ala	Leu	Ser	Ser	Pro
1370						1375					1380			

## ES 2 534 734 A1

Arg	Arg	Ser	Leu	Gly	Leu	Ala	Leu	Thr	His	Ser	Phe	Gly	Pro	Ser
	1385					1390					1395			
Leu	Ala	Asp	Thr	Asp	Leu	Ser	Pro	Met	Asp	Gly	Ile	Ser	Thr	Cys
	1400					1405					1410			
Gly	Pro	Lys	Glu	Glu	Val	Thr	Leu	Arg	Val	Val	Val	Arg	Met	Pro
	1415					1420					1425			
Pro	Gln	His	Ile	Ile	Lys	Gly	Asp	Leu	Lys	Gln	Gln	Glu	Phe	Phe
	1430					1435					1440			
Leu	Gly	Cys	Ser	Lys	Val	Ser	Gly	Lys	Val	Asp	Trp	Lys	Met	Leu
	1445					1450					1455			
Asp	Glu	Ala	Val	Phe	Gln	Val	Phe	Lys	Asp	Tyr	Ile	Ser	Lys	Met
	1460					1465					1470			
Asp	Pro	Ala	Ser	Thr	Leu	Gly	Leu	Ser	Thr	Glu	Ser	Ile	His	Gly
	1475					1480					1485			
Tyr	Ser	Ile	Ser	His	Val	Lys	Arg	Val	Leu	Asp	Ala	Glu	Pro	Pro
	1490					1495					1500			
Glu	Met	Pro	Pro	Cys	Arg	Arg	Gly	Val	Asn	Asn	Ile	Ser	Val	Ser
	1505					1510					1515			
Leu	Lys	Gly	Leu	Lys	Glu	Lys	Cys	Val	Asp	Ser	Leu	Val	Phe	Glu
	1520					1525					1530			
Thr	Leu	Ile	Pro	Lys	Pro	Met	Met	Gln	His	Tyr	Ile	Ser	Leu	Leu
	1535					1540					1545			
Leu	Lys	His	Arg	Arg	Leu	Val	Leu	Ser	Gly	Pro	Ser	Gly	Thr	Gly
	1550					1555					1560			
Lys	Thr	Tyr	Leu	Thr	Asn	Arg	Leu	Ala	Glu	Tyr	Leu	Val	Glu	Arg
	1565					1570					1575			
Ser	Gly	Arg	Glu	Val	Thr	Glu	Gly	Ile	Val	Ser	Thr	Phe	Asn	Met
	1580					1585					1590			
His	Gln	Gln	Ser	Cys	Lys	Asp	Leu	Gln	Leu	Tyr	Leu	Ser	Asn	Leu
	1595					1600					1605			

## ES 2 534 734 A1

Ala	Asn	Gln	Ile	Asp	Arg	Glu	Thr	Gly	Ile	Gly	Asp	Val	Pro	Leu
	1610					1615					1620			
Val	Ile	Leu	Leu	Asp	Asp	Leu	Ser	Glu	Ala	Gly	Ser	Ile	Ser	Glu
	1625					1630					1635			
Leu	Val	Asn	Gly	Ala	Leu	Thr	Cys	Lys	Tyr	His	Lys	Cys	Pro	Tyr
	1640					1645					1650			
Ile	Ile	Gly	Thr	Thr	Asn	Gln	Pro	Val	Lys	Met	Thr	Pro	Asn	His
	1655					1660					1665			
Gly	Leu	His	Leu	Ser	Phe	Arg	Met	Leu	Thr	Phe	Ser	Asn	Asn	Val
	1670					1675					1680			
Glu	Pro	Ala	Asn	Gly	Phe	Leu	Val	Arg	Tyr	Leu	Arg	Arg	Lys	Leu
	1685					1690					1695			
Val	Glu	Ser	Asp	Ser	Asp	Ile	Asn	Ala	Asn	Lys	Glu	Glu	Leu	Leu
	1700					1705					1710			
Arg	Val	Leu	Asp	Trp	Val	Pro	Lys	Leu	Trp	Tyr	His	Leu	His	Thr
	1715					1720					1725			
Phe	Leu	Glu	Lys	His	Ser	Thr	Ser	Asp	Phe	Leu	Ile	Gly	Pro	Cys
	1730					1735					1740			
Phe	Phe	Leu	Ser	Cys	Pro	Ile	Gly	Ile	Glu	Asp	Phe	Arg	Thr	Trp
	1745					1750					1755			
Phe	Ile	Asp	Leu	Trp	Asn	Asn	Ser	Ile	Ile	Pro	Tyr	Leu	Gln	Glu
	1760					1765					1770			
Gly	Ala	Lys	Asp	Gly	Ile	Lys	Val	His	Gly	Gln	Lys	Ala	Ala	Trp
	1775					1780					1785			
Glu	Asp	Pro	Val	Glu	Trp	Val	Arg	Asp	Thr	Leu	Pro	Trp	Pro	Ser
	1790					1795					1800			
Ala	Gln	Gln	Asp	Gln	Ser	Lys	Leu	Tyr	His	Leu	Pro	Pro	Pro	Thr
	1805					1810					1815			
Val	Gly	Pro	His	Ser	Ile	Ala	Ser	Pro	Pro	Glu	Asp	Arg	Thr	Val
	1820					1825					1830			



# ES 2 534 734 A1

Lys Asp Ser Thr Pro Ser Ser Leu Asp Ser Asp Pro Leu Met Ala  
 1835 1840 1845

Met Leu Leu Lys Leu Gln Glu Ala Ala Asn Tyr Ile Glu Ser Pro  
 1850 1855 1860

Asp Arg Glu Thr Ile Leu Asp Pro Asn Leu Gln Ala Thr Leu  
 1865 1870 1875

<210> 104  
 <211> 1483  
 <212> PRT  
 <213> Homo sapiens

<400> 104

Met Leu His Leu Pro Leu Pro Arg Ser Gly Arg Thr Val Asn Phe Pro  
 1 5 10 15

Arg Ser Trp Asp Glu Ser Ser Ser Ile Ser Ser Gly Leu Ser Asp Ala  
 20 25 30

Ser Asp Asn Leu Ser Ser Glu Glu Phe Asn Ala Ser Ser Ser Leu Asn  
 35 40 45

Ser Leu Pro Ser Thr Pro Thr Ala Ser Arg Arg Asn Ser Thr Ile Val  
 50 55 60

Leu Arg Thr Asp Ser Glu Lys Arg Ser Leu Ala Glu Ser Gly Leu Ser  
 65 70 75 80

Trp Phe Ser Glu Ser Glu Glu Lys Ala Pro Lys Lys Leu Glu Tyr Asp  
 85 90 95

Ser Gly Ser Leu Lys Met Glu Pro Gly Thr Ser Lys Trp Arg Arg Glu  
 100 105 110

Arg Pro Glu Ser Cys Asp Asp Ser Ser Lys Gly Gly Glu Leu Lys Lys  
 115 120 125

Pro Ile Ser Leu Gly His Pro Gly Ser Leu Lys Lys Gly Lys Thr Pro  
 130 135 140

Pro Val Ala Val Thr Ser Pro Ile Thr His Thr Ala Gln Ser Ala Leu  
 145 150 155 160

# ES 2 534 734 A1

Lys Val Ala Gly Lys Pro Glu Gly Lys Ala Thr Asp Lys Gly Lys Leu  
 165 170 175

Ala Val Lys Asn Thr Gly Leu Gln Arg Ser Ser Ser Asp Ala Gly Arg  
 180 185 190

Asp Arg Leu Ser Asp Ala Lys Lys Pro Pro Ser Gly Ile Ala Arg Pro  
 195 200 205

Ser Thr Ser Gly Ser Phe Gly Tyr Lys Lys Pro Pro Pro Ala Thr Gly  
 210 215 220

Thr Ala Thr Val Met Gln Thr Gly Gly Ser Ala Thr Leu Ser Lys Ile  
 225 230 235 240

Gln Lys Ser Ser Gly Ile Pro Val Lys Pro Val Asn Gly Arg Lys Thr  
 245 250 255

Ser Leu Asp Val Ser Asn Ser Ala Glu Pro Gly Phe Leu Ala Pro Gly  
 260 265 270

Ala Arg Ser Asn Ile Gln Tyr Arg Ser Leu Pro Arg Pro Ala Lys Ser  
 275 280 285

Ser Ser Met Ser Val Thr Gly Gly Arg Gly Gly Pro Arg Pro Val Ser  
 290 295 300

Ser Ser Ile Asp Pro Ser Leu Leu Ser Thr Lys Gln Gly Gly Leu Thr  
 305 310 315 320

Pro Ser Arg Leu Lys Glu Pro Thr Lys Val Ala Ser Gly Arg Thr Thr  
 325 330 335

Pro Ala Pro Val Asn Gln Thr Asp Arg Glu Lys Glu Lys Ala Lys Ala  
 340 345 350

Lys Ala Val Ala Leu Asp Ser Asp Asn Ile Ser Leu Lys Ser Ile Gly  
 355 360 365

Ser Pro Glu Ser Thr Pro Lys Asn Gln Ala Ser His Pro Thr Ala Thr  
 370 375 380

Lys Leu Ala Glu Leu Pro Pro Thr Pro Leu Arg Ala Thr Ala Lys Ser  
 385 390 395 400

# ES 2 534 734 A1

Phe Val Lys Pro Pro Ser Leu Ala Asn Leu Asp Lys Val Asn Ser Asn  
 405 410 415

Ser Leu Asp Leu Pro Ser Ser Ser Asp Thr Thr His Ala Ser Lys Val  
 420 425 430

Pro Asp Leu His Ala Thr Ser Ser Ala Ser Gly Gly Pro Leu Pro Ser  
 435 440 445

Cys Phe Thr Pro Ser Pro Ala Pro Ile Leu Asn Ile Asn Ser Ala Ser  
 450 455 460

Phe Ser Gln Gly Leu Glu Leu Met Ser Gly Phe Ser Val Pro Lys Glu  
 465 470 475 480

Thr Arg Met Tyr Pro Lys Leu Ser Gly Leu His Arg Ser Met Glu Ser  
 485 490 495

Leu Gln Met Pro Met Ser Leu Pro Ser Ala Phe Pro Ser Ser Thr Pro  
 500 505 510

Val Pro Thr Pro Pro Ala Pro Pro Ala Ala Pro Thr Glu Glu Glu Thr  
 515 520 525

Glu Glu Leu Thr Trp Ser Gly Ser Pro Arg Ala Gly Gln Leu Asp Ser  
 530 535 540

Asn Gln Arg Asp Arg Asn Thr Leu Pro Lys Lys Gly Leu Arg Tyr Gln  
 545 550 555 560

Leu Gln Ser Gln Glu Glu Thr Lys Glu Arg Arg His Ser His Thr Ile  
 565 570 575

Gly Gly Leu Pro Glu Ser Asp Asp Gln Ser Glu Leu Pro Ser Pro Pro  
 580 585 590

Ala Leu Pro Met Ser Leu Ser Ala Lys Gly Gln Leu Thr Asn Ile Val  
 595 600 605

Ser Pro Thr Ala Ala Thr Thr Pro Arg Ile Thr Arg Ser Asn Ser Ile  
 610 615 620

Pro Thr His Glu Ala Ala Phe Glu Leu Tyr Ser Gly Ser Gln Met Gly  
 625 630 635 640

# ES 2 534 734 A1

Ser Thr Leu Ser Leu Ala Glu Arg Pro Lys Gly Met Ile Arg Ser Gly  
 645 650 655

Ser Phe Arg Asp Pro Thr Asp Asp Val His Gly Ser Val Leu Ser Leu  
 660 665 670

Ala Ser Ser Ala Ser Ser Thr Tyr Ser Ser Ala Glu Glu Arg Met Gln  
 675 680 685

Ser Glu Gln Ile Arg Lys Leu Arg Arg Glu Leu Glu Ser Ser Gln Glu  
 690 695 700

Lys Val Ala Thr Leu Thr Ser Gln Leu Ser Ala Asn Ala Asn Leu Val  
 705 710 715 720

Ala Ala Phe Glu Gln Ser Leu Val Asn Met Thr Ser Arg Leu Arg His  
 725 730 735

Leu Ala Glu Thr Ala Glu Glu Lys Asp Thr Glu Leu Leu Asp Leu Arg  
 740 745 750

Glu Thr Ile Asp Phe Leu Lys Lys Lys Asn Ser Glu Ala Gln Ala Val  
 755 760 765

Ile Gln Gly Ala Leu Asn Ala Ser Glu Thr Thr Pro Lys Glu Leu Arg  
 770 775 780

Ile Lys Arg Gln Asn Ser Ser Asp Ser Ile Ser Ser Leu Asn Ser Ile  
 785 790 795 800

Thr Ser His Ser Ser Ile Gly Ser Ser Lys Asp Ala Asp Ala Lys Lys  
 805 810 815

Lys Lys Lys Lys Ser Trp Leu Arg Ser Ser Phe Asn Lys Ala Phe Ser  
 820 825 830

Ile Lys Lys Gly Pro Lys Ser Ala Ser Ser Tyr Ser Asp Ile Glu Glu  
 835 840 845

Ile Ala Thr Pro Asp Ser Ser Ala Pro Ser Ser Pro Lys Leu Gln His  
 850 855 860

Gly Ser Thr Glu Thr Ala Ser Pro Ser Ile Lys Ser Ser Thr Ser Ser  
 865 870 875 880

# ES 2 534 734 A1

Ser Val Gly Thr Asp Val Thr Glu Gly Pro Ala His Pro Ala Pro His  
 885 890 895

Thr Arg Leu Phe His Ala Asn Glu Glu Glu Glu Pro Glu Lys Lys Glu  
 900 905 910

Val Ser Glu Leu Arg Ser Glu Leu Trp Glu Lys Glu Met Lys Leu Thr  
 915 920 925

Asp Ile Arg Leu Glu Ala Leu Asn Ser Ala His Gln Leu Asp Gln Leu  
 930 935 940

Arg Glu Thr Met His Asn Met Gln Leu Glu Val Asp Leu Leu Lys Ala  
 945 950 955 960

Glu Asn Asp Arg Leu Lys Val Ala Pro Gly Pro Ser Ser Gly Ser Thr  
 965 970 975

Pro Gly Gln Val Pro Gly Ser Ser Ala Leu Ser Ser Pro Arg Arg Ser  
 980 985 990

Leu Gly Leu Ala Leu Thr His Ser Phe Gly Pro Ser Leu Ala Asp Thr  
 995 1000 1005

Asp Leu Ser Pro Met Asp Gly Ile Ser Thr Cys Gly Pro Lys Glu  
 1010 1015 1020

Glu Val Thr Leu Arg Val Val Val Arg Met Pro Pro Gln His Ile  
 1025 1030 1035

Ile Lys Gly Asp Leu Lys Gln Gln Glu Phe Phe Leu Gly Cys Ser  
 1040 1045 1050

Lys Val Ser Gly Lys Val Asp Trp Lys Met Leu Asp Glu Ala Val  
 1055 1060 1065

Phe Gln Val Phe Lys Asp Tyr Ile Ser Lys Met Asp Pro Ala Ser  
 1070 1075 1080

Thr Leu Gly Leu Ser Thr Glu Ser Ile His Gly Tyr Ser Ile Ser  
 1085 1090 1095

His Val Lys Arg Val Leu Asp Ala Glu Pro Pro Glu Met Pro Pro  
 1100 1105 1110

## ES 2 534 734 A1

Cys	Arg	Arg	Gly	Val	Asn	Asn	Ile	Ser	Val	Ser	Leu	Lys	Gly	Leu
1115						1120					1125			
Lys	Glu	Lys	Cys	Val	Asp	Ser	Leu	Val	Phe	Glu	Thr	Leu	Ile	Pro
1130						1135					1140			
Lys	Pro	Met	Met	Gln	His	Tyr	Ile	Ser	Leu	Leu	Leu	Lys	His	Arg
1145						1150					1155			
Arg	Leu	Val	Leu	Ser	Gly	Pro	Ser	Gly	Thr	Gly	Lys	Thr	Tyr	Leu
1160						1165					1170			
Thr	Asn	Arg	Leu	Ala	Glu	Tyr	Leu	Val	Glu	Arg	Ser	Gly	Arg	Glu
1175						1180					1185			
Val	Thr	Glu	Gly	Ile	Val	Ser	Thr	Phe	Asn	Met	His	Gln	Gln	Ser
1190						1195					1200			
Cys	Lys	Asp	Leu	Gln	Leu	Tyr	Leu	Ser	Asn	Leu	Ala	Asn	Gln	Ile
1205						1210					1215			
Asp	Arg	Glu	Thr	Gly	Ile	Gly	Asp	Val	Pro	Leu	Val	Ile	Leu	Leu
1220						1225					1230			
Asp	Asp	Leu	Ser	Glu	Ala	Gly	Ser	Ile	Ser	Glu	Leu	Val	Asn	Gly
1235						1240					1245			
Ala	Leu	Thr	Cys	Lys	Tyr	His	Lys	Cys	Pro	Tyr	Ile	Ile	Gly	Thr
1250						1255					1260			
Thr	Asn	Gln	Pro	Val	Lys	Met	Thr	Pro	Asn	His	Gly	Leu	His	Leu
1265						1270					1275			
Ser	Phe	Arg	Met	Leu	Thr	Phe	Ser	Asn	Asn	Val	Glu	Pro	Ala	Asn
1280						1285					1290			
Gly	Phe	Leu	Val	Arg	Tyr	Leu	Arg	Arg	Lys	Leu	Val	Glu	Ser	Asp
1295						1300					1305			
Ser	Asp	Ile	Asn	Ala	Asn	Lys	Glu	Glu	Leu	Leu	Arg	Val	Leu	Asp
1310						1315					1320			
Trp	Val	Pro	Lys	Leu	Trp	Tyr	His	Leu	His	Thr	Phe	Leu	Glu	Lys
1325						1330					1335			

# ES 2 534 734 A1

His Ser Thr Ser Asp Phe Leu Ile Gly Pro Cys Phe Phe Leu Ser  
 1340 1345 1350

Cys Pro Ile Gly Ile Glu Asp Phe Arg Thr Trp Phe Ile Asp Leu  
 1355 1360 1365

Trp Asn Asn Ser Ile Ile Pro Tyr Leu Gln Glu Gly Ala Lys Asp  
 1370 1375 1380

Gly Ile Lys Val His Gly Gln Lys Ala Ala Trp Glu Asp Pro Val  
 1385 1390 1395

Glu Trp Val Arg Asp Thr Leu Pro Trp Pro Ser Ala Gln Gln Asp  
 1400 1405 1410

Gln Ser Lys Leu Tyr His Leu Pro Pro Pro Thr Val Gly Pro His  
 1415 1420 1425

Ser Ile Ala Ser Pro Pro Glu Asp Arg Thr Val Lys Asp Ser Thr  
 1430 1435 1440

Pro Ser Ser Leu Asp Ser Asp Pro Leu Met Ala Met Leu Leu Lys  
 1445 1450 1455

Leu Gln Glu Ala Ala Asn Tyr Ile Glu Ser Pro Asp Arg Glu Thr  
 1460 1465 1470

Ile Leu Asp Pro Asn Leu Gln Ala Thr Leu  
 1475 1480

<210> 105  
 <211> 931  
 <212> PRT  
 <213> Homo sapiens

<400> 105

Met Lys Ile Gln Lys Lys Leu Thr Gly Cys Ser Arg Leu Met Leu Leu  
 1 5 10 15

Cys Leu Ser Leu Glu Leu Leu Leu Glu Ala Gly Ala Gly Asn Ile His  
 20 25 30

Tyr Ser Val Pro Glu Glu Thr Asp Lys Gly Ser Phe Val Gly Asn Ile  
 35 40 45

# ES 2 534 734 A1

Ala Lys Asp Leu Gly Leu Gln Pro Gln Glu Leu Ala Asp Gly Gly Val  
50 55 60

Arg Ile Val Ser Arg Gly Arg Met Pro Leu Phe Ala Leu Asn Pro Arg  
65 70 75 80

Ser Gly Ser Leu Ile Thr Ala Arg Arg Ile Asp Arg Glu Glu Leu Cys  
85 90 95

Ala Gln Ser Met Pro Cys Leu Val Ser Phe Asn Ile Leu Val Glu Asp  
100 105 110

Lys Met Lys Leu Phe Pro Val Glu Val Glu Ile Ile Asp Ile Asn Asp  
115 120 125

Asn Thr Pro Gln Phe Gln Leu Glu Glu Leu Glu Phe Lys Met Asn Glu  
130 135 140

Ile Thr Thr Pro Gly Thr Arg Val Ser Leu Pro Phe Gly Gln Asp Leu  
145 150 155 160

Asp Val Gly Met Asn Ser Leu Gln Ser Tyr Gln Leu Ser Ser Asn Pro  
165 170 175

His Phe Ser Leu Asp Val Gln Gln Gly Ala Asp Gly Pro Gln His Pro  
180 185 190

Glu Met Val Leu Gln Ser Pro Leu Asp Arg Glu Glu Glu Ala Val His  
195 200 205

His Leu Ile Leu Thr Ala Ser Asp Gly Gly Glu Pro Val Arg Ser Gly  
210 215 220

Thr Leu Arg Ile Tyr Ile Gln Val Val Asp Ala Asn Asp Asn Pro Pro  
225 230 235 240

Ala Phe Thr Gln Ala Gln Tyr His Ile Asn Val Pro Glu Asn Val Pro  
245 250 255

Leu Gly Thr Gln Leu Leu Met Val Asn Ala Thr Asp Pro Asp Glu Gly  
260 265 270

Ala Asn Gly Glu Val Thr Tyr Ser Phe His Asn Val Asp His Arg Val  
275 280 285



# ES 2 534 734 A1

Ala Gln Ile Phe Arg Leu Asp Ser Tyr Thr Gly Glu Ile Ser Asn Lys  
 290 295 300

Glu Pro Leu Asp Phe Glu Glu Tyr Lys Met Tyr Ser Met Glu Val Gln  
 305 310 315 320

Ala Gln Asp Gly Ala Gly Leu Met Ala Lys Val Lys Val Leu Ile Lys  
 325 330 335

Val Leu Asp Val Asn Asp Asn Ala Pro Glu Val Thr Ile Thr Ser Val  
 340 345 350

Thr Thr Ala Val Pro Glu Asn Phe Pro Pro Gly Thr Ile Ile Ala Leu  
 355 360 365

Ile Ser Val His Asp Gln Asp Ser Gly Asp Asn Gly Tyr Thr Thr Cys  
 370 375 380

Phe Ile Pro Gly Asn Leu Pro Phe Lys Leu Glu Lys Leu Val Asp Asn  
 385 390 395 400

Tyr Tyr Arg Leu Val Thr Glu Arg Thr Leu Asp Arg Glu Leu Ile Ser  
 405 410 415

Gly Tyr Asn Ile Thr Ile Thr Ala Ile Asp Gln Gly Thr Pro Ala Leu  
 420 425 430

Ser Thr Glu Thr His Ile Ser Leu Leu Val Thr Asp Ile Asn Asp Asn  
 435 440 445

Ser Pro Val Phe His Gln Asp Ser Tyr Ser Ala Tyr Ile Pro Glu Asn  
 450 455 460

Asn Pro Arg Gly Ala Ser Ile Phe Ser Val Arg Ala His Asp Leu Asp  
 465 470 475 480

Ser Asn Glu Asn Ala Gln Ile Thr Tyr Ser Leu Ile Glu Asp Thr Ile  
 485 490 495

Gln Gly Ala Pro Leu Ser Ala Tyr Leu Ser Ile Asn Ser Asp Thr Gly  
 500 505 510

Val Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln Phe Arg Asp Met  
 515 520 525

# ES 2 534 734 A1

Gln Leu Lys Val Met Ala Arg Asp Ser Gly Asp Pro Pro Leu Ser Ser  
 530 535 540

Asn Val Ser Leu Ser Leu Phe Leu Leu Asp Gln Asn Asp Asn Ala Pro  
 545 550 555 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu  
 565 570 575

Leu Ala Pro Leu Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu  
 595 600 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly  
 610 615 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln  
 625 630 635 640

Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala  
 645 650 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Arg Ile Ser Asp Ile Leu  
 660 665 670

Ala Asp Leu Gly Ser Leu Glu Pro Ser Ala Lys Pro Asn Asp Ser Asp  
 675 680 685

Leu Thr Leu Tyr Leu Val Val Ala Ala Ala Ala Val Ser Cys Val Phe  
 690 695 700

Leu Ala Phe Val Ile Val Leu Leu Ala His Arg Leu Arg Arg Trp His  
 705 710 715 720

Lys Ser Arg Leu Leu Gln Ala Ser Gly Gly Gly Leu Ala Ser Met Pro  
 725 730 735

Gly Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr  
 740 745 750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu  
 755 760 765

# ES 2 534 734 A1

Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile Ser Gln Glu Ser  
 770 775 780

Cys Glu Lys Lys Gly Phe Leu Ser Ala Pro Gln Ser Leu Leu Glu Asp  
 785 790 795 800

Lys Lys Glu Pro Phe Ser Gln Gln Ala Pro Pro Asn Thr Asp Trp Arg  
 805 810 815

Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp  
 820 825 830

Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln  
 835 840 845

Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr  
 850 855 860

Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro  
 865 870 875 880

Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile  
 885 890 895

Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly  
 900 905 910

Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys  
 915 920 925

Glu Lys Lys  
 930

<210> 106  
 <211> 932  
 <212> PRT  
 <213> Homo sapiens

<400> 106

Met Ala Ala Leu Gln Lys Leu Pro His Cys Arg Lys Leu Val Leu Leu  
 1 5 10 15

Cys Phe Leu Leu Ala Thr Leu Trp Glu Ala Arg Ala Gly Gln Ile Arg  
 20 25 30

# ES 2 534 734 A1

Tyr Ser Val Arg Glu Glu Ile Asp Arg Gly Ser Phe Val Gly Asn Ile  
 35 40 45

Ala Lys Asp Leu Gly Leu Glu Pro Leu Ala Leu Ala Glu Gln Gly Val  
 50 55 60

Arg Ile Val Ser Arg Gly Arg Ser Gln Leu Phe Ala Leu Asn Pro Arg  
 65 70 75 80

Ser Gly Ser Leu Val Thr Ala Asn Arg Ile Asp Arg Glu Glu Leu Cys  
 85 90 95

Ala Gln Ser Ala Pro Cys Leu Leu Asn Phe Asn Ile Leu Leu Glu Asp  
 100 105 110

Lys Leu Thr Ile Tyr Ser Val Glu Val Glu Ile Thr Asp Ile Asn Asp  
 115 120 125

Asn Ala Pro Arg Phe Gly Val Glu Glu Leu Glu Leu Lys Ile Ser Glu  
 130 135 140

Thr Thr Thr Pro Gly Phe Arg Ile Pro Leu Lys Asn Ala His Asp Ala  
 145 150 155 160

Asp Val Gly Glu Asn Ala Leu Gln Lys Tyr Ala Leu Asn Pro Asn Asp  
 165 170 175

His Phe Ser Leu Asp Val Arg Arg Gly Ala Asp Gly Asn Lys Tyr Pro  
 180 185 190

Glu Leu Val Leu Glu Arg Ser Leu Asp Arg Glu Glu Glu Ala Val His  
 195 200 205

His Leu Val Leu Val Ala Ser Asp Gly Gly Asp Pro Val Leu Ser Gly  
 210 215 220

Thr Ser Arg Ile Cys Val Lys Val Leu Asp Ala Asn Asp Asn Ala Pro  
 225 230 235 240

Val Phe Thr Gln Pro Glu Tyr Arg Ile Ser Ile Pro Glu Asn Thr Leu  
 245 250 255

Val Gly Thr Arg Ile Leu Thr Val Thr Ala Thr Asp Ala Asp Glu Gly  
 260 265 270

# ES 2 534 734 A1

Tyr Tyr Ala Gln Val Val Tyr Phe Leu Glu Lys Ser Pro Gly Glu Thr  
 275 280 285

Ser Glu Val Phe Glu Leu Lys Ser Thr Ser Gly Glu Leu Thr Ile Ile  
 290 295 300

Lys Asp Leu Asp Tyr Glu Asp Ala Thr Phe His Glu Ile Asp Ile Glu  
 305 310 315 320

Ala Gln Asp Gly Pro Gly Leu Leu Thr Arg Ala Lys Val Ile Val Thr  
 325 330 335

Val Leu Asp Val Asn Asp Asn Ala Pro Glu Phe Tyr Met Thr Ser Ala  
 340 345 350

Thr Ser Ser Val Ser Glu Asp Ser Leu Pro Gly Thr Ile Ile Gly Leu  
 355 360 365

Phe Asn Val His Asp Arg Asp Ser Gly Gln Asn Ala Phe Thr Thr Cys  
 370 375 380

Ser Leu Pro Glu Asp Leu Pro Phe Lys Leu Glu Lys Ser Val Asp Asn  
 385 390 395 400

Tyr Tyr Arg Leu Val Thr Thr Arg Ala Leu Asp Arg Glu Gln Phe Ser  
 405 410 415

Phe Tyr Asn Ile Thr Leu Thr Ala Lys Asp Gly Gly Asn Pro Ser Leu  
 420 425 430

Ser Thr Asp Ala His Ile Leu Leu Gln Val Ala Asp Ile Asn Asp Asn  
 435 440 445

Ala Pro Ala Phe Ser Arg Thr Ser Tyr Ser Thr Tyr Ile Pro Glu Asn  
 450 455 460

Asn Pro Arg Gly Ala Ser Val Phe Ser Val Thr Ala His Asp Pro Asp  
 465 470 475 480

Ser Asn Asp Asn Ala His Val Thr Tyr Ser Phe Ala Glu Asp Thr Val  
 485 490 495

Gln Gly Ala Pro Leu Ser Ser Tyr Ile Ser Ile Asn Ser Asp Thr Gly  
 500 505 510

# ES 2 534 734 A1

Val Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln Leu Arg Asp Leu  
 515 520 525

Gln Val Trp Val Ile Ala Arg Asp Ser Gly Asn Pro Pro Leu Ser Ser  
 530 535 540

Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala Pro  
 545 550 555 560

Glu Ile Leu Tyr Pro Ala Phe Pro Thr Asp Gly Ser Thr Gly Val Glu  
 565 570 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr His Leu  
 595 600 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly  
 610 615 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln  
 625 630 635 640

Ser Leu Val Val Ala Ile Gln Asp His Gly Gln Pro Pro Leu Ser Ala  
 645 650 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Arg Ile Pro Asp Ile Leu  
 660 665 670

Ala Asp Leu Gly Ser Leu Glu Pro Ser Ala Ile Pro Asn Asp Ser Asp  
 675 680 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val Ser Cys Val Phe  
 690 695 700

Leu Ala Phe Val Ile Val Leu Leu Ala His Arg Leu Arg Arg Trp His  
 705 710 715 720

Lys Ser Arg Leu Leu Gln Ala Ser Gly Gly Ser Leu Thr Gly Met Gln  
 725 730 735

Ser Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr  
 740 745 750

ES 2 534 734 A1

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu  
 755 760 765

Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile Ser Gln Glu Ser  
 770 775 780

Cys Glu Lys Lys Asp Phe Leu Ser Ala Pro Gln Ser Leu Leu Glu Glu  
 785 790 795 800

Glu Arg Glu Glu Thr Phe Ser Gln Gln Ala Pro Pro Asn Thr Asp Trp  
 805 810 815

Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly  
 820 825 830

Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu  
 835 840 845

Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser  
 850 855 860

Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly  
 865 870 875 880

Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr  
 885 890 895

Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp  
 900 905 910

Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys  
 915 920 925

Lys Glu Lys Lys  
 930

<210> 107  
 <211> 927  
 <212> PRT  
 <213> Homo sapiens

<400> 107

Met Gln Arg Ala Arg Glu Ala Glu Met Met Lys Ser Gln Val Leu Phe  
 1 5 10 15

# ES 2 534 734 A1

Pro Phe Leu Leu Ser Leu Phe Cys Gly Ala Ile Ser Gln Gln Ile Arg  
 20 25 30

Tyr Thr Ile Pro Glu Glu Leu Ala Asn Gly Ser Arg Val Gly Lys Leu  
 35 40 45

Ala Lys Asp Leu Gly Leu Ser Val Arg Glu Leu Pro Thr Arg Lys Leu  
 50 55 60

Arg Val Ser Ala Glu Asp Tyr Phe Asn Val Ser Leu Glu Ser Gly Asp  
 65 70 75 80

Leu Leu Val Asn Gly Arg Ile Asp Arg Glu Lys Ile Cys Gly Arg Lys  
 85 90 95

Leu Glu Cys Ala Leu Glu Phe Glu Thr Val Ala Glu Asn Pro Met Asn  
 100 105 110

Val Phe His Val Val Val Val Ile Gln Asp Ile Asn Asp Asn Ala Pro  
 115 120 125

Arg Phe Val Ala Lys Gly Ile Asp Leu Glu Ile Cys Glu Ser Ala Leu  
 130 135 140

Pro Gly Val Lys Phe Ser Leu Asp Ser Ala Gln Asp Ala Asp Val Glu  
 145 150 155 160

Gly Asn Ser Leu Lys Leu Tyr Thr Ile Asn Pro Asn Gln Tyr Phe Ser  
 165 170 175

Leu Ser Thr Lys Glu Ser Pro Asp Gly Ser Lys Tyr Pro Val Leu Leu  
 180 185 190

Leu Glu Lys Pro Leu Asp Arg Glu His Gln Ser Ser His Arg Leu Ile  
 195 200 205

Leu Thr Ala Met Asp Gly Gly Asp Pro Pro Leu Ser Gly Thr Thr His  
 210 215 220

Ile Trp Ile Arg Val Thr Asp Ala Asn Asp Asn Ala Pro Val Phe Ser  
 225 230 235 240

Gln Glu Val Tyr Arg Val Ser Leu Gln Glu Asn Val Pro Trp Gly Thr  
 245 250 255



# ES 2 534 734 A1

Ser Val Leu Arg Val Met Ala Thr Asp Gln Asp Glu Gly Ile Asn Ala  
 260 265 270

Glu Ile Thr Tyr Ala Phe Leu Asn Ser Pro Ile Ser Thr Ser Leu Phe  
 275 280 285

Asn Leu Asn Pro Asn Thr Gly Asp Ile Thr Thr Asn Gly Thr Leu Asp  
 290 295 300

Phe Glu Glu Thr Ser Arg Tyr Val Leu Ser Val Glu Ala Lys Asp Gly  
 305 310 315 320

Gly Val His Thr Ala His Cys Asn Val Gln Ile Glu Ile Val Asp Glu  
 325 330 335

Asn Asp Asn Ala Pro Glu Val Thr Phe Met Ser Phe Ser Asn Gln Ile  
 340 345 350

Pro Glu Asp Ser Asp Leu Gly Thr Val Ile Ala Leu Ile Lys Val Arg  
 355 360 365

Asp Lys Asp Ser Gly Gln Asn Gly Met Val Thr Cys Tyr Thr Gln Glu  
 370 375 380

Glu Val Pro Phe Lys Leu Glu Ser Thr Ser Lys Asn Tyr Tyr Lys Leu  
 385 390 395 400

Val Ile Ala Gly Ala Leu Asn Arg Glu Gln Thr Ala Asp Tyr Asn Val  
 405 410 415

Thr Ile Ile Ala Thr Asp Lys Gly Lys Pro Ala Leu Ser Ser Arg Thr  
 420 425 430

Ser Ile Thr Leu His Ile Ser Asp Ile Asn Asp Asn Ala Pro Val Phe  
 435 440 445

His Gln Ala Ser Tyr Val Val His Val Ser Glu Asn Asn Pro Pro Gly  
 450 455 460

Ala Ser Ile Ala Gln Val Ser Ala Ser Asp Pro Asp Leu Gly Pro Asn  
 465 470 475 480

Gly Arg Val Ser Tyr Ser Ile Leu Ala Ser Asp Leu Glu Pro Arg Glu  
 485 490 495

# ES 2 534 734 A1

Leu Leu Ser Tyr Val Ser Val Ser Pro Gln Ser Gly Val Val Phe Ala  
 500 505 510

Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe Glu Leu Thr Leu  
 515 520 525

Gln Ala Arg Asp Gln Gly Ser Pro Ala Leu Ser Ala Asn Val Ser Leu  
 530 535 540

Arg Val Leu Val Gly Asp Leu Asn Asp Asn Ala Pro Arg Val Leu Tyr  
 545 550 555 560

Pro Ala Leu Gly Pro Asp Gly Ser Ala Leu Phe Asp Met Val Pro Arg  
 565 570 575

Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val Ala Val Asp Ala  
 580 585 590

Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val Leu Gln Ala Ser  
 595 600 605

Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly Glu Val Arg Thr  
 610 615 620

Ala Arg Ala Leu Gly Asp Arg Asp Ala Ala Arg Gln Arg Leu Leu Val  
 625 630 635 640

Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala Thr Ala Thr Leu  
 645 650 655

His Leu Ile Phe Ala Asp Ser Leu Gln Glu Val Leu Pro Asp Leu Ser  
 660 665 670

Asp Arg Pro Glu Pro Ser Asp Pro Gln Thr Glu Leu Gln Phe Tyr Leu  
 675 680 685

Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu Leu Ala Val Ile  
 690 695 700

Leu Ala Ile Ala Leu Arg Leu Arg Arg Ser Ser Ser Leu Asp Thr Glu  
 705 710 715 720

Gly Cys Phe Gln Thr Gly Leu Cys Ser Lys Ser Gly Pro Gly Val Pro  
 725 730 735

# ES 2 534 734 A1

Pro Asn His Ser Glu Gly Thr Leu Pro Tyr Ser Tyr Asn Leu Cys Ile  
740 745 750

Ala Ser His Ser Ala Lys Thr Glu Phe Asn Ser Leu Asn Leu Thr Pro  
755 760 765

Glu Met Ala Pro Pro Gln Asp Leu Leu Cys Asp Asp Pro Ser Met Val  
770 775 780

Val Cys Ala Ser Asn Glu Asp His Lys Ile Ala Tyr Asp Pro Ser Leu  
785 790 795 800

Ser Ser His Gln Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser Gln Ala  
805 810 815

Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr Gly Thr  
820 825 830

Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln Ala Met Ile Leu  
835 840 845

Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly Gly Gly  
850 855 860

Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe Thr Leu  
865 870 875 880

Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly Ser Asn  
885 890 895

Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala Pro Ala  
900 905 910

Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys Lys  
915 920 925

<210> 108

<211> 931

<212> PRT

<213> Homo sapiens

<400> 108

Met Ala Ala Pro Pro Ala Arg Pro Asp His Thr Arg Leu Leu Gln Ile  
1 5 10 15

# ES 2 534 734 A1

Cys Leu Leu Leu Gly Val Leu Val Glu Ile Arg Ala Glu Gln Ile Leu  
 20 25 30

Tyr Ser Val Phe Glu Glu Gln Glu Glu Gly Ser Val Val Gly Asn Ile  
 35 40 45

Ala Lys Asp Leu Gly Leu Ala Pro Arg Glu Leu Ala Glu Arg Gly Val  
 50 55 60

Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ala Leu Asn Pro Arg  
 65 70 75 80

Ser Gly Thr Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys  
 85 90 95

Asp Arg Ser Pro Asn Cys Val Thr Asn Leu Glu Ile Leu Leu Glu Asp  
 100 105 110

Thr Val Lys Ile Leu Arg Val Glu Val Glu Ile Ile Asp Val Asn Asp  
 115 120 125

Asn Pro Pro Ser Phe Gly Thr Glu Gln Arg Glu Ile Lys Val Ala Glu  
 130 135 140

Asn Glu Asn Pro Gly Ala Arg Phe Pro Leu Pro Glu Ala Phe Asp Pro  
 145 150 155 160

Asp Val Gly Val Asn Ser Leu Gln Gly Tyr Gln Leu Asn Ser Asn Gly  
 165 170 175

Tyr Phe Ser Leu Asp Val Gln Ser Gly Ala Asp Gly Ile Lys Tyr Pro  
 180 185 190

Glu Leu Val Leu Glu Arg Ala Leu Asp Arg Glu Glu Glu Ala Val His  
 195 200 205

His Leu Val Leu Thr Ala Phe Asp Gly Gly Asp Pro Val Arg Ser Gly  
 210 215 220

Thr Ala Arg Ile Leu Ile Ile Leu Val Asp Thr Asn Asp Asn Ala Pro  
 225 230 235 240

Val Phe Thr Gln Pro Glu Tyr His Val Ser Val Arg Glu Asn Val Pro  
 245 250 255

# ES 2 534 734 A1

Val Gly Thr Arg Leu Leu Thr Val Lys Ala Thr Asp Pro Asp Glu Gly  
260 265 270

Ala Asn Gly Asp Val Thr Tyr Ser Phe Arg Lys Val Arg Asp Lys Ile  
275 280 285

Ser Gln Leu Phe Gln Leu Asn Ser Leu Ser Gly Asp Ile Thr Ile Leu  
290 295 300

Gly Gly Leu Asp Tyr Glu Asp Ser Gly Phe Tyr Asp Ile Asp Val Glu  
305 310 315 320

Ala His Asp Gly Pro Gly Leu Arg Ala Arg Ser Lys Val Leu Val Thr  
325 330 335

Val Leu Asp Glu Asn Asp Asn Ala Pro Glu Val Thr Val Thr Ser Leu  
340 345 350

Thr Ser Ser Val Gln Glu Ser Ser Ser Pro Gly Thr Val Ile Ala Leu  
355 360 365

Phe Asn Val His Asp Ser Asp Ser Gly Gly Asn Gly Leu Val Thr Cys  
370 375 380

Ser Ile Pro Asp Asn Leu Pro Phe Thr Leu Glu Lys Thr Tyr Gly Asn  
385 390 395 400

Tyr Tyr Arg Leu Leu Thr His Arg Thr Leu Asp Arg Glu Glu Val Ser  
405 410 415

Glu Tyr Asn Ile Thr Val Thr Ala Thr Asp Gln Gly Thr Pro Pro Leu  
420 425 430

Ser Thr Glu Thr His Ile Ser Leu Gln Val Met Asp Ile Asn Asp Asn  
435 440 445

Pro Pro Thr Phe Pro His Ala Ser Tyr Ser Ala Tyr Ile Pro Glu Asn  
450 455 460

Asn Pro Arg Gly Ala Ser Ile Leu Ser Met Thr Ala Gln Asp Pro Asp  
465 470 475 480

Ser Gly Asp Asn Ala Arg Ile Thr Tyr Ser Leu Ala Glu Asp Thr Phe  
485 490 495

# ES 2 534 734 A1

Gln Gly Ala Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asn Thr Gly  
 500 505 510

Ile Leu Tyr Ala Leu Cys Ser Phe Asp Tyr Glu Gln Phe Arg Asp Leu  
 515 520 525

Gln Leu Leu Met Thr Ala Ser Asp Ser Gly Asp Pro Pro Leu Ser Ser  
 530 535 540

Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Val Pro  
 545 550 555 560

Glu Ile Leu Tyr Pro Thr Phe Pro Thr Asp Gly Ser Thr Gly Val Glu  
 565 570 575

Leu Ala Pro Arg Ser Ala Asp Ser Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Ser Leu  
 595 600 605

Leu Lys Ser Ser Glu Pro Gly Leu Phe Ala Val Gly Leu His Thr Gly  
 610 615 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln  
 625 630 635 640

Arg Leu Val Val Val Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala  
 645 650 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile Pro Asp Val Leu  
 660 665 670

Ala Asp Leu Gly Ser Leu Lys Pro Ser Ala Asp Pro Asp Asp Ser Gly  
 675 680 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val Ser Cys Val Phe  
 690 695 700

Leu Ala Phe Val Thr Val Leu Leu Ala Leu Lys Leu Arg Arg Trp His  
 705 710 715 720

Lys Ser Arg Leu Leu His Ala Glu Gly Ser Arg Leu Ala Gly Val Pro  
 725 730 735

# ES 2 534 734 A1

Ala Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr  
                   740                                  745                                  750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu  
                   755                                  760                                  765

Ile Phe Ser Gln Pro Ser Tyr Ala Asp Thr Leu Ile Ser Arg Glu Ser  
           770                                  775                                  780

Cys Glu Lys Ser Glu Pro Leu Leu Ile Thr Gln Asp Leu Leu Glu Thr  
   785                                  790                                  795                                  800

Lys Gly Asp Pro Asn Leu Gln Gln Ala Pro Pro Asn Thr Asp Trp Arg  
                                   805                                  810                                  815

Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp  
                   820                                  825                                  830

Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln  
           835                                  840                                  845

Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr  
           850                                  855                                  860

Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro  
   865                                  870                                  875                                  880

Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile  
                   885                                  890                                  895

Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly  
                   900                                  905                                  910

Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys  
           915                                  920                                  925

Glu Lys Lys  
   930

- <210> 109
- <211> 931
- <212> PRT
- <213> Homo sapiens
  
- <400> 109

# ES 2 534 734 A1

Met Lys Ala Ser Ser Gly Arg Cys Gly Leu Val Arg Trp Leu Gln Val  
 1 5 10 15  
 Leu Leu Pro Phe Leu Leu Ser Leu Phe Pro Gly Ala Leu Pro Val Gln  
 20 25 30  
 Ile Arg Tyr Ser Ile Pro Glu Glu Leu Ala Lys Asn Ser Val Val Gly  
 35 40 45  
 Asn Leu Ala Lys Asp Leu Gly Leu Ser Val Arg Asp Leu Pro Ala Arg  
 50 55 60  
 Lys Leu Arg Val Ser Ala Glu Lys Glu Tyr Phe Thr Val Asn Pro Glu  
 65 70 75 80  
 Ser Gly Asp Leu Leu Val Ser Asp Arg Ile Asp Arg Glu Gln Ile Cys  
 85 90 95  
 Gly Lys Gln Pro Leu Cys Val Leu Asp Phe Asp Thr Val Ala Glu Asn  
 100 105 110  
 Pro Leu Asn Ile Phe Tyr Ile Ala Val Ile Val Gln Asp Ile Asn Asp  
 115 120 125  
 Asn Thr Pro Leu Phe Lys Gln Thr Lys Ile Asn Leu Lys Ile Gly Glu  
 130 135 140  
 Ser Thr Lys Pro Gly Thr Thr Phe Pro Leu Asp Pro Ala Leu Asp Ser  
 145 150 155 160  
 Asp Val Gly Pro Asn Ser Leu Gln Arg Tyr His Leu Asn Asp Asn Glu  
 165 170 175  
 Tyr Phe Asp Leu Ala Glu Lys Gln Thr Pro Asp Gly Arg Lys Tyr Pro  
 180 185 190  
 Glu Leu Ile Leu Lys His Ser Leu Asp Arg Glu Glu His Ser Leu His  
 195 200 205  
 Gln Leu Val Leu Thr Ala Val Asp Gly Gly Asp Pro Pro Gln Ser Gly  
 210 215 220  
 Thr Thr Gln Ile Arg Ile Lys Val Thr Asp Ala Asn Asp Asn Pro Pro  
 225 230 235 240



# ES 2 534 734 A1

Val Phe Ser Gln Asp Val Tyr Arg Val Thr Leu Arg Glu Asp Val Pro  
 245 250 255

Pro Gly Phe Phe Val Leu Gln Val Thr Ala Thr Asp Arg Asp Glu Gly  
 260 265 270

Ile Asn Ala Glu Ile Thr Tyr Ser Phe His Asn Val Asp Glu Gln Val  
 275 280 285

Lys His Phe Phe Asn Leu Asn Glu Lys Thr Gly Glu Ile Thr Thr Lys  
 290 295 300

Asp Asp Leu Asp Phe Glu Ile Ala Ser Ser Tyr Thr Leu Ser Ile Glu  
 305 310 315 320

Ala Lys Asp Pro Gly Asp Leu Ala Ala His Cys Ser Ile Gln Val Glu  
 325 330 335

Ile Leu Asp Asp Asn Asp Cys Ala Pro Glu Val Ile Val Thr Ser Val  
 340 345 350

Ser Thr Pro Leu Pro Glu Asp Ser Pro Pro Gly Thr Val Ile Ala Leu  
 355 360 365

Ile Lys Thr Arg Asp Arg Asp Ser Gly Glu Asn Gly Glu Val Tyr Cys  
 370 375 380

Gln Val Leu Gly Asn Ala Lys Phe Ile Leu Lys Ser Ser Ser Lys Asn  
 385 390 395 400

Tyr Tyr Lys Leu Val Thr Asp Gly Ala Leu Asp Arg Glu Glu Ile Pro  
 405 410 415

Glu Tyr Asn Leu Thr Ile Thr Ala Thr Asp Gly Gly Lys Pro Pro Leu  
 420 425 430

Ser Ser Ser Ile Ile Val Thr Leu His Ile Ser Asp Val Asn Asp Asn  
 435 440 445

Ala Pro Val Phe Gln Gln Thr Ser Tyr Met Val His Val Ala Glu Asn  
 450 455 460

Asn Pro Pro Gly Ala Ser Ile Ala Gln Ile Ser Ala Ser Asp Pro Asp  
 465 470 475 480

# ES 2 534 734 A1

Leu Gly Pro Ser Gly Gln Val Ser Tyr Ser Ile Val Ala Ser Asp Leu  
                                   485                                  490                                  495

Lys Pro Arg Glu Ile Leu Ser Tyr Val Ser Val Ser Ala Gln Ser Gly  
                                   500                                  505                                  510

Val Val Phe Ala Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe  
                                   515                                  520                                  525

Glu Leu Thr Leu Gln Ala Arg Asp Gln Gly Ser Pro Ala Leu Ser Ala  
                                   530                                  535                                  540

Asn Val Ser Leu Arg Val Leu Val Gly Asp Leu Asn Asp Asn Ala Pro  
                                   545                                  550                                  555                                  560

Arg Val Leu Tyr Pro Ala Leu Gly Pro Asp Gly Ser Ala Leu Phe Asp  
                                   565                                  570                                  575

Met Val Pro Arg Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val  
                                   580                                  585                                  590

Ala Val Asp Ala Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val  
                                   595                                  600                                  605

Leu Gln Ala Ser Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly  
                                   610                                  615                                  620

Glu Val Arg Thr Ala Arg Ala Leu Gly Asp Arg Asp Ala Ala Arg Gln  
                                   625                                  630                                  635                                  640

Arg Leu Leu Val Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala  
                                   645                                  650                                  655

Thr Ala Thr Leu His Leu Ile Phe Ala Asp Ser Leu Gln Glu Val Leu  
                                   660                                  665                                  670

Pro Asp Leu Ser Asp Arg Arg Glu Pro Ser Asp Pro Gln Ala Lys Leu  
                                   675                                  680                                  685

Gln Phe Tyr Leu Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Phe  
                                   690                                  695                                  700

Leu Ala Val Ile Leu Ala Ile Ser Leu Arg Leu Arg Leu Ser Ser Arg  
                                   705                                  710                                  715                                  720

ES 2 534 734 A1

Ser Asp Ala Trp Asp Cys Phe Gln Pro Gly Leu Ser Ser Lys Pro Gly  
 725 730 735

Pro Gly Val Leu Pro Asn Tyr Ser Glu Gly Thr Leu Pro Tyr Ser Tyr  
 740 745 750

Asn Leu Cys Val Ala Ser Gln Ser Ala Lys Thr Glu Phe Asn Phe Leu  
 755 760 765

Asn Ile Thr Pro Glu Leu Val Pro Ala Gln Asp Leu Val Cys Asp Asn  
 770 775 780

Ala Ser Trp Glu Gln Asn Thr Asn His Gly Ala Ala Gly Val Pro Phe  
 785 790 795 800

Ala Ser Asp Thr Ile Leu Lys Gln Ala Pro Pro Asn Thr Asp Trp Arg  
 805 810 815

Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp  
 820 825 830

Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln  
 835 840 845

Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr  
 850 855 860

Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro  
 865 870 875 880

Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile  
 885 890 895

Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly  
 900 905 910

Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys  
 915 920 925

Glu Lys Lys  
 930

<210> 110  
 <211> 931

ES 2 534 734 A1

<212> PRT

<213> Homo sapiens

<400> 110

Met Ala Ser Pro Pro Arg Gly Trp Gly Cys Gly Glu Leu Leu Leu Pro  
1 5 10 15

Phe Met Leu Leu Gly Thr Leu Cys Glu Pro Gly Ser Gly Gln Ile Arg  
20 25 30

Tyr Ser Met Pro Glu Glu Leu Asp Lys Gly Ser Phe Val Gly Asn Ile  
35 40 45

Ala Lys Asp Leu Gly Leu Glu Pro Gln Glu Leu Ala Glu Arg Gly Val  
50 55 60

Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ala Leu Asn Pro Arg  
65 70 75 80

Ser Gly Ser Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys  
85 90 95

Ala Gln Ser Pro Leu Cys Val Val Asn Phe Asn Ile Leu Val Glu Asn  
100 105 110

Lys Met Lys Ile Tyr Gly Val Glu Val Glu Ile Ile Asp Ile Asn Asp  
115 120 125

Asn Phe Pro Arg Phe Arg Asp Glu Glu Leu Lys Val Lys Val Asn Glu  
130 135 140

Asn Ala Ala Ala Gly Thr Arg Leu Val Leu Pro Phe Ala Arg Asp Ala  
145 150 155 160

Asp Val Gly Val Asn Ser Leu Arg Ser Tyr Gln Leu Ser Ser Asn Leu  
165 170 175

His Phe Ser Leu Asp Val Val Ser Gly Thr Asp Gly Gln Lys Tyr Pro  
180 185 190

Glu Leu Val Leu Glu Gln Pro Leu Asp Arg Glu Lys Glu Thr Val His  
195 200 205

# ES 2 534 734 A1

Asp Leu Leu Leu Thr Ala Leu Asp Gly Gly Asp Pro Val Leu Ser Gly  
 210 215 220

Thr Thr His Ile Arg Val Thr Val Leu Asp Ala Asn Asp Asn Ala Pro  
 225 230 235 240

Leu Phe Thr Pro Ser Glu Tyr Ser Val Ser Val Pro Glu Asn Ile Pro  
 245 250 255

Val Gly Thr Arg Leu Leu Met Leu Thr Ala Thr Asp Pro Asp Glu Gly  
 260 265 270

Ile Asn Gly Lys Leu Thr Tyr Ser Phe Arg Asn Glu Glu Glu Lys Ile  
 275 280 285

Ser Glu Thr Phe Gln Leu Asp Ser Asn Leu Gly Glu Ile Ser Thr Leu  
 290 295 300

Gln Ser Leu Asp Tyr Glu Glu Ser Arg Phe Tyr Leu Met Glu Val Val  
 305 310 315 320

Ala Gln Asp Gly Gly Ala Leu Val Ala Ser Ala Lys Val Val Val Thr  
 325 330 335

Val Gln Asp Val Asn Asp Asn Ala Pro Glu Val Ile Leu Thr Ser Leu  
 340 345 350

Thr Ser Ser Ile Ser Glu Asp Cys Leu Pro Gly Thr Val Ile Ala Leu  
 355 360 365

Phe Ser Val His Asp Gly Asp Ser Gly Glu Asn Gly Glu Ile Ala Cys  
 370 375 380

Ser Ile Pro Arg Asn Leu Pro Phe Lys Leu Glu Lys Ser Val Asp Asn  
 385 390 395 400

Tyr Tyr His Leu Leu Thr Thr Arg Asp Leu Asp Arg Glu Glu Thr Ser  
 405 410 415

Asp Tyr Asn Ile Thr Leu Thr Val Met Asp His Gly Thr Pro Pro Leu  
 420 425 430

Ser Thr Glu Ser His Ile Pro Leu Lys Val Ala Asp Val Asn Asp Asn  
 435 440 445

# ES 2 534 734 A1

Pro Pro Asn Phe Pro Gln Ala Ser Tyr Ser Thr Ser Val Thr Glu Asn  
 450 455 460

Asn Pro Arg Gly Val Ser Ile Phe Ser Val Thr Ala His Asp Pro Asp  
 465 470 475 480

Ser Gly Asp Asn Ala Arg Val Thr Tyr Ser Leu Ala Glu Asp Thr Phe  
 485 490 495

Gln Gly Ala Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asp Thr Gly  
 500 505 510

Val Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln Leu Arg Asp Leu  
 515 520 525

Gln Leu Trp Val Thr Ala Ser Asp Ser Gly Asn Pro Pro Leu Ser Ser  
 530 535 540

Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Thr Pro  
 545 550 555 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu  
 565 570 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

Ala Val Asp Lys Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu  
 595 600 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly Leu His Thr Gly  
 610 615 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln  
 625 630 635 640

Ser Leu Val Val Ala Val Glu Asp His Gly Gln Pro Pro Leu Ser Ala  
 645 650 655

Thr Phe Thr Val Thr Val Ala Val Ala Asp Arg Ile Pro Asp Ile Leu  
 660 665 670

Ala Asp Leu Gly Ser Ile Lys Thr Pro Ile Asp Pro Glu Asp Leu Asp  
 675 680 685

# ES 2 534 734 A1

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val Ser Cys Val Phe  
 690 695 700

Leu Ala Phe Val Ile Val Leu Leu Val Leu Arg Leu Arg Arg Trp His  
 705 710 715 720

Lys Ser Arg Leu Leu Gln Ala Glu Gly Ser Arg Leu Ala Gly Val Pro  
 725 730 735

Ala Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr  
 740 745 750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu  
 755 760 765

Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Leu Ser Glu Glu Ser  
 770 775 780

Cys Glu Lys Ser Glu Pro Leu Leu Met Ser Asp Lys Val Asp Ala Asn  
 785 790 795 800

Lys Glu Glu Arg Arg Val Gln Gln Ala Pro Pro Asn Thr Asp Trp Arg  
 805 810 815

Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp  
 820 825 830

Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln  
 835 840 845

Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr  
 850 855 860

Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro  
 865 870 875 880

Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile  
 885 890 895

Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly  
 900 905 910

Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys  
 915 920 925

# ES 2 534 734 A1

Glu Lys Lys  
930

<210> 111  
<211> 929  
<212> PRT  
<213> Homo sapiens

<400> 111

Met Gly Asn Ser Ser Gly Trp Arg Gly Pro Ala Gly Gln Arg Arg Met  
1 5 10 15

Leu Phe Leu Phe Leu Leu Ser Leu Leu Asp Gln Val Leu Ser Glu Pro  
20 25 30

Ile Arg Tyr Ala Ile Pro Glu Glu Leu Asp Arg Gly Ser Leu Val Gly  
35 40 45

Asn Leu Ala Lys Asp Leu Gly Phe Gly Val Gly Asp Leu Pro Thr Arg  
50 55 60

Asn Leu Arg Val Ile Ala Glu Lys Lys Phe Phe Thr Val Ser Pro Glu  
65 70 75 80

Asn Gly Asn Leu Leu Val Ser Asp Arg Ile Asp Arg Glu Glu Ile Cys  
85 90 95

Gly Lys Lys Ser Thr Cys Val Leu Glu Phe Glu Met Val Ala Glu Lys  
100 105 110

Pro Leu Asn Phe Phe His Val Thr Val Leu Ile Gln Asp Ile Asn Asp  
115 120 125

Asn Pro Pro Thr Phe Ser Gln Asn Ile Thr Glu Leu Glu Ile Ser Glu  
130 135 140

Leu Ala Leu Thr Gly Ala Thr Phe Ala Leu Glu Ser Ala Gln Asp Pro  
145 150 155 160

Asp Val Gly Val Asn Ser Leu Gln Gln Tyr Tyr Leu Ser Pro Asp Pro  
165 170 175

His Phe Ser Leu Ile Gln Lys Glu Asn Leu Asp Gly Ser Arg Tyr Pro  
180 185 190



# ES 2 534 734 A1

Glu Leu Val Leu Lys Ala Pro Leu Asp Arg Glu Glu Gln Pro His His  
 195 200 205

His Leu Val Leu Thr Ala Val Asp Gly Gly Glu Pro Ser Arg Ser Cys  
 210 215 220

Thr Thr Gln Ile Arg Val Ile Val Ala Asp Ala Asn Asp Asn Pro Pro  
 225 230 235 240

Val Phe Thr Gln Asp Met Tyr Arg Val Asn Val Ala Glu Asn Leu Pro  
 245 250 255

Ala Gly Ser Ser Val Leu Lys Val Met Ala Ile Asp Met Asp Glu Gly  
 260 265 270

Ile Asn Ala Glu Ile Ile Tyr Ala Phe Ile Asn Ile Gly Lys Glu Val  
 275 280 285

Arg Gln Leu Phe Lys Leu Asp Ser Lys Thr Gly Glu Leu Thr Thr Ile  
 290 295 300

Gly Glu Leu Asp Phe Glu Glu Arg Asp Ser Tyr Thr Ile Gly Val Glu  
 305 310 315 320

Ala Lys Asp Gly Gly His His Thr Ala Tyr Cys Lys Val Gln Ile Asp  
 325 330 335

Ile Ser Asp Glu Asn Asp Asn Ala Pro Glu Ile Thr Leu Ala Ser Glu  
 340 345 350

Ser Gln His Ile Gln Glu Asp Ala Glu Leu Gly Thr Ala Val Ala Leu  
 355 360 365

Ile Lys Thr His Asp Leu Asp Ser Gly Phe Asn Gly Glu Ile Leu Cys  
 370 375 380

Gln Leu Lys Gly Asn Phe Pro Phe Lys Ile Val Gln Asp Thr Lys Asn  
 385 390 395 400

Thr Tyr Arg Leu Val Thr Asp Gly Ala Leu Asp Arg Glu Gln Ile Pro  
 405 410 415

Glu Tyr Asn Val Thr Ile Thr Ala Thr Asp Lys Gly Asn Pro Pro Leu  
 420 425 430

# ES 2 534 734 A1

Ser Ser Ser Lys Thr Ile Thr Leu His Ile Leu Asp Val Asn Asp Asn  
 435 440 445

Val Pro Val Phe His Gln Ala Ser Tyr Thr Val His Val Ala Glu Asn  
 450 455 460

Asn Pro Pro Gly Ala Ser Ile Ala His Val Arg Ala Ser Asp Pro Asp  
 465 470 475 480

Leu Gly Pro Asn Gly Leu Val Ser Tyr Tyr Ile Val Ala Ser Asp Leu  
 485 490 495

Glu Pro Arg Glu Leu Ser Ser Tyr Val Ser Val Ser Ala Arg Ser Gly  
 500 505 510

Val Val Phe Ala Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe  
 515 520 525

Glu Leu Thr Leu Gln Ala Arg Asp Gln Gly Ser Pro Thr Leu Ser Ala  
 530 535 540

Asn Val Ser Leu Arg Val Leu Val Asp Asp Arg Asn Asp Asn Ala Pro  
 545 550 555 560

Leu Val Leu Tyr Pro Ala Leu Gly Pro Glu Gly Ser Ala Leu Phe Asp  
 565 570 575

Met Val Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

Ala Val Asp Ala Asp Ser Gly Tyr Asn Ala Trp Leu Ser Tyr His Ile  
 595 600 605

Val Gln Ala Ser Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly  
 610 615 620

Glu Val Arg Thr Ala Arg Thr Leu Gly Asp Arg Glu Ala Ala Arg Gln  
 625 630 635 640

Arg Leu Leu Val Thr Val Arg Asp Gly Gly Gln Gln Pro Leu Ser Ala  
 645 650 655

Thr Val Met Leu His Leu Ile Phe Ala Asp Ser Leu Gln Glu Ile Gln  
 660 665 670

# ES 2 534 734 A1

Pro Asp Leu Ser Asp Arg Pro Thr Pro Ser Asp Pro Gln Ala Glu Leu  
 675 680 685

Gln Phe His Leu Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu  
 690 695 700

Leu Ala Val Ile Leu Ala Ile Ser Leu Arg Leu Arg Cys Ser Ser Arg  
 705 710 715 720

Pro Ala Thr Glu Gly Tyr Phe Gln Pro Gly Val Cys Phe Lys Thr Val  
 725 730 735

Pro Gly Val Leu Pro Thr Tyr Ser Glu Arg Thr Leu Pro Tyr Ser Tyr  
 740 745 750

Asn Pro Cys Ala Ala Ser His Ser Ser Asn Thr Glu Phe Lys Phe Leu  
 755 760 765

Asn Ile Lys Ala Glu Asn Ala Ala Pro Gln Asp Leu Leu Cys Asp Glu  
 770 775 780

Ala Ser Trp Phe Glu Ser Asn Asp Asn Pro Glu Met Pro Ser Asn Ser  
 785 790 795 800

Gly Asn Leu Gln Lys Gln Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser  
 805 810 815

Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr  
 820 825 830

Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln Ala Met  
 835 840 845

Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly  
 850 855 860

Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe  
 865 870 875 880

Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly  
 885 890 895

Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala  
 900 905 910

# ES 2 534 734 A1

Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys  
 915 920 925

Lys

<210> 112  
 <211> 932  
 <212> PRT  
 <213> Homo sapiens  
 <400> 112

Met Ala Pro Pro Gln Arg His Pro Gln Arg Ser Glu Gln Val Leu Leu  
 1 5 10 15

Leu Thr Leu Leu Gly Thr Leu Trp Gly Ala Ala Ala Ala Gln Ile Arg  
 20 25 30

Tyr Ser Ile Pro Glu Glu Leu Glu Lys Gly Ser Phe Val Gly Asn Ile  
 35 40 45

Val Lys Asp Leu Gly Leu Glu Pro Gln Glu Leu Ala Glu His Gly Val  
 50 55 60

Arg Ile Val Ser Arg Gly Arg Met Gln Leu Phe Ser Leu Asn Pro Arg  
 65 70 75 80

Asn Gly Ser Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys  
 85 90 95

Ala Gln Ser Pro Arg Cys Leu Val Ser Phe Asn Ile Leu Val Glu Asp  
 100 105 110

Lys Leu Asn Leu Tyr Pro Val Glu Val Glu Ile Val Asp Ile Asn Asp  
 115 120 125

Asn Thr Pro Arg Phe Leu Lys Glu Glu Leu Glu Val Lys Ile Leu Glu  
 130 135 140

Asn Ala Ala Pro Ser Ser Arg Phe Pro Leu Met Glu Val Tyr Asp Pro  
 145 150 155 160

Asp Val Gly Met Asn Ser Leu Gln Gly Phe Lys Leu Ser Gly Asn Ser  
 165 170 175

# ES 2 534 734 A1

His Phe Ser Val Asp Val Gln Ser Glu Ala His Gly Pro Lys Tyr Pro  
 180 185 190

Glu Leu Val Leu Glu Gly Thr Leu Asp Arg Glu Gly Glu Ala Val Tyr  
 195 200 205

Arg Leu Val Leu Thr Ala Met Asp Gly Gly Asp Pro Val Arg Ser Ser  
 210 215 220

Val Ala Gln Ile Leu Val Thr Val Leu Asp Val Asn Asp Asn Thr Pro  
 225 230 235 240

Met Phe Thr Gln Pro Val Tyr Arg Val Ser Val Pro Glu Asn Leu Pro  
 245 250 255

Val Gly Thr Pro Val Leu Ala Val Thr Ala Thr Asp Gln Asp Glu Gly  
 260 265 270

Val His Gly Glu Val Thr Tyr Ser Phe Val Lys Ile Thr Glu Lys Ile  
 275 280 285

Ser Gln Ile Phe Cys Leu Asn Val Leu Thr Gly Glu Ile Ser Thr Ser  
 290 295 300

Ala Asn Leu Asp Tyr Glu Asp Ser Ser Phe Tyr Glu Leu Gly Val Glu  
 305 310 315 320

Ala Arg Asp Gly Pro Gly Leu Arg Asp Arg Ala Lys Val Leu Ile Thr  
 325 330 335

Ile Leu Asp Val Asn Asp Asn Val Pro Glu Val Val Val Thr Ser Gly  
 340 345 350

Ser Arg Thr Ile Ala Glu Ser Ala Pro Pro Gly Thr Val Ile Ala Leu  
 355 360 365

Phe Gln Val Phe Asp Arg Asp Ser Gly Leu Asn Gly Leu Val Thr Cys  
 370 375 380

Ser Ile Pro Arg Ser Leu Pro Phe Glu Leu Glu Lys Ser Val Gly Asn  
 385 390 395 400

Tyr Tyr Arg Leu Val Thr Asn Ala Ala Leu Asp Arg Glu Glu Val Phe  
 405 410 415

# ES 2 534 734 A1

Leu Tyr Asn Ile Thr Val Thr Ala Thr Asp Lys Gly Thr Pro Pro Leu  
 420 425 430

Ser Thr Glu Thr Ile Ile Ser Leu Asn Val Ala Asp Thr Asn Asp Asn  
 435 440 445

Pro Pro Thr Phe Pro His Ser Ser Tyr Ser Val Tyr Val Leu Glu Asn  
 450 455 460

Asn Pro Arg Gly Ala Ser Ile Phe Ser Val Asn Ala Leu Asp Pro Asp  
 465 470 475 480

Val Asp Gln Asn Ala Gln Val Ser Tyr Ser Leu Ala Glu Asp Thr Leu  
 485 490 495

Gln Gly Ala Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asp Thr Gly  
 500 505 510

Ile Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln Leu Arg Asp Leu  
 515 520 525

Gln Leu Trp Val Thr Ala Ser Asp Ser Gly Asp Pro Pro Leu Ser Ser  
 530 535 540

Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala Pro  
 545 550 555 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu  
 565 570 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu  
 595 600 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly  
 610 615 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln  
 625 630 635 640

Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala  
 645 650 655

# ES 2 534 734 A1

Thr Val Thr Leu Thr Val Ala Val Ala Asp Arg Ile Pro Asp Ile Leu  
 660 665 670

Ala Asp Leu Gly Ser Leu Glu Pro Ser Ala Lys Pro Asn Asp Ser Asp  
 675 680 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val Ser Cys Val Phe  
 690 695 700

Leu Ala Phe Val Ile Val Leu Leu Ala Leu Arg Leu Gln Arg Trp His  
 705 710 715 720

Lys Ser Arg Leu Leu Gln Ala Ser Gly Gly Gly Leu Ala Ser Met Pro  
 725 730 735

Gly Ser His Phe Val Gly Val Glu Gly Val Arg Ala Phe Leu Gln Thr  
 740 745 750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu  
 755 760 765

Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile Asn Gln Glu Ser  
 770 775 780

Tyr Glu Lys Ser Glu Pro Leu Leu Ile Thr Gln Asp Leu Leu Glu Thr  
 785 790 795 800

Lys Gly Glu Pro Arg Gln Leu Gln Gln Ala Pro Pro Asn Thr Asp Trp  
 805 810 815

Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly  
 820 825 830

Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu  
 835 840 845

Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser  
 850 855 860

Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly  
 865 870 875 880

Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr  
 885 890 895

# ES 2 534 734 A1

Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp  
 900 905 910

Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys  
 915 920 925

Lys Glu Lys Lys  
 930

<210> 113  
 <211> 932  
 <212> PRT  
 <213> Homo sapiens

<400> 113

Met Ala Ala Gln Pro Arg Gly Gly Asp Tyr Arg Gly Phe Phe Leu Leu  
 1 5 10 15

Ser Ile Leu Leu Gly Thr Pro Trp Glu Ala Trp Ala Gly Arg Ile Leu  
 20 25 30

Tyr Ser Val Ser Glu Glu Thr Asp Lys Gly Ser Phe Val Gly Asp Ile  
 35 40 45

Ala Lys Asp Leu Gly Leu Glu Pro Arg Glu Leu Ala Glu Arg Gly Val  
 50 55 60

Arg Ile Ile Ser Arg Gly Arg Thr Gln Leu Phe Ala Leu Asn Gln Arg  
 65 70 75 80

Ser Gly Ser Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Ile Cys  
 85 90 95

Ala Gln Ser Ala Arg Cys Leu Val Asn Phe Asn Ile Leu Met Glu Asp  
 100 105 110

Lys Met Asn Leu Tyr Pro Ile Asp Val Glu Ile Ile Asp Ile Asn Asp  
 115 120 125

Asn Val Pro Arg Phe Leu Thr Glu Glu Ile Asn Val Lys Ile Met Glu  
 130 135 140

Asn Thr Ala Pro Gly Val Arg Phe Pro Leu Ser Glu Ala Gly Asp Pro  
 145 150 155 160



# ES 2 534 734 A1

Asp Val Gly Thr Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn Arg  
 165 170 175

His Phe Ser Leu Ala Val Gln Ser Gly Asp Asp Glu Thr Lys Tyr Pro  
 180 185 190

Glu Leu Val Leu Glu Arg Val Leu Asp Arg Glu Glu Glu Arg Val His  
 195 200 205

His Leu Val Leu Thr Ala Ser Asp Gly Gly Asp Pro Pro Arg Ser Ser  
 210 215 220

Thr Ala His Ile Gln Val Thr Val Val Asp Val Asn Asp His Thr Pro  
 225 230 235 240

Val Phe Ser Leu Pro Gln Tyr Gln Val Thr Val Pro Glu Asn Val Pro  
 245 250 255

Val Gly Thr Arg Leu Leu Thr Val His Ala Ile Asp Leu Asp Glu Gly  
 260 265 270

Val Asn Gly Glu Val Thr Tyr Ser Phe Arg Lys Ile Thr Pro Lys Leu  
 275 280 285

Pro Lys Met Phe His Leu Asn Ser Leu Thr Gly Glu Ile Ser Thr Leu  
 290 295 300

Glu Gly Leu Asp Tyr Glu Glu Thr Ala Phe Tyr Glu Met Glu Val Gln  
 305 310 315 320

Ala Gln Asp Gly Pro Gly Ser Leu Thr Lys Ala Lys Val Leu Ile Thr  
 325 330 335

Val Leu Asp Val Asn Asp Asn Ala Pro Glu Val Thr Met Thr Ser Leu  
 340 345 350

Ser Ser Ser Ile Pro Glu Asp Thr Pro Leu Gly Thr Val Ile Ala Leu  
 355 360 365

Phe Tyr Leu Gln Asp Arg Asp Ser Gly Lys Asn Gly Glu Val Thr Cys  
 370 375 380

Thr Ile Pro Glu Asn Leu Pro Phe Lys Leu Glu Lys Ser Ile Asp Asn  
 385 390 395 400

# ES 2 534 734 A1

Tyr Tyr Arg Leu Val Thr Thr Lys Asn Leu Asp Arg Glu Thr Leu Ser  
 405 410 415

Leu Tyr Asn Ile Thr Leu Lys Ala Thr Asp Gly Gly Thr Pro Pro Leu  
 420 425 430

Ser Arg Glu Thr His Ile Phe Met Gln Val Ala Asp Thr Asn Asp Asn  
 435 440 445

Pro Pro Thr Phe Pro His Ser Ser Tyr Ser Val Tyr Ile Ala Glu Asn  
 450 455 460

Asn Pro Arg Gly Ala Ser Ile Phe Leu Val Thr Ala Gln Asp His Asp  
 465 470 475 480

Ser Glu Asp Asn Ala Gln Ile Thr Tyr Ser Leu Ala Glu Asp Thr Ile  
 485 490 495

Gln Gly Ala Pro Val Ser Ser Tyr Val Ser Ile Asn Ser Asp Thr Gly  
 500 505 510

Val Leu Tyr Ala Leu Gln Ser Phe Asp Tyr Glu Gln Leu Arg Glu Leu  
 515 520 525

Gln Leu Arg Val Thr Ala His Asp Ser Gly Asp Pro Pro Leu Ser Ser  
 530 535 540

Asn Met Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Pro Pro  
 545 550 555 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Met Glu  
 565 570 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

Ala Val Asp Lys Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Leu Leu  
 595 600 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly Leu Tyr Thr Gly  
 610 615 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln  
 625 630 635 640

# ES 2 534 734 A1

Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala  
645 650 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile Pro Glu Val Leu  
660 665 670

Ala Asp Leu Gly Ser Leu Glu Pro Ser Asp Gly Pro Tyr Asn Tyr Asp  
675 680 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Thr Val Ser Cys Val Phe  
690 695 700

Leu Ala Phe Val Leu Val Leu Leu Ala Leu Arg Leu Arg Arg Trp His  
705 710 715 720

Lys Ser Arg Leu Leu Gln Ala Ser Glu Gly Gly Leu Ala Asn Val Pro  
725 730 735

Thr Ser His Phe Val Gly Met Asp Gly Val Gln Ala Phe Leu Gln Thr  
740 745 750

Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu  
755 760 765

Ile Phe Pro Gln Pro Asn Tyr Val Asp Met Leu Ile Ser Gln Glu Ser  
770 775 780

Cys Glu Lys Asn Asp Ser Leu Leu Thr Ser Val Asp Phe Gln Glu Cys  
785 790 795 800

Lys Glu Asn Leu Pro Ser Ile Gln Gln Ala Pro Pro Asn Thr Asp Trp  
805 810 815

Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly  
820 825 830

Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu  
835 840 845

Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser  
850 855 860

Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly  
865 870 875 880

# ES 2 534 734 A1

Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr  
 885 890 895

Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp  
 900 905 910

Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys  
 915 920 925

Lys Glu Lys Lys  
 930

<210> 114  
 <211> 923  
 <212> PRT  
 <213> Homo sapiens

<400> 114

Met Gly Ser Gly Ala Gly Glu Leu Gly Arg Ala Glu Arg Leu Pro Val  
 1 5 10 15

Leu Phe Leu Phe Leu Leu Ser Leu Phe Cys Pro Ala Leu Cys Glu Gln  
 20 25 30

Ile Arg Tyr Arg Ile Pro Glu Glu Met Pro Lys Gly Ser Val Val Gly  
 35 40 45

Asn Leu Ala Thr Asp Leu Gly Phe Ser Val Gln Glu Leu Pro Thr Arg  
 50 55 60

Lys Leu Arg Val Ser Ser Glu Lys Pro Tyr Phe Thr Val Ser Ala Glu  
 65 70 75 80

Ser Gly Glu Leu Leu Val Ser Ser Arg Leu Asp Arg Glu Glu Ile Cys  
 85 90 95

Gly Lys Lys Pro Ala Cys Ala Leu Glu Phe Glu Ala Val Ala Glu Asn  
 100 105 110

Pro Leu Asn Phe Tyr His Val Asn Val Glu Ile Glu Asp Ile Asn Asp  
 115 120 125

His Thr Pro Lys Phe Thr Gln Asn Ser Phe Glu Leu Gln Ile Ser Glu  
 130 135 140

# ES 2 534 734 A1

Ser Ala Gln Pro Gly Thr Arg Phe Ile Leu Gly Ser Ala His Asp Ala  
 145 150 155 160

Asp Ile Gly Ser Asn Thr Leu Gln Asn Tyr Gln Leu Ser Pro Ser Asp  
 165 170 175

His Phe Ser Leu Ile Asn Lys Glu Lys Ser Asp Gly Ser Lys Tyr Pro  
 180 185 190

Glu Met Val Leu Lys Thr Pro Leu Asp Arg Glu Lys Gln Lys Ser Tyr  
 195 200 205

His Leu Thr Leu Thr Ala Leu Asp Phe Gly Ala Pro Pro Leu Ser Ser  
 210 215 220

Thr Ala Gln Ile His Val Leu Val Thr Asp Ala Asn Asp Asn Ala Pro  
 225 230 235 240

Val Phe Ser Gln Asp Val Tyr Arg Val Ser Leu Ser Glu Asn Val Tyr  
 245 250 255

Pro Gly Thr Thr Val Leu Gln Val Thr Ala Thr Asp Gln Asp Glu Gly  
 260 265 270

Val Asn Ala Glu Ile Thr Phe Ser Phe Ser Glu Ala Ser Gln Ile Thr  
 275 280 285

Gln Phe Asp Leu Asn Ser Asn Thr Gly Glu Ile Thr Val Leu Asn Thr  
 290 295 300

Leu Asp Phe Glu Glu Val Lys Glu Tyr Ser Ile Val Leu Glu Ala Arg  
 305 310 315 320

Asp Gly Gly Gly Met Ile Ala Gln Cys Thr Val Glu Val Glu Val Ile  
 325 330 335

Asp Glu Asn Asp Asn Ala Pro Glu Val Ile Phe Gln Ser Leu Pro Asn  
 340 345 350

Leu Ile Met Glu Asp Ala Glu Leu Gly Thr His Ile Ala Leu Leu Lys  
 355 360 365

Val Arg Asp Lys Asp Ser Arg His Asn Gly Glu Val Thr Cys Lys Leu  
 370 375 380

# ES 2 534 734 A1

Glu Gly Asp Val Pro Phe Lys Ile Leu Thr Ser Ser Arg Asn Thr Tyr  
 385 390 395 400

Lys Leu Val Thr Asp Ala Val Leu Asp Arg Glu Gln Asn Pro Glu Tyr  
 405 410 415

Asn Ile Thr Val Thr Ala Thr Asp Arg Gly Lys Pro Pro Leu Ser Ser  
 420 425 430

Ser Ser Ser Ile Thr Leu His Ile Gly Asp Val Asn Asp Asn Ala Pro  
 435 440 445

Val Phe Ser Gln Ser Ser Tyr Ile Val His Val Ala Glu Asn Asn Pro  
 450 455 460

Pro Gly Ala Ser Ile Ser Gln Val Arg Ala Ser Asp Pro Asp Leu Gly  
 465 470 475 480

Pro Asn Gly Gln Val Ser Tyr Cys Ile Met Ala Ser Asp Leu Glu Gln  
 485 490 495

Arg Glu Leu Ser Ser Tyr Val Ser Ile Ser Ala Glu Ser Gly Val Val  
 500 505 510

Phe Ala Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe Glu Leu  
 515 520 525

Thr Leu Gln Ala Arg Asp Gln Gly Ser Pro Ala Leu Ser Ala Asn Val  
 530 535 540

Ser Leu Arg Val Leu Val Asp Asp Arg Asn Asp Asn Ala Pro Arg Val  
 545 550 555 560

Leu Tyr Pro Ala Leu Gly Pro Asp Gly Ser Ala Leu Phe Asp Met Val  
 565 570 575

Pro His Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val Ala Val  
 580 585 590

Asp Ala Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val Leu Gln  
 595 600 605

Ala Ser Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly Glu Val  
 610 615 620

# ES 2 534 734 A1

Arg Thr Ala Arg Ala Leu Gly Asp Arg Asp Ala Val Arg Gln Arg Leu  
 625 630 635 640

Leu Val Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala Thr Ala  
 645 650 655

Thr Leu His Leu Val Phe Ala Asp Ser Leu Gln Glu Val Leu Pro Asp  
 660 665 670

Ile Thr Asp Arg Pro Asp Pro Ser Asp Leu Gln Ala Glu Leu Gln Phe  
 675 680 685

Tyr Leu Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu Val Ala  
 690 695 700

Met Ile Leu Ala Ile Ala Leu Arg Leu Arg Arg Ser Ser Ser Pro Ala  
 705 710 715 720

Ser Trp Ser Cys Phe Gln Pro Gly Leu Cys Val Lys Ser Glu Ser Val  
 725 730 735

Val Pro Pro Asn Tyr Ser Glu Gly Thr Leu Pro Tyr Ser Tyr Asn Leu  
 740 745 750

Cys Val Ala His Thr Gly Lys Thr Glu Phe Asn Phe Leu Lys Cys Ser  
 755 760 765

Glu Gln Leu Ser Ser Gly Gln Asp Ile Leu Cys Gly Asp Ser Ser Gly  
 770 775 780

Ala Leu Phe Pro Leu Cys Asn Ser Ser Glu Leu Thr Ser His Gln Gln  
 785 790 795 800

Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser Gln Ala Gln Arg Pro Gly  
 805 810 815

Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr Gly Thr Trp Pro Asn Asn  
 820 825 830

Gln Phe Asp Thr Glu Met Leu Gln Ala Met Ile Leu Ala Ser Ala Ser  
 835 840 845

Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly Gly Gly Ala Gly Thr Met  
 850 855 860

# ES 2 534 734 A1

Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe Thr Leu Gln His Val Pro  
 865 870 875 880

Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly Ser Asn Ala Thr Leu Thr  
 885 890 895

Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala Pro Ala Gly Gly Asn Gly  
 900 905 910

Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys Lys  
 915 920

<210> 115  
 <211> 932  
 <212> PRT  
 <213> Homo sapiens

<400> 115

Met Ala Ala Pro Gln Ser Arg Pro Arg Arg Gly Glu Leu Ile Leu Leu  
 1 5 10 15

Cys Ala Leu Leu Gly Thr Leu Trp Glu Ile Gly Arg Gly Gln Ile Arg  
 20 25 30

Tyr Ser Val Pro Glu Glu Thr Asp Lys Gly Ser Phe Val Gly Asn Ile  
 35 40 45

Ser Lys Asp Leu Gly Leu Asp Pro Arg Lys Leu Ala Lys His Gly Val  
 50 55 60

Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ala Leu Asn Pro Arg  
 65 70 75 80

Ser Gly Ser Leu Ile Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys  
 85 90 95

Ala Gln Ser Pro Arg Cys Leu Ile Asn Ile Asn Thr Leu Val Glu Asp  
 100 105 110

Lys Gly Lys Leu Phe Gly Val Glu Ile Glu Ile Ile Asp Ile Asn Asp  
 115 120 125

Asn Asn Pro Lys Phe Gln Val Glu Asp Leu Glu Val Lys Ile Asn Glu  
 130 135 140



# ES 2 534 734 A1

Ile Ala Val Pro Gly Ala Arg Tyr Pro Leu Pro Glu Ala Val Asp Pro  
 145 150 155 160

Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn His  
 165 170 175

His Phe Ser Leu Asp Val Gln Thr Gly Asp Asn Gly Ala Ile Asn Pro  
 180 185 190

Glu Leu Val Leu Glu Arg Ala Leu Asp Arg Glu Glu Glu Ala Ala His  
 195 200 205

His Leu Val Leu Thr Ala Ser Asp Gly Gly Lys Pro Pro Arg Ser Ser  
 210 215 220

Thr Val Arg Ile His Val Thr Val Leu Asp Thr Asn Asp Asn Ala Pro  
 225 230 235 240

Val Phe Pro His Pro Ile Tyr Arg Val Lys Val Leu Glu Asn Met Pro  
 245 250 255

Pro Gly Thr Arg Leu Leu Thr Val Thr Ala Ser Asp Pro Asp Glu Gly  
 260 265 270

Ile Asn Gly Lys Val Ala Tyr Lys Phe Arg Lys Ile Asn Glu Lys Gln  
 275 280 285

Thr Pro Leu Phe Gln Leu Asn Glu Asn Thr Gly Glu Ile Ser Ile Ala  
 290 295 300

Lys Ser Leu Asp Tyr Glu Glu Cys Ser Phe Tyr Glu Met Glu Ile Gln  
 305 310 315 320

Ala Glu Asp Val Gly Ala Leu Leu Gly Arg Thr Lys Leu Leu Ile Ser  
 325 330 335

Val Glu Asp Val Asn Asp Asn Arg Pro Glu Val Ile Ile Thr Ser Leu  
 340 345 350

Phe Ser Pro Val Leu Glu Asn Ser Leu Pro Gly Thr Val Ile Ala Phe  
 355 360 365

Leu Ser Val His Asp Gln Asp Ser Gly Lys Asn Gly Gln Val Val Cys  
 370 375 380

# ES 2 534 734 A1

Tyr Thr Arg Asp Asn Leu Pro Phe Lys Leu Glu Lys Ser Ile Gly Asn  
 385 390 395 400

Tyr Tyr Arg Leu Val Thr Arg Lys Tyr Leu Asp Arg Glu Asn Val Ser  
 405 410 415

Ile Tyr Asn Ile Thr Val Met Ala Ser Asp Leu Gly Thr Pro Pro Leu  
 420 425 430

Ser Thr Glu Thr Gln Ile Ala Leu His Val Ala Asp Ile Asn Asp Asn  
 435 440 445

Pro Pro Thr Phe Pro His Ala Ser Tyr Ser Ala Tyr Ile Leu Glu Asn  
 450 455 460

Asn Leu Arg Gly Ala Ser Ile Phe Ser Leu Thr Ala His Asp Pro Asp  
 465 470 475 480

Ser Gln Glu Asn Ala Gln Val Thr Tyr Ser Val Thr Glu Asp Thr Leu  
 485 490 495

Gln Gly Ala Pro Leu Ser Ser Tyr Ile Ser Ile Asn Ser Asp Thr Gly  
 500 505 510

Val Leu Tyr Ala Leu Gln Ser Phe Asp Tyr Glu Gln Ile Arg Asp Leu  
 515 520 525

Gln Leu Leu Val Thr Ala Ser Asp Ser Gly Asp Pro Pro Leu Ser Ser  
 530 535 540

Asn Met Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala Pro  
 545 550 555 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu  
 565 570 575

Leu Ala Pro Arg Ser Ala Glu Arg Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu  
 595 600 605

Leu Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly  
 610 615 620

# ES 2 534 734 A1

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln  
 625 630 635 640

Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala  
 645 650 655

Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile Pro Glu Val Leu  
 660 665 670

Thr Glu Leu Gly Ser Leu Lys Pro Ser Val Asp Pro Asn Asp Ser Ser  
 675 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Ile Ser Cys Val Phe  
 690 695 700

Leu Ala Phe Val Ala Val Leu Leu Gly Leu Arg Leu Arg Arg Trp His  
 705 710 715 720

Lys Ser Arg Leu Leu Gln Asp Ser Gly Gly Arg Leu Val Gly Val Pro  
 725 730 735

Ala Ser His Phe Val Gly Val Glu Glu Val Gln Ala Phe Leu Gln Thr  
 740 745 750

Tyr Ser Gln Glu Val Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu  
 755 760 765

Ile Phe Pro Gln Pro Asn Tyr Ala Asp Met Leu Ile Ser Gln Glu Gly  
 770 775 780

Cys Glu Lys Asn Asp Ser Leu Leu Thr Ser Val Asp Phe His Glu Tyr  
 785 790 795 800

Lys Asn Glu Ala Asp His Gly Gln Gln Ala Pro Pro Asn Thr Asp Trp  
 805 810 815

Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly  
 820 825 830

Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu  
 835 840 845

Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser  
 850 855 860

# ES 2 534 734 A1

Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly  
 865 870 875 880

Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr  
 885 890 895

Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp  
 900 905 910

Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys  
 915 920 925

Lys Glu Lys Lys  
 930

<210> 116  
 <211> 923  
 <212> PRT  
 <213> Homo sapiens

<400> 116

Met Gly Ser Gly Ala Gly Glu Leu Gly Arg Ala Glu Arg Leu Pro Val  
 1 5 10 15

Leu Phe Leu Phe Leu Leu Ser Leu Phe Cys Pro Ala Leu Cys Glu Gln  
 20 25 30

Ile Arg Tyr Arg Ile Pro Glu Glu Met Pro Lys Gly Ser Val Val Gly  
 35 40 45

Asn Leu Ala Thr Asp Leu Gly Phe Ser Val Gln Glu Leu Pro Thr Arg  
 50 55 60

Lys Leu Arg Val Ser Ser Glu Lys Pro Tyr Phe Thr Val Ser Ala Glu  
 65 70 75 80

Ser Gly Glu Leu Leu Val Ser Ser Arg Leu Asp Arg Glu Glu Ile Cys  
 85 90 95

Gly Lys Lys Pro Ala Cys Ala Leu Glu Phe Glu Ala Val Ala Glu Asn  
 100 105 110

Pro Leu Asn Phe Tyr His Val Asn Val Glu Ile Glu Asp Ile Asn Asp  
 115 120 125

# ES 2 534 734 A1

His Thr Pro Lys Phe Thr Gln Asn Ser Phe Glu Leu Gln Ile Ser Glu  
 130 135 140

Ser Ala Gln Pro Gly Thr Arg Phe Ile Leu Glu Val Ala Glu Asp Ala  
 145 150 155 160

Asp Ile Gly Leu Asn Ser Leu Gln Lys Tyr Lys Leu Ser Leu Asn Pro  
 165 170 175

Ser Phe Ser Leu Ile Ile Lys Glu Lys Gln Asp Gly Ser Lys Tyr Pro  
 180 185 190

Glu Leu Ala Leu Glu Lys Thr Leu Asp Arg Glu Gln Gln Ser Tyr His  
 195 200 205

Arg Leu Val Leu Thr Ala Leu Asp Gly Gly His Pro Pro Leu Ser Gly  
 210 215 220

Thr Thr Glu Leu Arg Ile Gln Val Thr Asp Ala Asn Asp Asn Pro Pro  
 225 230 235 240

Val Phe Asn Arg Asp Val Tyr Arg Val Ser Leu Arg Glu Asn Val Pro  
 245 250 255

Pro Gly Thr Thr Val Leu Gln Val Ser Ala Thr Asp Gln Asp Glu Gly  
 260 265 270

Ile Asn Ser Glu Ile Thr Tyr Ser Phe Tyr Arg Thr Gly Gln Ile Phe  
 275 280 285

Ser Leu Asn Ser Lys Ser Gly Glu Ile Thr Thr Gln Lys Lys Leu Asp  
 290 295 300

Phe Glu Glu Thr Lys Glu Tyr Ser Met Val Val Glu Gly Arg Asp Gly  
 305 310 315 320

Gly Gly Leu Val Ala Gln Cys Thr Val Glu Ile Asn Ile Gln Asp Glu  
 325 330 335

Asn Asp Asn Ser Pro Glu Val Thr Phe His Ser Leu Leu Glu Met Ile  
 340 345 350

Leu Glu Asn Ala Val Pro Gly Thr Leu Ile Ala Leu Ile Lys Ile His  
 355 360 365

# ES 2 534 734 A1

Asp Gln Asp Ser Gly Glu Asn Gly Glu Val Asn Cys Gln Leu Gln Gly  
 370 375 380

Glu Val Pro Phe Lys Ile Ile Ser Ser Ser Lys Asn Ser Tyr Lys Leu  
 385 390 395 400

Val Thr Asp Gly Thr Leu Asp Arg Glu Gln Thr Pro Glu Tyr Asn Val  
 405 410 415

Thr Ile Thr Ala Thr Asp Arg Gly Lys Pro Pro Leu Ser Ser Ser Ile  
 420 425 430

Ser Val Ile Leu His Ile Arg Asp Val Asn Asp Asn Ala Pro Val Phe  
 435 440 445

His Gln Ala Ser Tyr Leu Val Ser Val Pro Glu Asn Asn Pro Pro Gly  
 450 455 460

Ala Ser Ile Ala Gln Val Cys Ala Ser Asp Leu Asp Leu Gly Leu Asn  
 465 470 475 480

Gly Gln Val Ser Tyr Ser Ile Met Ala Ser Asp Leu Glu Pro Leu Ala  
 485 490 495

Leu Ala Ser Tyr Val Ser Met Ser Ala Gln Ser Gly Val Val Phe Ala  
 500 505 510

Gln Arg Ala Phe Asp Tyr Glu Gln Leu Arg Thr Phe Glu Leu Thr Leu  
 515 520 525

Gln Ala Arg Asp Gln Gly Ser Pro Ala Leu Ser Ala Asn Val Ser Leu  
 530 535 540

Arg Val Leu Val Gly Asp Arg Asn Asp Asn Ala Pro Arg Val Leu Tyr  
 545 550 555 560

Pro Ala Leu Gly Pro Asp Gly Ser Ala Leu Phe Asp Met Val Pro Arg  
 565 570 575

Ala Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val Ala Val Asp Ala  
 580 585 590

Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val Leu Gln Ala Ser  
 595 600 605

# ES 2 534 734 A1

Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly Glu Val Arg Thr  
 610 615 620

Ala Arg Ala Leu Gly Asp Arg Asp Ala Ala Arg Gln Arg Leu Leu Val  
 625 630 635 640

Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala Thr Ala Thr Leu  
 645 650 655

His Leu Val Phe Ala Asp Ser Leu Gln Glu Val Leu Pro Asp Ile Thr  
 660 665 670

Asp Arg Pro Val Pro Ser Asp Pro Gln Ala Glu Leu Gln Phe Tyr Leu  
 675 680 685

Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu Leu Ala Val Ile  
 690 695 700

Leu Ala Val Ala Leu Arg Leu Arg Arg Ser Ser Ser Pro Ala Ala Trp  
 705 710 715 720

Ser Cys Phe Gln Pro Gly Leu Cys Val Lys Ser Gly Pro Val Val Pro  
 725 730 735

Pro Asn Tyr Ser Gln Gly Thr Leu Pro Tyr Ser Tyr Asn Leu Cys Val  
 740 745 750

Ala His Thr Gly Lys Thr Glu Phe Asn Phe Leu Lys Cys Ser Glu Gln  
 755 760 765

Leu Ser Ser Gly Gln Asp Ile Leu Cys Gly Asp Ser Ser Gly Ala Leu  
 770 775 780

Phe Pro Leu Cys Asn Ser Ser Glu Ser Thr Ser His Pro Glu Leu Gln  
 785 790 795 800

Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser Gln Ala Gln Arg Pro Gly  
 805 810 815

Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr Gly Thr Trp Pro Asn Asn  
 820 825 830

Gln Phe Asp Thr Glu Met Leu Gln Ala Met Ile Leu Ala Ser Ala Ser  
 835 840 845

# ES 2 534 734 A1

Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly Gly Gly Ala Gly Thr Met  
 850 855 860

Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe Thr Leu Gln His Val Pro  
 865 870 875 880

Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly Ser Asn Ala Thr Leu Thr  
 885 890 895

Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala Pro Ala Gly Gly Asn Gly  
 900 905 910

Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys Lys  
 915 920

<210> 117  
 <211> 932  
 <212> PRT  
 <213> Homo sapiens

<400> 117

Met Ala Ala Pro Thr Lys Cys Gln Leu Arg Gly Arg Leu Val Leu Leu  
 1 5 10 15

Cys Ser Leu Leu Gly Met Leu Trp Glu Ala Arg Ala Ser Gln Ile Arg  
 20 25 30

Tyr Ser Val Pro Glu Glu Thr Glu Lys Gly Tyr Ile Val Gly Asn Ile  
 35 40 45

Ser Lys Asp Leu Ala Leu Glu Pro Arg Glu Leu Ala Glu Arg Arg Val  
 50 55 60

Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ser Leu Asn Pro Arg  
 65 70 75 80

Ser Gly Thr Leu Val Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu Cys  
 85 90 95

Ala Gln Ser Pro Arg Cys Leu Val Asn Phe Lys Val Leu Val Glu Asp  
 100 105 110

Arg Val Lys Leu Tyr Gly Ile Glu Ile Glu Val Thr Asp Ile Asn Asp  
 115 120 125



# ES 2 534 734 A1

Ser Ala Pro Lys Phe Gln Ala Glu Ser Leu Glu Val Lys Ile Asn Glu  
 130 135 140

Ile Ala Val Pro Gly Ala Arg Tyr Pro Leu Pro Glu Ala Ile Asp Pro  
 145 150 155 160

Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn His  
 165 170 175

His Phe Ser Leu Asn Val Gln Thr Gly Asp Asn Gly Ala Ile Asn Pro  
 180 185 190

Glu Leu Val Leu Glu Arg Ala Leu Asp Arg Glu Glu Ala Thr Ala His  
 195 200 205

His Leu Val Leu Thr Ala Ser Asp Gly Gly Glu Pro Arg Arg Ser Ser  
 210 215 220

Thr Val Arg Ile His Val Thr Val Leu Asp Thr Asn Asp Asn Ala Pro  
 225 230 235 240

Val Phe Ala Gln Arg Ile Tyr Arg Val Lys Val Leu Glu Asn Val Pro  
 245 250 255

Pro Gly Thr Trp Leu Leu Thr Ala Thr Ala Ser Asp Leu Asp Glu Gly  
 260 265 270

Ile Asn Gly Lys Val Ala Tyr Lys Phe Trp Lys Ile Asn Glu Lys Gln  
 275 280 285

Ser Leu Leu Phe Gln Leu Asn Glu Asn Thr Gly Glu Ile Ser Thr Ala  
 290 295 300

Lys Ser Leu Asp Tyr Glu Glu Cys Ser Phe Tyr Glu Met Glu Ile Gln  
 305 310 315 320

Ala Glu Asp Gly Gly Gly Leu Lys Gly Trp Thr Lys Val Leu Ile Ser  
 325 330 335

Val Glu Asp Val Asn Asp Asn Arg Pro Glu Val Thr Ile Thr Ser Leu  
 340 345 350

Phe Ser Pro Val Arg Glu Asp Ala Pro Gln Gly Thr Val Ile Leu Leu  
 355 360 365

# ES 2 534 734 A1

Phe Asn Ala His Asp Arg Asp Ser Gly Lys Asn Gly Gln Val Val Cys  
 370 375 380

Ser Ile Gln Glu Asn Leu Ser Phe Thr Leu Glu Asn Ser Glu Glu Asp  
 385 390 395 400

Tyr Tyr Arg Leu Leu Thr Ala Gln Ile Leu Asp Arg Glu Lys Ala Ser  
 405 410 415

Glu Tyr Asn Ile Thr Val Thr Ala Thr Asp Arg Gly Thr Pro Pro Leu  
 420 425 430

Ser Thr Glu Ile His Ile Thr Leu Gln Val Thr Asp Ile Asn Asp Asn  
 435 440 445

Pro Pro Ala Phe Ser Gln Ala Ser Tyr Ser Val Tyr Leu Pro Glu Asn  
 450 455 460

Asn Ala Arg Gly Thr Ser Ile Phe Ser Val Ile Ala Tyr Asp Pro Asp  
 465 470 475 480

Ser Asn Glu Asn Ser Arg Val Ile Tyr Ser Leu Ala Glu Asp Thr Ile  
 485 490 495

Gln Gly Ser Pro Leu Ser Thr Tyr Val Ser Ile Asn Ser Asp Thr Gly  
 500 505 510

Val Leu Tyr Ala Leu Cys Ser Phe Asp Tyr Glu Gln Phe Arg Asp Leu  
 515 520 525

Gln Met Gln Val Thr Ala Ser Asp Ser Gly Ser Pro Pro Leu Ser Ser  
 530 535 540

Asn Val Ser Leu Arg Leu Phe Val Leu Asp Gln Asn Asp Asn Ala Pro  
 545 550 555 560

Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val Glu  
 565 570 575

Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg Leu  
 595 600 605

# ES 2 534 734 A1

Phe Lys Ala Ser Glu Pro Gly Leu Phe Ser Val Gly Leu His Thr Gly  
 610 615 620

Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys Gln  
 625 630 635 640

Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser Ala  
 645 650 655

Thr Val Thr Leu Thr Val Ala Ile Ala Asp Ser Ile Pro Asp Ile Leu  
 660 665 670

Ala Asp Leu Gly Ser Leu Gln Ile Pro Ala Asp Leu Glu Ala Ser Asp  
 675 685

Leu Thr Leu Tyr Leu Val Val Ala Val Ala Val Val Ser Cys Val Phe  
 690 695 700

Leu Thr Phe Val Ile Thr Leu Leu Ala Leu Arg Leu Arg His Trp His  
 705 710 715 720

Ser Ser His Leu Leu Arg Ala Thr Ser Asp Gly Leu Ala Gly Val Pro  
 725 730 735

Thr Ser His Phe Val Gly Val Asp Gly Val Arg Ala Phe Leu Gln Thr  
 740 745 750

Tyr Ser Gln Glu Phe Ser Leu Thr Ala Asp Ser Arg Lys Ser His Leu  
 755 760 765

Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile Ser Gln Gln Ser  
 770 775 780

Cys Glu Lys Asn Glu Pro Leu Cys Val Ser Val Asp Ser Lys Phe Pro  
 785 790 795 800

Ile Glu Asp Thr Pro Leu Val Pro Gln Ala Pro Pro Asn Thr Asp Trp  
 805 810 815

Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly  
 820 825 830

Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu  
 835 840 845

ES 2 534 734 A1

Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser  
 850 855 860

Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly  
 865 870 875 880

Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr  
 885 890 895

Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp  
 900 905 910

Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys  
 915 920 925

Lys Glu Lys Lys  
 930

<210> 118  
 <211> 930  
 <212> PRT  
 <213> Homo sapiens

<400> 118

Met Gly Gly Ser Cys Ala Gln Arg Arg Arg Ala Gly Pro Arg Gln Val  
 1 5 10 15

Leu Phe Pro Leu Leu Leu Pro Leu Phe Tyr Pro Thr Leu Ser Glu Pro  
 20 25 30

Ile Arg Tyr Ser Ile Pro Glu Glu Leu Ala Lys Gly Ser Val Val Gly  
 35 40 45

Asn Leu Ala Lys Asp Leu Gly Leu Ser Val Leu Asp Val Ser Ala Arg  
 50 55 60

Lys Leu Arg Val Ser Ala Glu Lys Leu His Phe Ser Val Asp Ala Glu  
 65 70 75 80

Ser Gly Asp Leu Leu Val Lys Asn Arg Ile Asp Arg Glu Gln Ile Cys  
 85 90 95

Lys Glu Arg Arg Arg Cys Glu Leu Gln Leu Glu Ala Val Val Glu Asn  
 100 105 110

# ES 2 534 734 A1

Pro Leu Asn Ile Phe His Val Ile Val Val Ile Glu Asp Val Asn Asp  
 115 120 125

His Ala Pro Gln Phe Asp Lys Lys Glu Ile His Leu Glu Ile Phe Glu  
 130 135 140

Ser Ala Ser Ala Gly Thr Arg Leu Ser Leu Asp Pro Ala Thr Asp Pro  
 145 150 155 160

Asp Ile Asn Ile Asn Ser Ile Lys Asp Tyr Lys Ile Asn Ser Asn Pro  
 165 170 175

Tyr Phe Ser Leu Met Val Arg Val Asn Ser Asp Gly Gly Lys Tyr Pro  
 180 185 190

Glu Leu Ser Leu Glu Lys Leu Leu Asp Arg Glu Glu Gln Arg Ser His  
 195 200 205

Ser Leu Ile Leu Thr Ala Leu Asp Gly Gly Asp Pro Pro Arg Ser Ala  
 210 215 220

Thr Ala His Ile Glu Ile Ser Val Lys Asp Thr Asn Asp Asn Pro Pro  
 225 230 235 240

Val Phe Ser Arg Asp Glu Tyr Arg Ile Ser Leu Ser Glu Asn Leu Pro  
 245 250 255

Pro Gly Ser Pro Val Leu Gln Val Thr Ala Thr Asp Gln Asp Glu Gly  
 260 265 270

Val Asn Ala Glu Ile Asn Tyr Tyr Phe Arg Ser Thr Ala Gln Ser Thr  
 275 280 285

Lys His Met Phe Ser Leu Asp Glu Lys Thr Gly Met Ile Lys Asn Asn  
 290 295 300

Gln Ser Phe Asp Phe Glu Asp Val Glu Arg Tyr Thr Met Glu Val Glu  
 305 310 315 320

Ala Lys Asp Gly Gly Gly Leu Ser Thr Gln Cys Lys Val Ile Ile Glu  
 325 330 335

Ile Leu Asp Glu Asn Asp Asn Ser Pro Glu Ile Ile Ile Thr Ser Leu  
 340 345 350

# ES 2 534 734 A1

Ser Asp Gln Ile Leu Glu Asn Ser Pro Pro Gly Met Val Val Ala Leu  
 355 360 365

Phe Lys Thr Arg Asp Leu Asp Phe Gly Gly Asn Gly Glu Val Arg Cys  
 370 375 380

Asn Ile Glu Thr Asp Ile Pro Phe Lys Ile Tyr Ser Ser Ser Asn Asn  
 385 390 395 400

Tyr Tyr Lys Leu Val Thr Asp Gly Ala Leu Asp Arg Glu Gln Thr Pro  
 405 410 415

Glu Tyr Asn Val Thr Ile Val Ala Thr Asp Arg Gly Lys Pro Pro Leu  
 420 425 430

Ser Ser Ser Arg Ser Ile Thr Leu Tyr Val Ala Asp Ile Asn Asp Asn  
 435 440 445

Ala Pro Val Phe Asp Gln Thr Ser Tyr Val Val His Val Ala Glu Asn  
 450 455 460

Asn Pro Pro Gly Ala Ser Ile Ala Gln Val Ser Ala Ser Asp Pro Asp  
 465 470 475 480

Leu Gly Leu Asn Gly His Ile Ser Tyr Ser Ile Val Ala Ser Asp Leu  
 485 490 495

Glu Pro Leu Ala Val Ser Ser Tyr Val Ser Val Ser Ala Gln Ser Gly  
 500 505 510

Val Val Phe Ala Gln Arg Ala Phe Asp His Glu Gln Leu Arg Ala Phe  
 515 520 525

Ala Leu Thr Leu Gln Ala Arg Asp His Gly Ser Pro Thr Leu Ser Ala  
 530 535 540

Asn Val Ser Leu Arg Val Leu Val Gly Asp Arg Asn Asp Asn Ala Pro  
 545 550 555 560

Arg Val Leu Tyr Pro Ala Leu Gly Pro Asp Gly Ser Ala Phe Phe Asp  
 565 570 575

Met Val Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val Val  
 580 585 590

# ES 2 534 734 A1

Ala Val Asp Ala Asp Ser Gly His Asn Ala Trp Leu Ser Tyr His Val  
595 600 605

Leu Gln Ala Ser Glu Pro Gly Leu Phe Ser Leu Gly Leu Arg Thr Gly  
610 615 620

Glu Val Arg Thr Ala Arg Ala Leu Gly Asp Arg Asp Ala Ala Arg Gln  
625 630 635 640

Arg Leu Leu Val Ala Val Arg Asp Gly Gly Gln Pro Pro Leu Ser Ala  
645 650 655

Thr Ala Thr Leu His Leu Val Phe Ala Asp Asn Leu Gln Glu Ile Leu  
660 665 670

Pro Asp Leu Ser Asp Arg Pro Val Leu Ser Asp Pro Gln Ala Glu Leu  
675 680 685

Gln Phe Tyr Leu Val Val Ala Leu Ala Leu Ile Ser Val Leu Phe Leu  
690 695 700

Leu Ala Val Ile Leu Ala Ile Ala Leu Arg Leu Arg Arg Ser Leu Ser  
705 710 715 720

Pro Ala Thr Trp Asp Cys Phe His Pro Gly Leu Cys Val Lys Ser Gly  
725 730 735

Pro Val Val Pro Pro Asn Tyr Ser Glu Gly Thr Leu Pro Tyr Ser Tyr  
740 745 750

Asn Leu Cys Ile Ala His Thr Gly Thr Lys Glu Phe Asn Phe Leu Lys  
755 760 765

Cys Ser Val Pro Leu His Ser Asn Glu Asp Met Val Cys Ser Val Ser  
770 775 780

Pro Gly Ala Leu Ile Pro Pro His Gly Gly Glu Asp Leu Thr Ser His  
785 790 795 800

Pro Glu Thr Leu Thr Ser Gln Ala Pro Pro Asn Thr Asp Trp Arg Phe  
805 810 815

Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp Asp  
820 825 830

# ES 2 534 734 A1

Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln Ala  
 835 840 845

Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr Leu  
 850 855 860

Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro Gln  
 865 870 875 880

Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile Pro  
 885 890 895

Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly Lys  
 900 905 910

Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys Glu  
 915 920 925

Lys Lys  
 930

<210> 119  
 <211> 936  
 <212> PRT  
 <213> Homo sapiens

<400> 119

Met Ala Ala Gln Arg Asn Arg Ser Lys Glu Ser Lys Asp Cys Ser Gly  
 1 5 10 15

Leu Val Leu Leu Cys Leu Phe Phe Gly Ile Pro Trp Glu Ala Gly Ala  
 20 25 30

Arg Gln Ile Ser Tyr Ser Ile Pro Glu Glu Leu Glu Lys Gly Ser Phe  
 35 40 45

Val Gly Asn Ile Ser Lys Asp Leu Gly Leu Ala Pro Arg Glu Leu Ala  
 50 55 60

Glu Arg Gly Val Arg Ile Val Ser Arg Gly Arg Thr Gln Leu Phe Ser  
 65 70 75 80

Leu Asn Pro Arg Ser Gly Ser Leu Ile Thr Ala Gly Arg Ile Asp Arg  
 85 90 95



# ES 2 534 734 A1

Glu Glu Leu Cys Ala Gln Ser Ala Arg Cys Val Val Ser Phe Asn Ile  
 100 105 110

Leu Val Glu Asp Arg Val Lys Leu Phe Gly Ile Glu Ile Glu Val Thr  
 115 120 125

Asp Ile Asn Asp Asn Ala Pro Lys Phe Gln Ala Glu Asn Leu Asp Val  
 130 135 140

Lys Ile Asn Glu Asn Val Ala Ala Gly Met Arg Phe Pro Leu Pro Glu  
 145 150 155 160

Ala Ile Asp Pro Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu  
 165 170 175

Ser Pro Asn Lys His Phe Ser Leu Arg Val Gln Ser Arg Ala Asn Gly  
 180 185 190

Val Lys Tyr Pro Glu Leu Val Leu Glu His Ser Leu Asp Arg Glu Glu  
 195 200 205

Glu Ala Ile His His Leu Val Leu Thr Ala Ser Asp Gly Gly Asp Pro  
 210 215 220

Leu Arg Ser Gly Thr Val Leu Val Ser Val Thr Val Phe Asp Ala Asn  
 225 230 235 240

Asp Asn Ala Pro Val Phe Thr Leu Pro Glu Tyr Arg Val Ser Val Pro  
 245 250 255

Glu Asn Leu Pro Val Gly Thr Gln Leu Leu Thr Val Thr Ala Thr Asp  
 260 265 270

Arg Asp Glu Gly Ala Asn Gly Glu Val Thr Tyr Ser Phe Arg Lys Leu  
 275 280 285

Pro Asp Thr Gln Leu Leu Lys Phe Gln Leu Asn Lys Tyr Thr Gly Glu  
 290 295 300

Ile Lys Ile Ser Glu Asn Leu Asp Tyr Glu Glu Thr Gly Phe Tyr Glu  
 305 310 315 320

Ile Glu Ile Gln Ala Glu Asp Gly Gly Ala Tyr Leu Ala Thr Ala Lys  
 325 330 335

# ES 2 534 734 A1

Val Leu Ile Thr Val Glu Asp Val Asn Asp Asn Ser Pro Glu Leu Thr  
 340 345 350

Ile Thr Ser Leu Phe Ser Pro Val Thr Glu Asp Ser Pro Leu Gly Thr  
 355 360 365

Val Val Ala Leu Leu Asn Val His Asp Leu Asp Ser Glu Gln Asn Gly  
 370 375 380

Gln Val Thr Cys Ser Ile Leu Ala Tyr Leu Pro Phe Lys Leu Glu Lys  
 385 390 395 400

Ser Ile Asp Ser Tyr Tyr Arg Leu Val Ile His Arg Ala Leu Asp Arg  
 405 410 415

Glu Gln Val Ser Ser Tyr Asn Ile Thr Val Thr Ala Thr Asp Gly Gly  
 420 425 430

Ser Pro Pro Leu Ser Thr Glu Ala His Phe Met Leu Gln Val Ala Asp  
 435 440 445

Ile Asn Asp Asn Pro Pro Thr Phe Ser Gln Val Ser Tyr Phe Thr Tyr  
 450 455 460

Ile Pro Glu Asn Asn Ala Arg Gly Ala Ser Ile Phe Ser Val Thr Ala  
 465 470 475 480

Leu Asp Pro Asp Ser Lys Glu Asn Ala Gln Ile Ile Tyr Ser Leu Ala  
 485 490 495

Glu Asp Thr Ile Gln Gly Val Pro Leu Ser Ser Tyr Ile Ser Ile Asn  
 500 505 510

Ser Asp Thr Gly Val Leu Tyr Ala Leu Arg Ser Phe Asp Tyr Glu Gln  
 515 520 525

Phe His Glu Leu Gln Met Gln Val Thr Ala Ser Asp Ser Gly Asp Pro  
 530 535 540

Pro Leu Ser Ser Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn  
 545 550 555 560

Asp Asn Ala Pro Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser  
 565 570 575

# ES 2 534 734 A1

Thr Gly Val Glu Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val  
 580 585 590

Thr Lys Val Val Ala Val Asp Arg Asp Ser Gly Gln Asn Ala Trp Leu  
 595 600 605

Ser Tyr Arg Leu Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly  
 610 615 620

Glu His Thr Gly Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp  
 625 630 635 640

Ala Leu Lys Gln Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro  
 645 650 655

Pro Leu Ser Ala Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile  
 660 665 670

Pro Gln Val Leu Ala Asp Leu Gly Ser Phe Glu Ser Pro Ala Asn Ser  
 675 680 685

Glu Thr Ser Asp Leu Thr Leu Tyr Leu Val Val Ala Val Ala Ala Val  
 690 695 700

Ser Cys Val Phe Leu Ala Phe Val Ile Val Leu Leu Ala His Arg Leu  
 705 710 715 720

Arg Arg Trp His Lys Ser Arg Leu Leu Gln Ala Ser Gly Gly Gly Leu  
 725 730 735

Thr Gly Val Ser Gly Ser His Phe Val Gly Val Asp Gly Val Arg Ala  
 740 745 750

Phe Leu Gln Thr Tyr Ser His Glu Val Ser Leu Thr Ala Asp Ser Arg  
 755 760 765

Lys Ser His Leu Ile Phe Pro Gln Pro Asn Tyr Ala Asp Thr Leu Ile  
 770 775 780

Ser Gln Glu Ser Cys Glu Lys Asn Asp Pro Leu Ser Leu Leu Asp Asp  
 785 790 795 800

Ser Lys Phe Pro Ile Glu Asp Thr Pro Leu Val Pro Gln Ala Pro Pro  
 805 810 815

# ES 2 534 734 A1

Asn Thr Asp Trp Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly  
 820 825 830

Ser Gln Asn Gly Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp  
 835 840 845

Thr Glu Met Leu Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala  
 850 855 860

Asp Gly Ser Ser Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser  
 865 870 875 880

Ala Arg Tyr Gly Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg  
 885 890 895

Gln Asn Val Tyr Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala  
 900 905 910

Gly Lys Arg Asp Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys  
 915 920 925

Lys Ser Gly Lys Lys Glu Lys Lys  
 930 935

<210> 120  
 <211> 935  
 <212> PRT  
 <213> Homo sapiens

<400> 120

Met Ala Asn Arg Leu Gln Arg Gly Asp Arg Ser Arg Leu Leu Leu Leu  
 1 5 10 15

Leu Cys Ile Phe Leu Gly Thr Leu Arg Gly Phe Arg Ala Arg Gln Ile  
 20 25 30

Arg Tyr Ser Val Pro Glu Glu Thr Glu Lys Gly Ser Phe Val Gly Asn  
 35 40 45

Ile Ser Lys Asp Leu Gly Leu Glu Pro Arg Glu Leu Ala Lys Arg Gly  
 50 55 60

Val Arg Ile Val Ser Arg Gly Lys Thr Gln Leu Phe Ala Val Asn Pro  
 65 70 75 80

# ES 2 534 734 A1

Arg Ser Gly Ser Leu Ile Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu  
 85 90 95

Cys Glu Thr Val Ser Ser Cys Phe Leu Asn Met Glu Leu Leu Val Glu  
 100 105 110

Asp Thr Leu Lys Ile Tyr Gly Val Glu Val Glu Ile Ile Asp Ile Asn  
 115 120 125

Asp Asn Ala Pro Ser Phe Gln Glu Asp Glu Val Glu Ile Lys Val Ser  
 130 135 140

Glu His Ala Ile Pro Gly Ala Arg Phe Ala Leu Pro Asn Ala Arg Asp  
 145 150 155 160

Pro Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn  
 165 170 175

Asn Tyr Phe Ser Leu Gln Leu Arg Gly Arg Thr Asp Gly Ala Lys Asn  
 180 185 190

Pro Glu Leu Val Leu Glu Gly Ser Leu Asp Arg Glu Lys Glu Ala Ala  
 195 200 205

His Leu Leu Leu Leu Thr Ala Leu Asp Gly Gly Asp Pro Ile Arg Lys  
 210 215 220

Gly Ala Val Pro Ile Arg Val Val Val Leu Asp Val Asn Asp His Ile  
 225 230 235 240

Pro Met Phe Thr Gln Ser Val Tyr Arg Val Ser Val Pro Glu Asn Ile  
 245 250 255

Ser Ser Gly Thr Arg Val Leu Met Val Asn Ala Thr Asp Pro Asp Glu  
 260 265 270

Gly Ile Asn Gly Glu Val Met Tyr Ser Phe Arg Asn Met Glu Ser Lys  
 275 280 285

Ala Ser Glu Ile Phe Gln Leu Asp Ser Gln Thr Gly Glu Val Gln Val  
 290 295 300

Arg Gly Ser Leu Asp Phe Glu Lys Tyr Arg Phe Tyr Glu Met Glu Ile  
 305 310 315 320

# ES 2 534 734 A1

Gln Gly Gln Asp Gly Gly Gly Leu Phe Thr Thr Thr Thr Met Leu Ile  
 325 330 335

Thr Val Val Asp Val Asn Asp Asn Ala Pro Glu Ile Thr Ile Thr Ser  
 340 345 350

Ser Ile Asn Ser Ile Leu Glu Asn Ser Pro Pro Gly Thr Val Ile Ala  
 355 360 365

Leu Leu Asn Val Gln Asp Gln Asp Ser Gly Glu Asn Gly Gln Val Ser  
 370 375 380

Cys Phe Ile Pro Asn His Leu Pro Phe Lys Leu Glu Lys Thr Tyr Gly  
 385 390 395 400

Asn Tyr Tyr Lys Leu Ile Thr Ser Arg Val Leu Asp Arg Glu Leu Val  
 405 410 415

Gln Ser Tyr Asn Ile Thr Leu Thr Ala Thr Asp Gln Gly Ser Pro Pro  
 420 425 430

Leu Ser Ala Glu Thr His Val Trp Leu Asn Val Ala Asp Asp Asn Asp  
 435 440 445

Asn Pro Pro Val Phe Pro His Ser Ser Tyr Ser Ala Tyr Ile Pro Glu  
 450 455 460

Asn Asn Pro Arg Gly Ala Ser Ile Phe Ser Val Thr Ala Leu Asp Pro  
 465 470 475 480

Asp Ser Lys Gln Asn Ala Leu Val Thr Tyr Ser Leu Thr Asp Asp Thr  
 485 490 495

Val Gln Gly Val Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asn Thr  
 500 505 510

Gly Val Leu Tyr Ala Leu Gln Ser Phe Asp Tyr Glu Gln Phe Arg Asp  
 515 520 525

Leu Glu Leu Arg Val Ile Ala Arg Asp Ser Gly Asp Pro Pro Leu Ser  
 530 535 540

Ser Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala  
 545 550 555 560

# ES 2 534 734 A1

Pro Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val  
 565 570 575

Glu Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val  
 580 585 590

Val Ala Val Asp Lys Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg  
 595 600 605

Leu Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly Glu His Thr  
 610 615 620

Gly Glu Val Arg Thr Ala Arg Ala Leu Leu Asp Arg Asp Ala Leu Lys  
 625 630 635 640

Gln Ser Leu Val Val Ala Val Gln Asp His Gly Gln Pro Pro Leu Ser  
 645 650 655

Ala Thr Val Thr Leu Thr Val Ala Val Ala Asp Ser Ile Pro Glu Val  
 660 665 670

Leu Ala Asp Leu Gly Ser Leu Glu Ser Leu Ala Asn Ser Glu Thr Ser  
 675 680 685

Asp Leu Ser Leu Tyr Leu Val Val Ala Val Ala Val Ser Cys Ile  
 690 695 700

Phe Leu Val Phe Val Ile Val Leu Leu Ala Leu Arg Leu Trp Arg Trp  
 705 710 715 720

His Lys Ser Arg Leu Leu Gln Ala Ser Glu Gly Gly Leu Ala Gly Met  
 725 730 735

Pro Thr Ser His Phe Val Gly Val Asp Gly Val Gln Ala Phe Leu Gln  
 740 745 750

Thr Tyr Ser His Glu Val Ser Leu Ile Ala Asp Ser Gln Lys Ser His  
 755 760 765

Leu Ile Phe Pro Gln Pro Asn Tyr Gly Asp Thr Leu Ile Ser Gln Glu  
 770 775 780

Ser Cys Glu Lys Ser Glu Pro Leu Leu Ile Ala Glu Asp Ser Ala Ile  
 785 790 795 800

# ES 2 534 734 A1

Ile Leu Gly Lys Cys Asp Pro Thr Ser Asn Gln Gln Ala Pro Pro Asn  
805 810 815

Thr Asp Trp Arg Phe Ser Gln Ala Gln Arg Pro Gly Thr Ser Gly Ser  
820 825 830

Gln Asn Gly Asp Asp Thr Gly Thr Trp Pro Asn Asn Gln Phe Asp Thr  
835 840 845

Glu Met Leu Gln Ala Met Ile Leu Ala Ser Ala Ser Glu Ala Ala Asp  
850 855 860

Gly Ser Ser Thr Leu Gly Gly Gly Ala Gly Thr Met Gly Leu Ser Ala  
865 870 875 880

Arg Tyr Gly Pro Gln Phe Thr Leu Gln His Val Pro Asp Tyr Arg Gln  
885 890 895

Asn Val Tyr Ile Pro Gly Ser Asn Ala Thr Leu Thr Asn Ala Ala Gly  
900 905 910

Lys Arg Asp Gly Lys Ala Pro Ala Gly Gly Asn Gly Asn Lys Lys Lys  
915 920 925

Ser Gly Lys Lys Glu Lys Lys  
930 935

<210> 121  
<211> 750  
<212> PRT  
<213> Homo sapiens

<400> 121

Met Ala Asn Arg Leu Gln Arg Gly Asp Arg Ser Arg Leu Leu Leu Leu  
1 5 10 15

Leu Cys Ile Phe Leu Gly Thr Leu Arg Gly Phe Arg Ala Arg Gln Ile  
20 25 30

Arg Tyr Ser Val Pro Glu Glu Thr Glu Lys Gly Ser Phe Val Gly Asn  
35 40 45

Ile Ser Lys Asp Leu Gly Leu Glu Pro Arg Glu Leu Ala Lys Arg Gly  
50 55 60



# ES 2 534 734 A1

Val Arg Ile Val Ser Arg Gly Lys Thr Gln Leu Phe Ala Val Asn Pro  
 65 70 75 80

Arg Ser Gly Ser Leu Ile Thr Ala Gly Arg Ile Asp Arg Glu Glu Leu  
 85 90 95

Cys Glu Thr Val Ser Ser Cys Phe Leu Asn Met Glu Leu Leu Val Glu  
 100 105 110

Asp Thr Leu Lys Ile Tyr Gly Val Glu Val Glu Ile Ile Asp Ile Asn  
 115 120 125

Asp Asn Ala Pro Ser Phe Gln Glu Asp Glu Val Glu Ile Lys Val Ser  
 130 135 140

Glu His Ala Ile Pro Gly Ala Arg Phe Ala Leu Pro Asn Ala Arg Asp  
 145 150 155 160

Pro Asp Val Gly Val Asn Ser Leu Gln Ser Tyr Gln Leu Ser Pro Asn  
 165 170 175

Asn Tyr Phe Ser Leu Gln Leu Arg Gly Arg Thr Asp Gly Ala Lys Asn  
 180 185 190

Pro Glu Leu Val Leu Glu Gly Ser Leu Asp Arg Glu Lys Glu Ala Ala  
 195 200 205

His Leu Leu Leu Leu Thr Ala Leu Asp Gly Gly Asp Pro Ile Arg Lys  
 210 215 220

Gly Ala Val Pro Ile Arg Val Val Val Leu Asp Val Asn Asp His Ile  
 225 230 235 240

Pro Met Phe Thr Gln Ser Val Tyr Arg Val Ser Val Pro Glu Asn Ile  
 245 250 255

Ser Ser Gly Thr Arg Val Leu Met Val Asn Ala Thr Asp Pro Asp Glu  
 260 265 270

Gly Ile Asn Gly Glu Val Met Tyr Ser Phe Arg Asn Met Glu Ser Lys  
 275 280 285

Ala Ser Glu Ile Phe Gln Leu Asp Ser Gln Thr Gly Glu Val Gln Val  
 290 295 300

# ES 2 534 734 A1

Arg Gly Ser Leu Asp Phe Glu Lys Tyr Arg Phe Tyr Glu Met Glu Ile  
 305 310 315 320

Gln Gly Gln Asp Gly Gly Gly Leu Phe Thr Thr Thr Thr Met Leu Ile  
 325 330 335

Thr Val Val Asp Val Asn Asp Asn Ala Pro Glu Ile Thr Ile Thr Ser  
 340 345 350

Ser Ile Asn Ser Ile Leu Glu Asn Ser Pro Pro Gly Thr Val Ile Ala  
 355 360 365

Leu Leu Asn Val Gln Asp Gln Asp Ser Gly Glu Asn Gly Gln Val Ser  
 370 375 380

Cys Phe Ile Pro Asn His Leu Pro Phe Lys Leu Glu Lys Thr Tyr Gly  
 385 390 395 400

Asn Tyr Tyr Lys Leu Ile Thr Ser Arg Val Leu Asp Arg Glu Leu Val  
 405 410 415

Gln Ser Tyr Asn Ile Thr Leu Thr Ala Thr Asp Gln Gly Ser Pro Pro  
 420 425 430

Leu Ser Ala Glu Thr His Val Trp Leu Asn Val Ala Asp Asp Asn Asp  
 435 440 445

Asn Pro Pro Val Phe Pro His Ser Ser Tyr Ser Ala Tyr Ile Pro Glu  
 450 455 460

Asn Asn Pro Arg Gly Ala Ser Ile Phe Ser Val Thr Ala Leu Asp Pro  
 465 470 475 480

Asp Ser Lys Gln Asn Ala Leu Val Thr Tyr Ser Leu Thr Asp Asp Thr  
 485 490 495

Val Gln Gly Val Pro Leu Ser Ser Tyr Val Ser Ile Asn Ser Asn Thr  
 500 505 510

Gly Val Leu Tyr Ala Leu Gln Ser Phe Asp Tyr Glu Gln Phe Arg Asp  
 515 520 525

Leu Glu Leu Arg Val Ile Ala Arg Asp Ser Gly Asp Pro Pro Leu Ser  
 530 535 540

# ES 2 534 734 A1

Ser Asn Val Ser Leu Ser Leu Phe Val Leu Asp Gln Asn Asp Asn Ala  
 545 550 555 560

Pro Glu Ile Leu Tyr Pro Ala Leu Pro Thr Asp Gly Ser Thr Gly Val  
 565 570 575

Glu Leu Ala Pro Arg Ser Ala Glu Pro Gly Tyr Leu Val Thr Lys Val  
 580 585 590

Val Ala Val Asp Lys Asp Ser Gly Gln Asn Ala Trp Leu Ser Tyr Arg  
 595 600 605

Leu Leu Lys Ala Ser Glu Pro Gly Leu Phe Ala Val Gly Glu His Thr  
 610 615 620

Gly Glu Gln Ala Pro Pro Asn Thr Asp Trp Arg Phe Ser Gln Ala Gln  
 625 630 635 640

Arg Pro Gly Thr Ser Gly Ser Gln Asn Gly Asp Asp Thr Gly Thr Trp  
 645 650 655

Pro Asn Asn Gln Phe Asp Thr Glu Met Leu Gln Ala Met Ile Leu Ala  
 660 665 670

Ser Ala Ser Glu Ala Ala Asp Gly Ser Ser Thr Leu Gly Gly Gly Ala  
 675 680 685

Gly Thr Met Gly Leu Ser Ala Arg Tyr Gly Pro Gln Phe Thr Leu Gln  
 690 695 700

His Val Pro Asp Tyr Arg Gln Asn Val Tyr Ile Pro Gly Ser Asn Ala  
 705 710 715 720

Thr Leu Thr Asn Ala Ala Gly Lys Arg Asp Gly Lys Ala Pro Ala Gly  
 725 730 735

Gly Asn Gly Asn Lys Lys Lys Ser Gly Lys Lys Glu Lys Lys  
 740 745 750

- <210> 122
- <211> 462
- <212> PRT
- <213> Homo sapiens
- <400> 122

# ES 2 534 734 A1

Met Ala Ser Asn Ser Ser Ser Cys Pro Thr Pro Gly Gly Gly His Leu  
 1 5 10 15

Asn Gly Tyr Pro Val Pro Pro Tyr Ala Phe Phe Phe Pro Pro Met Leu  
 20 25 30

Gly Gly Leu Ser Pro Pro Gly Ala Leu Thr Thr Leu Gln His Gln Leu  
 35 40 45

Pro Val Ser Gly Tyr Ser Thr Pro Ser Pro Ala Thr Ile Glu Thr Gln  
 50 55 60

Ser Ser Ser Ser Glu Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro  
 65 70 75 80

Leu Pro Arg Ile Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser  
 85 90 95

Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe  
 100 105 110

Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys  
 115 120 125

Asn Cys Ile Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg  
 130 135 140

Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn  
 145 150 155 160

Asp Arg Asn Lys Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu  
 165 170 175

Ser Tyr Thr Leu Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg  
 180 185 190

Lys Ala His Gln Glu Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr  
 195 200 205

Thr Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu  
 210 215 220

Trp Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val  
 225 230 235 240

ES 2 534 734 A1

Glu Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp  
 245 250 255

Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg  
 260 265 270

Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp  
 275 280 285

Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro  
 290 295 300

Leu Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu  
 305 310 315 320

Met Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys  
 325 330 335

Gly Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln  
 340 345 350

Glu Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro  
 355 360 365

Ser Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu  
 370 375 380

Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met  
 385 390 395 400

Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn  
 405 410 415

Ser Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg  
 420 425 430

Asp Gly Gly Gly Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu  
 435 440 445

Ser Pro Ser Ser Asn Arg Ser Ser Pro Ala Thr His Ser Pro  
 450 455 460

<210> 123  
 <211> 462

ES 2 534 734 A1

<212> PRT

<213> Homo sapiens

<400> 123

Met Ala Ser Asn Ser Ser Ser Cys Pro Thr Pro Gly Gly Gly His Leu  
1 5 10 15

Asn Gly Tyr Pro Val Pro Pro Tyr Ala Phe Phe Phe Pro Pro Met Leu  
20 25 30

Gly Gly Leu Ser Pro Pro Gly Ala Leu Thr Thr Leu Gln His Gln Leu  
35 40 45

Pro Val Ser Gly Tyr Ser Thr Pro Ser Pro Ala Thr Ile Glu Thr Gln  
50 55 60

Ser Ser Ser Ser Glu Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro  
65 70 75 80

Leu Pro Arg Ile Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser  
85 90 95

Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe  
100 105 110

Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys  
115 120 125

Asn Cys Ile Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg  
130 135 140

Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn  
145 150 155 160

Asp Arg Asn Lys Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu  
165 170 175

Ser Tyr Thr Leu Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg  
180 185 190

Lys Ala His Gln Glu Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr  
195 200 205

# ES 2 534 734 A1

Thr Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu  
 210 215 220

Trp Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val  
 225 230 235 240

Glu Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp  
 245 250 255

Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg  
 260 265 270

Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp  
 275 280 285

Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro  
 290 295 300

Leu Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu  
 305 310 315 320

Met Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys  
 325 330 335

Gly Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln  
 340 345 350

Glu Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro  
 355 360 365

Ser Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu  
 370 375 380

Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met  
 385 390 395 400

Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn  
 405 410 415

Ser Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg  
 420 425 430

Asp Gly Gly Gly Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu  
 435 440 445

# ES 2 534 734 A1

Ser Pro Ser Ser Asn Arg Ser Ser Pro Ala Thr His Ser Pro  
 450 455 460

<210> 124  
 <211> 365  
 <212> PRT  
 <213> Homo sapiens  
 <400> 124

Met Ala Ser Asn Ser Ser Ser Cys Pro Thr Pro Gly Gly Gly His Leu  
 1 5 10 15

Asn Gly Tyr Pro Val Pro Pro Tyr Ala Phe Phe Phe Pro Pro Met Leu  
 20 25 30

Gly Gly Leu Ser Pro Pro Gly Ala Leu Thr Thr Leu Gln His Gln Leu  
 35 40 45

Pro Val Ser Gly Tyr Ser Thr Pro Ser Pro Ala Thr Val Arg Asn Asp  
 50 55 60

Arg Asn Lys Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu Ser  
 65 70 75 80

Tyr Thr Leu Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg Lys  
 85 90 95

Ala His Gln Glu Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr Thr  
 100 105 110

Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu Trp  
 115 120 125

Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val Glu  
 130 135 140

Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp Gln  
 145 150 155 160

Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg Ile  
 165 170 175

Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp Gly  
 180 185 190



# ES 2 534 734 A1

Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro Leu  
 195 200 205

Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu Met  
 210 215 220

Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys Gly  
 225 230 235 240

Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln Glu  
 245 250 255

Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro Ser  
 260 265 270

Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu Arg  
 275 280 285

Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met Glu  
 290 295 300

Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn Ser  
 305 310 315 320

Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg Asp  
 325 330 335

Gly Gly Gly Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu Ser  
 340 345 350

Pro Ser Ser Asn Arg Ser Ser Pro Ala Thr His Ser Pro  
 355 360 365

<210> 125  
 <211> 457  
 <212> PRT  
 <213> Homo sapiens

<400> 125

Met Tyr Glu Ser Val Glu Val Gly Gly Pro Thr Pro Asn Pro Phe Leu  
 1 5 10 15

Val Val Asp Phe Tyr Asn Gln Asn Arg Ala Cys Leu Leu Pro Glu Lys  
 20 25 30

# ES 2 534 734 A1

Gly Leu Pro Ala Pro Gly Pro Tyr Ser Thr Pro Leu Arg Thr Pro Leu  
 35 40 45

Trp Asn Gly Ser Asn His Ser Ile Glu Thr Gln Ser Ser Ser Ser Glu  
 50 55 60

Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro Leu Pro Arg Ile Tyr  
 65 70 75 80

Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser Gly Tyr His Tyr Gly  
 85 90 95

Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile Gln  
 100 105 110

Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys Asn Cys Ile Ile Asn  
 115 120 125

Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg Leu Gln Lys Cys Phe  
 130 135 140

Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn Asp Arg Asn Lys Lys  
 145 150 155 160

Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu Ser Tyr Thr Leu Thr  
 165 170 175

Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg Lys Ala His Gln Glu  
 180 185 190

Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr Thr Thr Asn Asn Ser  
 195 200 205

Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu Trp Asp Lys Phe Ser  
 210 215 220

Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val Glu Phe Ala Lys Gln  
 225 230 235 240

Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp Gln Ile Thr Leu Leu  
 245 250 255

Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg Ile Cys Thr Arg Tyr  
 260 265 270

# ES 2 534 734 A1

Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp Gly Leu Thr Leu Asn  
 275 280 285

Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro Leu Thr Asp Leu Val  
 290 295 300

Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu Met Asp Asp Ala Glu  
 305 310 315 320

Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys Gly Asp Arg Gln Asp  
 325 330 335

Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln Glu Pro Leu Leu Glu  
 340 345 350

Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro Ser Arg Pro His Met  
 355 360 365

Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu Arg Ser Ile Ser Ala  
 370 375 380

Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met Glu Ile Pro Gly Ser  
 385 390 395 400

Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn Ser Glu Gly Leu Asp  
 405 410 415

Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg Asp Gly Gly Gly Leu  
 420 425 430

Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu Ser Pro Ser Ser Asn  
 435 440 445

Arg Ser Ser Pro Ala Thr His Ser Pro  
 450 455

<210> 126  
 <211> 1441  
 <212> PRT  
 <213> Homo sapiens

<400> 126

Met Ala Thr Ala Ala Ala Ala Ala Val Met Ala Pro Pro Gly Cys  
 1 5 10 15

# ES 2 534 734 A1

Pro Gly Ser Cys Pro Asn Phe Ala Val Val Cys Ser Phe Leu Glu Arg  
 20 25 30

Tyr Gly Pro Leu Leu Asp Leu Pro Glu Leu Pro Phe Pro Glu Leu Glu  
 35 40 45

Arg Val Leu Gln Ala Pro Pro Pro Asp Val Gly Asn Gly Glu Val Pro  
 50 55 60

Lys Glu Leu Val Glu Leu His Leu Lys Leu Met Arg Lys Ile Gly Lys  
 65 70 75 80

Ser Val Thr Ala Asp Arg Trp Glu Lys Tyr Leu Ile Lys Ile Cys Gln  
 85 90 95

Glu Phe Asn Ser Thr Trp Ala Trp Glu Met Glu Lys Lys Gly Tyr Leu  
 100 105 110

Glu Met Ser Val Glu Cys Lys Leu Ala Leu Leu Lys Tyr Leu Cys Glu  
 115 120 125

Cys Gln Phe Asp Asp Asn Leu Lys Phe Lys Asn Ile Ile Asn Glu Glu  
 130 135 140

Asp Ala Asp Thr Met Arg Leu Gln Pro Ile Gly Arg Asp Lys Asp Gly  
 145 150 155 160

Leu Met Tyr Trp Tyr Gln Leu Asp Gln Asp His Asn Val Arg Met Tyr  
 165 170 175

Ile Glu Glu Gln Asp Asp Gln Asp Gly Ser Ser Trp Lys Cys Ile Val  
 180 185 190

Arg Asn Arg Asn Glu Leu Ala Glu Thr Leu Ala Leu Leu Lys Ala Gln  
 195 200 205

Ile Asp Pro Val Leu Leu Lys Asn Ser Ser Gln Gln Asp Asn Ser Ser  
 210 215 220

Arg Glu Ser Pro Ser Leu Glu Asp Glu Glu Thr Lys Lys Glu Glu Glu  
 225 230 235 240

Thr Pro Lys Gln Glu Glu Gln Lys Glu Ser Glu Lys Met Lys Ser Glu  
 245 250 255

# ES 2 534 734 A1

Glu Gln Pro Met Asp Leu Glu Asn Arg Ser Thr Ala Asn Val Leu Glu  
 260 265 270

Glu Thr Thr Val Lys Lys Glu Lys Glu Asp Glu Lys Glu Leu Val Lys  
 275 280 285

Leu Pro Val Ile Val Lys Leu Glu Lys Pro Leu Pro Glu Asn Glu Glu  
 290 295 300

Lys Lys Ile Ile Lys Glu Glu Ser Asp Ser Phe Lys Glu Asn Val Lys  
 305 310 315 320

Pro Ile Lys Val Glu Val Lys Glu Cys Arg Ala Asp Pro Lys Asp Thr  
 325 330 335

Lys Ser Ser Met Glu Lys Pro Val Ala Gln Glu Pro Glu Arg Ile Glu  
 340 345 350

Phe Gly Gly Asn Ile Lys Ser Ser His Glu Ile Thr Glu Lys Ser Thr  
 355 360 365

Glu Glu Thr Glu Lys Leu Lys Asn Asp Gln Gln Ala Lys Ile Pro Leu  
 370 375 380

Lys Lys Arg Glu Ile Lys Leu Ser Asp Asp Phe Asp Ser Pro Val Lys  
 385 390 395 400

Gly Pro Leu Cys Lys Ser Val Thr Pro Thr Lys Glu Phe Leu Lys Asp  
 405 410 415

Glu Ile Lys Gln Glu Glu Glu Thr Cys Lys Arg Ile Ser Thr Ile Thr  
 420 425 430

Ala Leu Gly His Glu Gly Lys Gln Leu Val Asn Gly Glu Val Ser Asp  
 435 440 445

Glu Arg Val Ala Pro Asn Phe Lys Thr Glu Pro Ile Glu Thr Lys Phe  
 450 455 460

Tyr Glu Thr Lys Glu Glu Ser Tyr Ser Pro Ser Lys Asp Arg Asn Ile  
 465 470 475 480

Ile Thr Glu Gly Asn Gly Thr Glu Ser Leu Asn Ser Val Ile Thr Ser  
 485 490 495

# ES 2 534 734 A1

Met Lys Thr Gly Glu Leu Glu Lys Glu Thr Ala Pro Leu Arg Lys Asp  
500 505 510

Ala Asp Ser Ser Ile Ser Val Leu Glu Ile His Ser Gln Lys Ala Gln  
515 520 525

Ile Glu Glu Pro Asp Pro Pro Glu Met Glu Thr Ser Leu Asp Ser Ser  
530 535 540

Glu Met Ala Lys Asp Leu Ser Ser Lys Thr Ala Leu Ser Ser Thr Glu  
545 550 555 560

Ser Cys Thr Met Lys Gly Glu Glu Lys Ser Pro Lys Thr Lys Lys Asp  
565 570 575

Lys Arg Pro Pro Ile Leu Glu Cys Leu Glu Lys Leu Glu Lys Ser Lys  
580 585 590

Lys Thr Phe Leu Asp Lys Asp Ala Gln Arg Leu Ser Pro Ile Pro Glu  
595 600 605

Glu Val Pro Lys Ser Thr Leu Glu Ser Glu Lys Pro Gly Ser Pro Glu  
610 615 620

Ala Ala Glu Thr Ser Pro Pro Ser Asn Ile Ile Asp His Cys Glu Lys  
625 630 635 640

Leu Ala Ser Glu Lys Glu Val Val Glu Cys Gln Ser Thr Ser Thr Val  
645 650 655

Gly Gly Gln Ser Val Lys Lys Val Asp Leu Glu Thr Leu Lys Glu Asp  
660 665 670

Ser Glu Phe Thr Lys Val Glu Met Asp Asn Leu Asp Asn Ala Gln Thr  
675 680 685

Ser Gly Ile Glu Glu Pro Ser Glu Thr Lys Gly Ser Met Gln Lys Ser  
690 695 700

Lys Phe Lys Tyr Lys Leu Val Pro Glu Glu Glu Thr Thr Ala Ser Glu  
705 710 715 720

Asn Thr Glu Ile Thr Ser Glu Arg Gln Lys Glu Gly Ile Lys Leu Thr  
725 730 735

# ES 2 534 734 A1

Ile Arg Ile Ser Ser Arg Lys Lys Lys Pro Asp Ser Pro Pro Lys Val  
 740 745 750

Leu Glu Pro Glu Asn Lys Gln Glu Lys Thr Glu Lys Glu Glu Glu Lys  
 755 760 765

Thr Asn Val Gly Arg Thr Leu Arg Arg Ser Pro Arg Ile Ser Arg Pro  
 770 775 780

Thr Ala Lys Val Ala Glu Ile Arg Asp Gln Lys Ala Asp Lys Lys Arg  
 785 790 795 800

Gly Glu Gly Glu Asp Glu Val Glu Glu Glu Ser Thr Ala Leu Gln Lys  
 805 810 815

Thr Asp Lys Lys Glu Ile Leu Lys Lys Ser Glu Lys Asp Thr Asn Ser  
 820 825 830

Lys Val Ser Lys Val Lys Pro Lys Gly Lys Val Arg Trp Thr Gly Ser  
 835 840 845

Arg Thr Arg Gly Arg Trp Lys Tyr Ser Ser Asn Asp Glu Ser Glu Gly  
 850 855 860

Ser Gly Ser Glu Lys Ser Ser Ala Ala Ser Glu Glu Glu Glu Lys  
 865 870 875 880

Glu Ser Glu Glu Ala Ile Leu Ala Asp Asp Asp Glu Pro Cys Lys Lys  
 885 890 895

Cys Gly Leu Pro Asn His Pro Glu Leu Ile Leu Leu Cys Asp Ser Cys  
 900 905 910

Asp Ser Gly Tyr His Thr Ala Cys Leu Arg Pro Pro Leu Met Ile Ile  
 915 920 925

Pro Asp Gly Glu Trp Phe Cys Pro Pro Cys Gln His Lys Leu Leu Cys  
 930 935 940

Glu Lys Leu Glu Glu Gln Leu Gln Asp Leu Asp Val Ala Leu Lys Lys  
 945 950 955 960

Lys Glu Arg Ala Glu Arg Arg Lys Glu Arg Leu Val Tyr Val Gly Ile  
 965 970 975

ES 2 534 734 A1

Ser Ile Glu Asn Ile Ile Pro Pro Gln Glu Pro Asp Phe Ser Glu Asp  
 980 985 990

Gln Glu Glu Lys Lys Lys Asp Ser Lys Lys Ser Lys Ala Asn Leu Leu  
 995 1000 1005

Glu Arg Arg Ser Thr Arg Thr Arg Lys Cys Ile Ser Tyr Arg Phe  
 1010 1015 1020

Asp Glu Phe Asp Glu Ala Ile Asp Glu Ala Ile Glu Asp Asp Ile  
 1025 1030 1035

Lys Glu Ala Asp Gly Gly Gly Val Gly Arg Gly Lys Asp Ile Ser  
 1040 1045 1050

Thr Ile Thr Gly His Arg Gly Lys Asp Ile Ser Thr Ile Leu Asp  
 1055 1060 1065

Glu Glu Arg Lys Glu Asn Lys Arg Pro Gln Arg Ala Ala Ala Ala  
 1070 1075 1080

Arg Arg Lys Lys Arg Arg Arg Leu Asn Asp Leu Asp Ser Asp Ser  
 1085 1090 1095

Asn Leu Asp Glu Glu Glu Ser Glu Asp Glu Phe Lys Ile Ser Asp  
 1100 1105 1110

Gly Ser Gln Asp Glu Phe Val Val Ser Asp Glu Asn Pro Asp Glu  
 1115 1120 1125

Ser Glu Glu Asp Pro Pro Ser Asn Asp Asp Ser Asp Thr Asp Phe  
 1130 1135 1140

Cys Ser Arg Arg Leu Arg Arg His Pro Ser Arg Pro Met Arg Gln  
 1145 1150 1155

Ser Arg Arg Leu Arg Arg Lys Thr Pro Lys Lys Lys Tyr Ser Asp  
 1160 1165 1170

Asp Asp Glu Glu Glu Glu Ser Glu Glu Asn Ser Arg Asp Ser Glu  
 1175 1180 1185

Ser Asp Phe Ser Asp Asp Phe Ser Asp Asp Phe Val Glu Thr Arg  
 1190 1195 1200



## ES 2 534 734 A1

Arg	Arg	Arg	Ser	Arg	Arg	Asn	Gln	Lys	Arg	Gln	Ile	Asn	Tyr	Lys
	1205					1210					1215			
Glu	Asp	Ser	Glu	Ser	Asp	Gly	Ser	Gln	Lys	Ser	Leu	Arg	Arg	Gly
	1220					1225					1230			
Lys	Glu	Ile	Arg	Arg	Val	His	Lys	Arg	Arg	Leu	Ser	Ser	Ser	Glu
	1235					1240					1245			
Ser	Glu	Glu	Ser	Tyr	Leu	Ser	Lys	Asn	Ser	Glu	Asp	Asp	Glu	Leu
	1250					1255					1260			
Ala	Lys	Glu	Ser	Lys	Arg	Ser	Val	Arg	Lys	Arg	Gly	Arg	Ser	Thr
	1265					1270					1275			
Asp	Glu	Tyr	Ser	Glu	Ala	Asp	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Gly
	1280					1285					1290			
Lys	Pro	Ser	Arg	Lys	Arg	Leu	His	Arg	Ile	Glu	Thr	Asp	Glu	Glu
	1295					1300					1305			
Glu	Ser	Cys	Asp	Asn	Ala	His	Gly	Asp	Ala	Asn	Gln	Pro	Ala	Arg
	1310					1315					1320			
Asp	Ser	Gln	Pro	Arg	Val	Leu	Pro	Ser	Glu	Gln	Glu	Ser	Thr	Lys
	1325					1330					1335			
Lys	Pro	Tyr	Arg	Ile	Glu	Ser	Asp	Glu	Glu	Glu	Asp	Phe	Glu	Asn
	1340					1345					1350			
Val	Gly	Lys	Val	Gly	Ser	Pro	Leu	Asp	Tyr	Ser	Leu	Val	Asp	Leu
	1355					1360					1365			
Pro	Ser	Thr	Asn	Gly	Gln	Ser	Pro	Gly	Lys	Ala	Ile	Glu	Asn	Leu
	1370					1375					1380			
Ile	Gly	Lys	Pro	Thr	Glu	Lys	Ser	Gln	Thr	Pro	Lys	Asp	Asn	Ser
	1385					1390					1395			
Thr	Ala	Ser	Ala	Ser	Leu	Ala	Ser	Asn	Gly	Thr	Ser	Gly	Gly	Gln
	1400					1405					1410			
Glu	Ala	Gly	Ala	Pro	Glu	Glu	Glu	Glu	Asp	Glu	Leu	Leu	Arg	Val
	1415					1420					1425			

# ES 2 534 734 A1

Thr Asp Leu Val Asp Tyr Val Cys Asn Ser Glu Gln Leu  
 1430 1435 1440

<210> 127  
 <211> 1285  
 <212> PRT  
 <213> Homo sapiens  
 <400> 127

Met Glu Arg Arg Trp Asp Leu Asp Leu Thr Tyr Val Thr Glu Arg Ile  
 1 5 10 15

Leu Ala Ala Ala Phe Pro Ala Arg Pro Asp Glu Gln Arg His Arg Gly  
 20 25 30

His Leu Arg Glu Leu Ala His Val Leu Gln Ser Lys His Arg Asp Lys  
 35 40 45

Tyr Leu Leu Phe Asn Leu Ser Glu Lys Arg His Asp Leu Thr Arg Leu  
 50 55 60

Asn Pro Lys Val Gln Asp Phe Gly Trp Pro Glu Leu His Ala Pro Pro  
 65 70 75 80

Leu Asp Lys Leu Cys Ser Ile Cys Lys Ala Met Glu Thr Trp Leu Ser  
 85 90 95

Ala Asp Pro Gln His Val Val Val Leu Tyr Cys Lys Gly Asn Lys Gly  
 100 105 110

Lys Leu Gly Val Ile Val Ser Ala Tyr Met His Tyr Ser Lys Ile Ser  
 115 120 125

Ala Gly Ala Asp Gln Ala Leu Ala Thr Leu Thr Met Arg Lys Phe Cys  
 130 135 140

Glu Asp Lys Val Ala Thr Glu Leu Gln Pro Ser Gln Arg Arg Tyr Ile  
 145 150 155 160

Ser Tyr Phe Ser Gly Leu Leu Ser Gly Ser Ile Arg Met Asn Ser Ser  
 165 170 175

Pro Leu Phe Leu His Tyr Val Leu Ile Pro Met Leu Pro Ala Phe Glu  
 180 185 190

# ES 2 534 734 A1

Pro Gly Thr Gly Phe Gln Pro Phe Leu Lys Ile Tyr Gln Ser Met Gln  
 195 200 205

Leu Val Tyr Thr Ser Gly Val Tyr His Ile Ala Gly Pro Gly Pro Gln  
 210 215 220

Gln Leu Cys Ile Ser Leu Glu Pro Ala Leu Leu Leu Lys Gly Asp Val  
 225 230 235 240

Met Val Thr Cys Tyr His Lys Gly Gly Arg Gly Thr Asp Arg Thr Leu  
 245 250 255

Val Phe Arg Val Gln Phe His Thr Cys Thr Ile His Gly Pro Gln Leu  
 260 265 270

Thr Phe Pro Lys Asp Gln Leu Asp Glu Ala Trp Thr Asp Glu Arg Phe  
 275 280 285

Pro Phe Gln Ala Ser Val Glu Phe Val Phe Ser Ser Ser Pro Glu Lys  
 290 295 300

Ile Lys Gly Ser Thr Pro Arg Asn Asp Pro Ser Val Ser Val Asp Tyr  
 305 310 315 320

Asn Thr Thr Glu Pro Ala Val Arg Trp Asp Ser Tyr Glu Asn Phe Asn  
 325 330 335

Gln His His Glu Asp Ser Val Asp Gly Ser Leu Thr His Thr Arg Gly  
 340 345 350

Pro Leu Asp Gly Ser Pro Tyr Ala Gln Val Gln Arg Pro Pro Arg Gln  
 355 360 365

Thr Pro Pro Ala Pro Ser Pro Glu Pro Pro Pro Pro Pro Met Leu Ser  
 370 375 380

Val Ser Ser Asp Ser Gly His Ser Ser Thr Leu Thr Thr Glu Pro Ala  
 385 390 395 400

Ala Glu Ser Pro Gly Arg Pro Pro Pro Thr Ala Ala Glu Arg Gln Glu  
 405 410 415

Leu Asp Arg Leu Leu Gly Gly Cys Gly Val Ala Ser Gly Gly Arg Gly  
 420 425 430

# ES 2 534 734 A1

Ala Gly Arg Glu Thr Ala Ile Leu Asp Asp Glu Glu Gln Pro Thr Val  
435 440 445

Gly Gly Gly Pro His Leu Gly Val Tyr Pro Gly His Arg Pro Gly Leu  
450 455 460

Ser Arg His Cys Ser Cys Arg Gln Gly Tyr Arg Glu Pro Cys Gly Val  
465 470 475 480

Pro Asn Gly Gly Tyr Tyr Arg Pro Glu Gly Thr Leu Glu Arg Arg Arg  
485 490 495

Leu Ala Tyr Gly Gly Tyr Glu Gly Ser Pro Gln Gly Tyr Ala Glu Ala  
500 505 510

Ser Met Glu Lys Arg Arg Leu Cys Arg Ser Leu Ser Glu Gly Leu Tyr  
515 520 525

Pro Tyr Pro Pro Glu Met Gly Lys Pro Ala Thr Gly Asp Phe Gly Tyr  
530 535 540

Arg Ala Pro Gly Tyr Arg Glu Val Val Ile Leu Glu Asp Pro Gly Leu  
545 550 555 560

Pro Ala Leu Tyr Pro Cys Pro Ala Cys Glu Glu Lys Leu Ala Leu Pro  
565 570 575

Thr Ala Ala Leu Tyr Gly Leu Arg Leu Glu Arg Glu Ala Gly Glu Gly  
580 585 590

Trp Ala Ser Glu Ala Gly Lys Pro Leu Leu His Pro Val Arg Pro Gly  
595 600 605

His Pro Leu Pro Leu Leu Leu Pro Ala Cys Gly His His His Ala Pro  
610 615 620

Met Pro Asp Tyr Ser Cys Leu Lys Pro Pro Lys Ala Gly Glu Glu Gly  
625 630 635 640

His Glu Gly Cys Ser Tyr Thr Met Cys Pro Glu Gly Arg Tyr Gly His  
645 650 655

Pro Gly Tyr Pro Ala Leu Val Thr Tyr Ser Tyr Gly Gly Ala Val Pro  
660 665 670

# ES 2 534 734 A1

Ser Tyr Cys Pro Ala Tyr Gly Arg Val Pro His Ser Cys Gly Ser Pro  
 675 680 685

Gly Glu Gly Arg Gly Tyr Pro Ser Pro Gly Ala His Ser Pro Arg Ala  
 690 700

Gly Ser Ile Ser Pro Gly Ser Pro Pro Tyr Pro Gln Ser Arg Lys Leu  
 705 710 715 720

Ser Tyr Glu Ile Pro Thr Glu Glu Gly Gly Asp Arg Tyr Pro Leu Pro  
 725 730 735

Gly His Leu Ala Ser Ala Gly Pro Leu Ala Ser Ala Glu Ser Leu Glu  
 740 745 750

Pro Val Ser Trp Arg Glu Gly Pro Ser Gly His Ser Thr Leu Pro Arg  
 755 760 765

Ser Pro Arg Asp Ala Pro Cys Ser Ala Ser Ser Glu Leu Ser Gly Pro  
 770 775 780

Ser Thr Pro Leu His Thr Ser Ser Pro Val Gln Gly Lys Glu Ser Thr  
 785 790 795 800

Arg Arg Gln Asp Thr Arg Ser Pro Thr Ser Ala Pro Thr Gln Arg Leu  
 805 810 815

Ser Pro Gly Glu Ala Leu Pro Pro Val Ser Gln Ala Gly Thr Gly Lys  
 820 825 830

Ala Pro Glu Leu Pro Ser Gly Ser Gly Pro Glu Pro Leu Ala Pro Ser  
 835 840 845

Pro Val Ser Pro Thr Phe Pro Pro Ser Ser Pro Ser Asp Trp Pro Gln  
 850 855 860

Glu Arg Ser Pro Gly Gly His Ser Asp Gly Ala Ser Pro Arg Ser Pro  
 865 870 875 880

Val Pro Thr Thr Leu Pro Gly Leu Arg His Ala Pro Trp Gln Gly Pro  
 885 890 895

Arg Gly Pro Pro Asp Ser Pro Asp Gly Ser Pro Leu Thr Pro Val Pro  
 900 905 910

# ES 2 534 734 A1

Ser Gln Met Pro Trp Leu Val Ala Ser Pro Glu Pro Pro Gln Ser Ser  
 915 920 925

Pro Thr Pro Ala Phe Pro Leu Ala Ala Ser Tyr Asp Thr Asn Gly Leu  
 930 935 940

Ser Gln Pro Pro Leu Pro Glu Lys Arg His Leu Pro Gly Pro Gly Gln  
 945 950 955 960

Gln Pro Gly Pro Trp Gly Pro Glu Gln Ala Ser Ser Pro Ala Arg Gly  
 965 970 975

Ile Ser His His Val Thr Phe Ala Pro Leu Leu Ser Asp Asn Val Pro  
 980 985 990

Gln Thr Pro Glu Pro Pro Thr Gln Glu Ser Gln Ser Asn Val Lys Phe  
 995 1000 1005

Val Gln Asp Thr Ser Lys Phe Trp Tyr Lys Pro His Leu Ser Arg  
 1010 1015 1020

Asp Gln Ala Ile Ala Leu Leu Lys Asp Lys Asp Pro Gly Ala Phe  
 1025 1030 1035

Leu Ile Arg Asp Ser His Ser Phe Gln Gly Ala Tyr Gly Leu Ala  
 1040 1045 1050

Leu Lys Val Ala Thr Pro Pro Pro Ser Ala Gln Pro Trp Lys Gly  
 1055 1060 1065

Asp Pro Val Glu Gln Leu Val Arg His Phe Leu Ile Glu Thr Gly  
 1070 1075 1080

Pro Lys Gly Val Lys Ile Lys Gly Cys Pro Ser Glu Pro Tyr Phe  
 1085 1090 1095

Gly Ser Leu Ser Ala Leu Val Ser Gln His Ser Ile Ser Pro Ile  
 1100 1105 1110

Ser Leu Pro Cys Cys Leu Arg Ile Pro Ser Lys Asp Pro Leu Glu  
 1115 1120 1125

Glu Thr Pro Glu Ala Pro Val Pro Thr Asn Met Ser Thr Ala Ala  
 1130 1135 1140

ES 2 534 734 A1

Asp Leu Leu Arg Gln Gly Ala Ala Cys Ser Val Leu Tyr Leu Thr  
 1145 1150 1155

Ser Val Glu Thr Glu Ser Leu Thr Gly Pro Gln Ala Val Ala Arg  
 1160 1165 1170

Ala Ser Ser Ala Ala Leu Ser Cys Ser Pro Arg Pro Thr Pro Ala  
 1175 1180 1185

Val Val His Phe Lys Val Ser Ala Gln Gly Ile Thr Leu Thr Asp  
 1190 1195 1200

Asn Gln Arg Lys Leu Phe Phe Arg Arg His Tyr Pro Val Asn Ser  
 1205 1210 1215

Ile Thr Phe Ser Ser Thr Asp Pro Gln Asp Arg Arg Trp Thr Asn  
 1220 1225 1230

Pro Asp Gly Thr Thr Ser Lys Ile Phe Gly Phe Val Ala Lys Lys  
 1235 1240 1245

Pro Gly Ser Pro Trp Glu Asn Val Cys His Leu Phe Ala Glu Leu  
 1250 1255 1260

Asp Pro Asp Gln Pro Ala Gly Ala Ile Val Thr Phe Ile Thr Lys  
 1265 1270 1275

Val Leu Leu Gly Gln Arg Lys  
 1280 1285

<210> 128  
 <211> 1419  
 <212> PRT  
 <213> Homo sapiens

<400> 128

Met Asp Gly Gly Gly Val Cys Val Gly Arg Gly Asp Leu Leu Ser Ser  
 1 5 10 15

Pro Gln Ala Leu Gly Gln Leu Leu Arg Lys Glu Ser Arg Pro Arg Arg  
 20 25 30

Ala Met Lys Pro Arg Lys Ala Glu Pro His Ser Phe Arg Glu Lys Val  
 35 40 45

# ES 2 534 734 A1

Phe Arg Lys Lys Pro Pro Val Cys Ala Val Cys Lys Val Thr Ile Asp  
 50 55 60

Gly Thr Gly Val Ser Cys Arg Val Cys Lys Val Ala Thr His Arg Lys  
 65 70 75 80

Cys Glu Ala Lys Val Thr Ser Ala Cys Gln Ala Leu Pro Pro Val Glu  
 85 90 95

Leu Arg Arg Asn Thr Ala Pro Val Arg Arg Ile Glu His Leu Gly Ser  
 100 105 110

Thr Lys Ser Leu Asn His Ser Lys Gln Arg Ser Thr Leu Pro Arg Ser  
 115 120 125

Phe Ser Leu Asp Pro Leu Met Glu Arg Arg Trp Asp Leu Asp Leu Thr  
 130 135 140

Tyr Val Thr Glu Arg Ile Leu Ala Ala Ala Phe Pro Ala Arg Pro Asp  
 145 150 155 160

Glu Gln Arg His Arg Gly His Leu Arg Glu Leu Ala His Val Leu Gln  
 165 170 175

Ser Lys His Arg Asp Lys Tyr Leu Leu Phe Asn Leu Ser Glu Lys Arg  
 180 185 190

His Asp Leu Thr Arg Leu Asn Pro Lys Val Gln Asp Phe Gly Trp Pro  
 195 200 205

Glu Leu His Ala Pro Pro Leu Asp Lys Leu Cys Ser Ile Cys Lys Ala  
 210 215 220

Met Glu Thr Trp Leu Ser Ala Asp Pro Gln His Val Val Val Leu Tyr  
 225 230 235 240

Cys Lys Gly Asn Lys Gly Lys Leu Gly Val Ile Val Ser Ala Tyr Met  
 245 250 255

His Tyr Ser Lys Ile Ser Ala Gly Ala Asp Gln Ala Leu Ala Thr Leu  
 260 265 270

Thr Met Arg Lys Phe Cys Glu Asp Lys Val Ala Thr Glu Leu Gln Pro  
 275 280 285



# ES 2 534 734 A1

Ser Gln Arg Arg Tyr Ile Ser Tyr Phe Ser Gly Leu Leu Ser Gly Ser  
 290 295 300

Ile Arg Met Asn Ser Ser Pro Leu Phe Leu His Tyr Val Leu Ile Pro  
 305 310 315 320

Met Leu Pro Ala Phe Glu Pro Gly Thr Gly Phe Gln Pro Phe Leu Lys  
 325 330 335

Ile Tyr Gln Ser Met Gln Leu Val Tyr Thr Ser Gly Val Tyr His Ile  
 340 345 350

Ala Gly Pro Gly Pro Gln Gln Leu Cys Ile Ser Leu Glu Pro Ala Leu  
 355 360 365

Leu Leu Lys Gly Asp Val Met Val Thr Cys Tyr His Lys Gly Gly Arg  
 370 375 380

Gly Thr Asp Arg Thr Leu Val Phe Arg Val Gln Phe His Thr Cys Thr  
 385 390 395 400

Ile His Gly Pro Gln Leu Thr Phe Pro Lys Asp Gln Leu Asp Glu Ala  
 405 410 415

Trp Thr Asp Glu Arg Phe Pro Phe Gln Ala Ser Val Glu Phe Val Phe  
 420 425 430

Ser Ser Ser Pro Glu Lys Ile Lys Gly Ser Thr Pro Arg Asn Asp Pro  
 435 440 445

Ser Val Ser Val Asp Tyr Asn Thr Thr Glu Pro Ala Val Arg Trp Asp  
 450 455 460

Ser Tyr Glu Asn Phe Asn Gln His His Glu Asp Ser Val Asp Gly Ser  
 465 470 475 480

Leu Thr His Thr Arg Gly Pro Leu Asp Gly Ser Pro Tyr Ala Gln Val  
 485 490 495

Gln Arg Pro Pro Arg Gln Thr Pro Pro Ala Pro Ser Pro Glu Pro Pro  
 500 505 510

Pro Pro Pro Met Leu Ser Val Ser Ser Asp Ser Gly His Ser Ser Thr  
 515 520 525

# ES 2 534 734 A1

Leu Thr Thr Glu Pro Ala Ala Glu Ser Pro Gly Arg Pro Pro Pro Thr  
 530 535 540

Ala Ala Glu Arg Gln Glu Leu Asp Arg Leu Leu Gly Gly Cys Gly Val  
 545 550 555 560

Ala Ser Gly Gly Arg Gly Ala Gly Arg Glu Thr Ala Ile Leu Asp Asp  
 565 570 575

Glu Glu Gln Pro Thr Val Gly Gly Gly Pro His Leu Gly Val Tyr Pro  
 580 585 590

Gly His Arg Pro Gly Leu Ser Arg His Cys Ser Cys Arg Gln Gly Tyr  
 595 600 605

Arg Glu Pro Cys Gly Val Pro Asn Gly Gly Tyr Tyr Arg Pro Glu Gly  
 610 615 620

Thr Leu Glu Arg Arg Arg Leu Ala Tyr Gly Gly Tyr Glu Gly Ser Pro  
 625 630 635 640

Gln Gly Tyr Ala Glu Ala Ser Met Glu Lys Arg Arg Leu Cys Arg Ser  
 645 650 655

Leu Ser Glu Gly Leu Tyr Pro Tyr Pro Pro Glu Met Gly Lys Pro Ala  
 660 665 670

Thr Gly Asp Phe Gly Tyr Arg Ala Pro Gly Tyr Arg Glu Val Val Ile  
 675 680 685

Leu Glu Asp Pro Gly Leu Pro Ala Leu Tyr Pro Cys Pro Ala Cys Glu  
 690 695 700

Glu Lys Leu Ala Leu Pro Thr Ala Ala Leu Tyr Gly Leu Arg Leu Glu  
 705 710 715 720

Arg Glu Ala Gly Glu Gly Trp Ala Ser Glu Ala Gly Lys Pro Leu Leu  
 725 730 735

His Pro Val Arg Pro Gly His Pro Leu Pro Leu Leu Leu Pro Ala Cys  
 740 745 750

Gly His His His Ala Pro Met Pro Asp Tyr Ser Cys Leu Lys Pro Pro  
 755 760 765

# ES 2 534 734 A1

Lys Ala Gly Glu Glu Gly His Glu Gly Cys Ser Tyr Thr Met Cys Pro  
 770 775 780

Glu Gly Arg Tyr Gly His Pro Gly Tyr Pro Ala Leu Val Thr Tyr Ser  
 785 790 795 800

Tyr Gly Gly Ala Val Pro Ser Tyr Cys Pro Ala Tyr Gly Arg Val Pro  
 805 810 815

His Ser Cys Gly Ser Pro Gly Glu Gly Arg Gly Tyr Pro Ser Pro Gly  
 820 825 830

Ala His Ser Pro Arg Ala Gly Ser Ile Ser Pro Gly Ser Pro Pro Tyr  
 835 840 845

Pro Gln Ser Arg Lys Leu Ser Tyr Glu Ile Pro Thr Glu Glu Gly Gly  
 850 855 860

Asp Arg Tyr Pro Leu Pro Gly His Leu Ala Ser Ala Gly Pro Leu Ala  
 865 870 875 880

Ser Ala Glu Ser Leu Glu Pro Val Ser Trp Arg Glu Gly Pro Ser Gly  
 885 890 895

His Ser Thr Leu Pro Arg Ser Pro Arg Asp Ala Pro Cys Ser Ala Ser  
 900 905 910

Ser Glu Leu Ser Gly Pro Ser Thr Pro Leu His Thr Ser Ser Pro Val  
 915 920 925

Gln Gly Lys Glu Ser Thr Arg Arg Gln Asp Thr Arg Ser Pro Thr Ser  
 930 935 940

Ala Pro Thr Gln Arg Leu Ser Pro Gly Glu Ala Leu Pro Pro Val Ser  
 945 950 955 960

Gln Ala Gly Thr Gly Lys Ala Pro Glu Leu Pro Ser Gly Ser Gly Pro  
 965 970 975

Glu Pro Leu Ala Pro Ser Pro Val Ser Pro Thr Phe Pro Pro Ser Ser  
 980 985 990

Pro Ser Asp Trp Pro Gln Glu Arg Ser Pro Gly Gly His Ser Asp Gly  
 995 1000 1005

# ES 2 534 734 A1

Ala	Ser	Pro	Arg	Ser	Pro	Val	Pro	Thr	Thr	Leu	Pro	Gly	Leu	Arg
1010						1015					1020			
His	Ala	Pro	Trp	Gln	Gly	Pro	Arg	Gly	Pro	Pro	Asp	Ser	Pro	Asp
1025						1030					1035			
Gly	Ser	Pro	Leu	Thr	Pro	Val	Pro	Ser	Gln	Met	Pro	Trp	Leu	Val
1040						1045					1050			
Ala	Ser	Pro	Glu	Pro	Pro	Gln	Ser	Ser	Pro	Thr	Pro	Ala	Phe	Pro
1055						1060					1065			
Leu	Ala	Ala	Ser	Tyr	Asp	Thr	Asn	Gly	Leu	Ser	Gln	Pro	Pro	Leu
1070						1075					1080			
Pro	Glu	Lys	Arg	His	Leu	Pro	Gly	Pro	Gly	Gln	Gln	Pro	Gly	Pro
1085						1090					1095			
Trp	Gly	Pro	Glu	Gln	Ala	Ser	Ser	Pro	Ala	Arg	Gly	Ile	Ser	His
1100						1105					1110			
His	Val	Thr	Phe	Ala	Pro	Leu	Leu	Ser	Asp	Asn	Val	Pro	Gln	Thr
1115						1120					1125			
Pro	Glu	Pro	Pro	Thr	Gln	Glu	Ser	Gln	Ser	Asn	Val	Lys	Phe	Val
1130						1135					1140			
Gln	Asp	Thr	Ser	Lys	Phe	Trp	Tyr	Lys	Pro	His	Leu	Ser	Arg	Asp
1145						1150					1155			
Gln	Ala	Ile	Ala	Leu	Leu	Lys	Asp	Lys	Asp	Pro	Gly	Ala	Phe	Leu
1160						1165					1170			
Ile	Arg	Asp	Ser	His	Ser	Phe	Gln	Gly	Ala	Tyr	Gly	Leu	Ala	Leu
1175						1180					1185			
Lys	Val	Ala	Thr	Pro	Pro	Pro	Ser	Ala	Gln	Pro	Trp	Lys	Gly	Asp
1190						1195					1200			
Pro	Val	Glu	Gln	Leu	Val	Arg	His	Phe	Leu	Ile	Glu	Thr	Gly	Pro
1205						1210					1215			
Lys	Gly	Val	Lys	Ile	Lys	Gly	Cys	Pro	Ser	Glu	Pro	Tyr	Phe	Gly
1220						1225					1230			

# ES 2 534 734 A1

Ser Leu Ser Ala Leu Val Ser Gln His Ser Ile Ser Pro Ile Ser  
 1235 1240 1245  
  
 Leu Pro Cys Cys Leu Arg Ile Pro Ser Lys Asp Pro Leu Glu Glu  
 1250 1255 1260  
  
 Thr Pro Glu Ala Pro Val Pro Thr Asn Met Ser Thr Ala Ala Asp  
 1265 1270 1275  
  
 Leu Leu Arg Gln Gly Ala Ala Cys Ser Val Leu Tyr Leu Thr Ser  
 1280 1285 1290  
  
 Val Glu Thr Glu Ser Leu Thr Gly Pro Gln Ala Val Ala Arg Ala  
 1295 1300 1305  
  
 Ser Ser Ala Ala Leu Ser Cys Ser Pro Arg Pro Thr Pro Ala Val  
 1310 1315 1320  
  
 Val His Phe Lys Val Ser Ala Gln Gly Ile Thr Leu Thr Asp Asn  
 1325 1330 1335  
  
 Gln Arg Lys Leu Phe Phe Arg Arg His Tyr Pro Val Asn Ser Ile  
 1340 1345 1350  
  
 Thr Phe Ser Ser Thr Asp Pro Gln Asp Arg Arg Trp Thr Asn Pro  
 1355 1360 1365  
  
 Asp Gly Thr Thr Ser Lys Ile Phe Gly Phe Val Ala Lys Lys Pro  
 1370 1375 1380  
  
 Gly Ser Pro Trp Glu Asn Val Cys His Leu Phe Ala Glu Leu Asp  
 1385 1390 1395  
  
 Pro Asp Gln Pro Ala Gly Ala Ile Val Thr Phe Ile Thr Lys Val  
 1400 1405 1410  
  
 Leu Leu Gly Gln Arg Lys  
 1415

<210> 129  
 <211> 1409  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 129

# ES 2 534 734 A1

Met Lys Ser Ser Gly Pro Val Glu Arg Leu Leu Arg Ala Leu Gly Arg  
 1 5 10 15  
 Arg Asp Ser Ser Arg Ala Ala Ser Arg Pro Arg Lys Ala Glu Pro His  
 20 25 30  
 Ser Phe Arg Glu Lys Val Phe Arg Lys Lys Pro Pro Val Cys Ala Val  
 35 40 45  
 Cys Lys Val Thr Ile Asp Gly Thr Gly Val Ser Cys Arg Val Cys Lys  
 50 55 60  
 Val Ala Thr His Arg Lys Cys Glu Ala Lys Val Thr Ser Ala Cys Gln  
 65 70 75 80  
 Ala Leu Pro Pro Val Glu Leu Arg Arg Asn Thr Ala Pro Val Arg Arg  
 85 90 95  
 Ile Glu His Leu Gly Ser Thr Lys Ser Leu Asn His Ser Lys Gln Arg  
 100 105 110  
 Ser Thr Leu Pro Arg Ser Phe Ser Leu Asp Pro Leu Met Glu Arg Arg  
 115 120 125  
 Trp Asp Leu Asp Leu Thr Tyr Val Thr Glu Arg Ile Leu Ala Ala Ala  
 130 135 140  
 Phe Pro Ala Arg Pro Asp Glu Gln Arg His Arg Gly His Leu Arg Glu  
 145 150 155 160  
 Leu Ala His Val Leu Gln Ser Lys His Arg Asp Lys Tyr Leu Leu Phe  
 165 170 175  
 Asn Leu Ser Glu Lys Arg His Asp Leu Thr Arg Leu Asn Pro Lys Val  
 180 185 190  
 Gln Asp Phe Gly Trp Pro Glu Leu His Ala Pro Pro Leu Asp Lys Leu  
 195 200 205  
 Cys Ser Ile Cys Lys Ala Met Glu Thr Trp Leu Ser Ala Asp Pro Gln  
 210 215 220  
 His Val Val Val Leu Tyr Cys Lys Gly Asn Lys Gly Lys Leu Gly Val  
 225 230 235 240

# ES 2 534 734 A1

Ile Val Ser Ala Tyr Met His Tyr Ser Lys Ile Ser Ala Gly Ala Asp  
 245 250 255

Gln Ala Leu Ala Thr Leu Thr Met Arg Lys Phe Cys Glu Asp Lys Val  
 260 265 270

Ala Thr Glu Leu Gln Pro Ser Gln Arg Arg Tyr Ile Ser Tyr Phe Ser  
 275 280 285

Gly Leu Leu Ser Gly Ser Ile Arg Met Asn Ser Ser Pro Leu Phe Leu  
 290 295 300

His Tyr Val Leu Ile Pro Met Leu Pro Ala Phe Glu Pro Gly Thr Gly  
 305 310 315 320

Phe Gln Pro Phe Leu Lys Ile Tyr Gln Ser Met Gln Leu Val Tyr Thr  
 325 330 335

Ser Gly Val Tyr His Ile Ala Gly Pro Gly Pro Gln Gln Leu Cys Ile  
 340 345 350

Ser Leu Glu Pro Ala Leu Leu Leu Lys Gly Asp Val Met Val Thr Cys  
 355 360 365

Tyr His Lys Gly Gly Arg Gly Thr Asp Arg Thr Leu Val Phe Arg Val  
 370 375 380

Gln Phe His Thr Cys Thr Ile His Gly Pro Gln Leu Thr Phe Pro Lys  
 385 390 395 400

Asp Gln Leu Asp Glu Ala Trp Thr Asp Glu Arg Phe Pro Phe Gln Ala  
 405 410 415

Ser Val Glu Phe Val Phe Ser Ser Ser Pro Glu Lys Ile Lys Gly Ser  
 420 425 430

Thr Pro Arg Asn Asp Pro Ser Val Ser Val Asp Tyr Asn Thr Thr Glu  
 435 440 445

Pro Ala Val Arg Trp Asp Ser Tyr Glu Asn Phe Asn Gln His His Glu  
 450 455 460

Asp Ser Val Asp Gly Ser Leu Thr His Thr Arg Gly Pro Leu Asp Gly  
 465 470 475 480

# ES 2 534 734 A1

Ser Pro Tyr Ala Gln Val Gln Arg Pro Pro Arg Gln Thr Pro Pro Ala  
 485 490 495

Pro Ser Pro Glu Pro Pro Pro Pro Pro Pro Met Leu Ser Val Ser Ser Asp  
 500 505 510

Ser Gly His Ser Ser Thr Leu Thr Thr Glu Pro Ala Ala Glu Ser Pro  
 515 520 525

Gly Arg Pro Pro Pro Thr Ala Ala Glu Arg Gln Glu Leu Asp Arg Leu  
 530 535 540

Leu Gly Gly Cys Gly Val Ala Ser Gly Gly Arg Gly Ala Gly Arg Glu  
 545 550 555 560

Thr Ala Ile Leu Asp Asp Glu Glu Gln Pro Thr Val Gly Gly Gly Pro  
 565 570 575

His Leu Gly Val Tyr Pro Gly His Arg Pro Gly Leu Ser Arg His Cys  
 580 585 590

Ser Cys Arg Gln Gly Tyr Arg Glu Pro Cys Gly Val Pro Asn Gly Gly  
 595 600 605

Tyr Tyr Arg Pro Glu Gly Thr Leu Glu Arg Arg Arg Leu Ala Tyr Gly  
 610 615 620

Gly Tyr Glu Gly Ser Pro Gln Gly Tyr Ala Glu Ala Ser Met Glu Lys  
 625 630 635 640

Arg Arg Leu Cys Arg Ser Leu Ser Glu Gly Leu Tyr Pro Tyr Pro Pro  
 645 650 655

Glu Met Gly Lys Pro Ala Thr Gly Asp Phe Gly Tyr Arg Ala Pro Gly  
 660 665 670

Tyr Arg Glu Val Val Ile Leu Glu Asp Pro Gly Leu Pro Ala Leu Tyr  
 675 680 685

Pro Cys Pro Ala Cys Glu Glu Lys Leu Ala Leu Pro Thr Ala Ala Leu  
 690 695 700

Tyr Gly Leu Arg Leu Glu Arg Glu Ala Gly Glu Gly Trp Ala Ser Glu  
 705 710 715 720



# ES 2 534 734 A1

Ala Gly Lys Pro Leu Leu His Pro Val Arg Pro Gly His Pro Leu Pro  
725 730 735

Leu Leu Leu Pro Ala Cys Gly His His His Ala Pro Met Pro Asp Tyr  
740 745 750

Ser Cys Leu Lys Pro Pro Lys Ala Gly Glu Glu Gly His Glu Gly Cys  
755 760 765

Ser Tyr Thr Met Cys Pro Glu Gly Arg Tyr Gly His Pro Gly Tyr Pro  
770 775 780

Ala Leu Val Thr Tyr Ser Tyr Gly Gly Ala Val Pro Ser Tyr Cys Pro  
785 790 795 800

Ala Tyr Gly Arg Val Pro His Ser Cys Gly Ser Pro Gly Glu Gly Arg  
805 810 815

Gly Tyr Pro Ser Pro Gly Ala His Ser Pro Arg Ala Gly Ser Ile Ser  
820 825 830

Pro Gly Ser Pro Pro Tyr Pro Gln Ser Arg Lys Leu Ser Tyr Glu Ile  
835 840 845

Pro Thr Glu Glu Gly Gly Asp Arg Tyr Pro Leu Pro Gly His Leu Ala  
850 855 860

Ser Ala Gly Pro Leu Ala Ser Ala Glu Ser Leu Glu Pro Val Ser Trp  
865 870 875 880

Arg Glu Gly Pro Ser Gly His Ser Thr Leu Pro Arg Ser Pro Arg Asp  
885 890 895

Ala Pro Cys Ser Ala Ser Ser Glu Leu Ser Gly Pro Ser Thr Pro Leu  
900 905 910

His Thr Ser Ser Pro Val Gln Gly Lys Glu Ser Thr Arg Arg Gln Asp  
915 920 925

Thr Arg Ser Pro Thr Ser Ala Pro Thr Gln Arg Leu Ser Pro Gly Glu  
930 935 940

Ala Leu Pro Pro Val Ser Gln Ala Gly Thr Gly Lys Ala Pro Glu Leu  
945 950 955 960

# ES 2 534 734 A1

Pro Ser Gly Ser Gly Pro Glu Pro Leu Ala Pro Ser Pro Val Ser Pro  
 965 970 975

Thr Phe Pro Pro Ser Ser Pro Ser Asp Trp Pro Gln Glu Arg Ser Pro  
 980 985 990

Gly Gly His Ser Asp Gly Ala Ser Pro Arg Ser Pro Val Pro Thr Thr  
 995 1000 1005

Leu Pro Gly Leu Arg His Ala Pro Trp Gln Gly Pro Arg Gly Pro  
 1010 1015 1020

Pro Asp Ser Pro Asp Gly Ser Pro Leu Thr Pro Val Pro Ser Gln  
 1025 1030 1035

Met Pro Trp Leu Val Ala Ser Pro Glu Pro Pro Gln Ser Ser Pro  
 1040 1045 1050

Thr Pro Ala Phe Pro Leu Ala Ala Ser Tyr Asp Thr Asn Gly Leu  
 1055 1060 1065

Ser Gln Pro Pro Leu Pro Glu Lys Arg His Leu Pro Gly Pro Gly  
 1070 1075 1080

Gln Gln Pro Gly Pro Trp Gly Pro Glu Gln Ala Ser Ser Pro Ala  
 1085 1090 1095

Arg Gly Ile Ser His His Val Thr Phe Ala Pro Leu Leu Ser Asp  
 1100 1105 1110

Asn Val Pro Gln Thr Pro Glu Pro Pro Thr Gln Glu Ser Gln Ser  
 1115 1120 1125

Asn Val Lys Phe Val Gln Asp Thr Ser Lys Phe Trp Tyr Lys Pro  
 1130 1135 1140

His Leu Ser Arg Asp Gln Ala Ile Ala Leu Leu Lys Asp Lys Asp  
 1145 1150 1155

Pro Gly Ala Phe Leu Ile Arg Asp Ser His Ser Phe Gln Gly Ala  
 1160 1165 1170

Tyr Gly Leu Ala Leu Lys Val Ala Thr Pro Pro Pro Ser Ala Gln  
 1175 1180 1185

## ES 2 534 734 A1

Pro	Trp	Lys	Gly	Asp	Pro	Val	Glu	Gln	Leu	Val	Arg	His	Phe	Leu
1190						1195					1200			
Ile	Glu	Thr	Gly	Pro	Lys	Gly	Val	Lys	Ile	Lys	Gly	Cys	Pro	Ser
1205						1210					1215			
Glu	Pro	Tyr	Phe	Gly	Ser	Leu	Ser	Ala	Leu	Val	Ser	Gln	His	Ser
1220						1225					1230			
Ile	Ser	Pro	Ile	Ser	Leu	Pro	Cys	Cys	Leu	Arg	Ile	Pro	Ser	Lys
1235						1240					1245			
Asp	Pro	Leu	Glu	Glu	Thr	Pro	Glu	Ala	Pro	Val	Pro	Thr	Asn	Met
1250						1255					1260			
Ser	Thr	Ala	Ala	Asp	Leu	Leu	Arg	Gln	Gly	Ala	Ala	Cys	Ser	Val
1265						1270					1275			
Leu	Tyr	Leu	Thr	Ser	Val	Glu	Thr	Glu	Ser	Leu	Thr	Gly	Pro	Gln
1280						1285					1290			
Ala	Val	Ala	Arg	Ala	Ser	Ser	Ala	Ala	Leu	Ser	Cys	Ser	Pro	Arg
1295						1300					1305			
Pro	Thr	Pro	Ala	Val	Val	His	Phe	Lys	Val	Ser	Ala	Gln	Gly	Ile
1310						1315					1320			
Thr	Leu	Thr	Asp	Asn	Gln	Arg	Lys	Leu	Phe	Phe	Arg	Arg	His	Tyr
1325						1330					1335			
Pro	Val	Asn	Ser	Ile	Thr	Phe	Ser	Ser	Thr	Asp	Pro	Gln	Asp	Arg
1340						1345					1350			
Arg	Trp	Thr	Asn	Pro	Asp	Gly	Thr	Thr	Ser	Lys	Ile	Phe	Gly	Phe
1355						1360					1365			
Val	Ala	Lys	Lys	Pro	Gly	Ser	Pro	Trp	Glu	Asn	Val	Cys	His	Leu
1370						1375					1380			
Phe	Ala	Glu	Leu	Asp	Pro	Asp	Gln	Pro	Ala	Gly	Ala	Ile	Val	Thr
1385						1390					1395			
Phe	Ile	Thr	Lys	Val	Leu	Leu	Gly	Gln	Arg	Lys				
1400						1405								

# ES 2 534 734 A1

<210> 130  
 <211> 914  
 <212> PRT  
 <213> Homo sapiens

<400> 130

Met Ser Gln Ser Gln Asn Ala Ile Phe Thr Ser Pro Thr Gly Glu Glu  
 1 5 10 15

Asn Leu Met Asn Ser Asn His Arg Asp Ser Glu Ser Ile Thr Asp Val  
 20 25 30

Cys Ser Asn Glu Asp Leu Pro Glu Val Glu Leu Val Ser Leu Leu Glu  
 35 40 45

Glu Gln Leu Pro Gln Tyr Arg Leu Lys Val Asp Thr Leu Phe Leu Tyr  
 50 55 60

Glu Asn Gln Asp Trp Thr Gln Ser Pro His Gln Arg Gln His Ala Ser  
 65 70 75 80

Asp Ala Leu Ser Pro Val Leu Ala Glu Glu Thr Phe Arg Tyr Met Ile  
 85 90 95

Leu Gly Thr Asp Arg Val Glu Gln Met Thr Lys Thr Tyr Asn Asp Ile  
 100 105 110

Asp Met Val Thr His Leu Leu Ala Glu Arg Asp Arg Asp Leu Glu Leu  
 115 120 125

Ala Ala Arg Ile Gly Gln Ala Leu Leu Lys Arg Asn His Val Leu Ser  
 130 135 140

Glu Gln Asn Glu Ser Leu Glu Glu Gln Leu Gly Gln Ala Phe Asp Gln  
 145 150 155 160

Val Asn Gln Leu Gln His Glu Leu Cys Lys Lys Asp Glu Leu Leu Arg  
 165 170 175

Ile Val Ser Ile Ala Ser Glu Glu Ser Glu Thr Asp Ser Ser Cys Ser  
 180 185 190

Thr Pro Leu Arg Phe Asn Glu Ser Phe Ser Leu Ser Gln Gly Leu Leu  
 195 200 205

# ES 2 534 734 A1

Gln Leu Glu Met Leu Gln Glu Lys Leu Lys Glu Leu Glu Glu Glu Asn  
 210 215 220

Met Ala Leu Arg Ser Lys Ala Cys His Ile Lys Thr Glu Thr Val Thr  
 225 230 235 240

Tyr Glu Glu Lys Glu Gln Gln Leu Val Ser Asp Cys Val Lys Glu Leu  
 245 250 255

Arg Glu Thr Asn Ala Gln Met Ser Arg Met Thr Glu Glu Leu Ser Gly  
 260 265 270

Lys Ser Asp Glu Leu Ile Arg Tyr Gln Glu Glu Leu Ser Ser Leu Leu  
 275 280 285

Ser Gln Ile Val Asp Leu Gln His Lys Leu Lys Glu His Val Ile Glu  
 290 295 300

Lys Glu Glu Leu Lys Leu His Leu Gln Ala Ser Lys Asp Ala Gln Arg  
 305 310 315 320

Gln Leu Thr Met Glu Leu His Glu Leu Gln Asp Arg Asn Met Glu Cys  
 325 330 335

Leu Gly Met Leu His Glu Ser Gln Glu Glu Ile Lys Glu Leu Arg Ser  
 340 345 350

Arg Ser Gly Pro Thr Ala His Leu Tyr Phe Ser Gln Ser Tyr Gly Ala  
 355 360 365

Phe Thr Gly Glu Ser Leu Ala Ala Glu Ile Glu Gly Thr Met Arg Lys  
 370 375 380

Lys Leu Ser Leu Asp Glu Glu Ser Ser Leu Phe Lys Gln Lys Ala Gln  
 385 390 395 400

Gln Lys Arg Val Phe Asp Thr Val Arg Ile Ala Asn Asp Thr Arg Gly  
 405 410 415

Arg Ser Ile Ser Phe Pro Ala Leu Leu Pro Ile Pro Gly Ser Asn Arg  
 420 425 430

Ser Ser Val Ile Met Thr Ala Lys Pro Phe Glu Ser Gly Leu Gln Gln  
 435 440 445

# ES 2 534 734 A1

Thr Glu Asp Lys Ser Leu Leu Asn Gln Gly Ser Ser Ser Glu Glu Val  
 450 455 460

Ala Gly Ser Ser Gln Lys Met Gly Gln Pro Gly Pro Ser Gly Asp Ser  
 465 470 475 480

Asp Leu Ala Thr Ala Leu His Arg Leu Ser Leu Arg Arg Gln Asn Tyr  
 485 490 495

Leu Ser Glu Lys Gln Phe Phe Ala Glu Glu Trp Gln Arg Lys Ile Gln  
 500 505 510

Val Leu Ala Asp Gln Lys Glu Gly Val Ser Gly Cys Val Thr Pro Thr  
 515 520 525

Glu Ser Leu Ala Ser Leu Cys Thr Thr Gln Ser Glu Ile Thr Asp Leu  
 530 535 540

Ser Ser Ala Ser Cys Leu Arg Gly Phe Met Pro Glu Lys Leu Gln Ile  
 545 550 555 560

Val Lys Pro Leu Glu Gly Ser Gln Thr Leu Tyr His Trp Gln Gln Leu  
 565 570 575

Ala Gln Pro Asn Leu Gly Thr Ile Leu Asp Pro Arg Pro Gly Val Ile  
 580 585 590

Thr Lys Gly Phe Thr Gln Leu Pro Gly Asp Ala Ile Tyr His Ile Ser  
 595 600 605

Asp Leu Glu Glu Asp Glu Glu Glu Gly Ile Thr Phe Gln Val Gln Gln  
 610 615 620

Pro Leu Glu Val Glu Glu Lys Leu Ser Thr Ser Lys Pro Val Thr Gly  
 625 630 635 640

Ile Phe Leu Pro Pro Ile Thr Ser Ala Gly Gly Pro Val Thr Val Ala  
 645 650 655

Thr Ala Asn Pro Gly Lys Cys Leu Ser Cys Thr Asn Ser Thr Phe Thr  
 660 665 670

Phe Thr Thr Cys Arg Ile Leu His Pro Ser Asp Ile Thr Gln Val Thr  
 675 680 685

# ES 2 534 734 A1

Pro Ser Ser Gly Phe Pro Ser Leu Ser Cys Gly Ser Ser Gly Ser Ser  
 690 695 700

Ser Ser Asn Thr Ala Val Asn Ser Pro Ala Leu Ser Tyr Arg Leu Ser  
 705 710 715 720

Ile Gly Glu Ser Ile Thr Asn Arg Arg Asp Ser Thr Thr Thr Phe Ser  
 725 730 735

Ser Thr Met Ser Leu Ala Lys Leu Leu Gln Glu Arg Gly Ile Ser Ala  
 740 745 750

Lys Val Tyr His Ser Pro Ile Ser Glu Asn Pro Leu Gln Pro Leu Pro  
 755 760 765

Lys Ser Leu Ala Ile Pro Ser Thr Pro Pro Asn Ser Pro Ser His Ser  
 770 775 780

Pro Cys Pro Ser Pro Leu Pro Phe Glu Pro Arg Val His Leu Ser Glu  
 785 790 795 800

Asn Phe Leu Ala Ser Arg Pro Ala Glu Thr Phe Leu Gln Glu Met Tyr  
 805 810 815

Gly Leu Arg Pro Ser Arg Asn Pro Pro Asp Val Gly Gln Leu Lys Met  
 820 825 830

Asn Leu Val Asp Arg Leu Lys Arg Leu Gly Ile Ala Arg Val Val Lys  
 835 840 845

Asn Pro Gly Ala Gln Glu Asn Gly Arg Cys Gln Glu Ala Glu Ile Gly  
 850 855 860

Pro Gln Lys Pro Asp Ser Ala Val Tyr Leu Asn Ser Gly Ser Ser Leu  
 865 870 875 880

Leu Gly Gly Leu Arg Arg Asn Gln Ser Leu Pro Val Ile Met Gly Ser  
 885 890 895

Phe Ala Ala Pro Val Cys Thr Ser Ser Pro Lys Met Gly Val Leu Lys  
 900 905 910

Glu Asp

ES 2 534 734 A1

<210> 131  
 <211> 94  
 <212> PRT  
 <213> Homo sapiens

<400> 131

Met Arg Thr Ile Ala Ile Leu Ala Ala Ile Leu Leu Val Ala Leu Gln  
 1 5 10 15

Ala Gln Ala Glu Ser Leu Gln Glu Arg Ala Asp Glu Ala Thr Thr Gln  
 20 25 30

Lys Gln Ser Gly Glu Asp Asn Gln Asp Leu Ala Ile Ser Phe Ala Gly  
 35 40 45

Asn Gly Leu Ser Ala Leu Arg Thr Ser Gly Ser Gln Ala Arg Ala Thr  
 50 55 60

Cys Tyr Cys Arg Thr Gly Arg Cys Ala Thr Arg Glu Ser Leu Ser Gly  
 65 70 75 80

Val Cys Glu Ile Ser Gly Arg Leu Tyr Arg Leu Cys Cys Arg  
 85 90

<210> 132  
 <211> 504  
 <212> PRT  
 <213> Homo sapiens

<400> 132

Met Val Ala Pro Gly Ser Val Thr Ser Arg Leu Gly Ser Val Phe Pro  
 1 5 10 15

Phe Leu Leu Val Leu Val Asp Leu Gln Tyr Glu Gly Ala Glu Cys Gly  
 20 25 30

Val Asn Ala Asp Val Glu Lys His Leu Glu Leu Gly Lys Lys Leu Leu  
 35 40 45

Ala Ala Gly Gln Leu Ala Asp Ala Leu Ser Gln Phe His Ala Ala Val  
 50 55 60

Asp Gly Asp Pro Asp Asn Tyr Ile Ala Tyr Tyr Arg Arg Ala Thr Val  
 65 70 75 80



# ES 2 534 734 A1

Phe Leu Ala Met Gly Lys Ser Lys Ala Ala Leu Pro Asp Leu Thr Lys  
 85 90 95

Val Ile Gln Leu Lys Met Asp Phe Thr Ala Ala Arg Leu Gln Arg Gly  
 100 105 110

His Leu Leu Leu Lys Gln Gly Lys Leu Asp Glu Ala Glu Asp Asp Phe  
 115 120 125

Lys Lys Val Leu Lys Ser Asn Pro Ser Glu Asn Glu Glu Lys Glu Ala  
 130 135 140

Gln Ser Gln Leu Ile Lys Ser Asp Glu Met Gln Arg Leu Arg Ser Gln  
 145 150 155 160

Ala Leu Asn Ala Phe Gly Ser Gly Asp Tyr Thr Ala Ala Ile Ala Phe  
 165 170 175

Leu Asp Lys Ile Leu Glu Val Cys Val Trp Asp Ala Glu Leu Arg Glu  
 180 185 190

Leu Arg Ala Glu Cys Phe Ile Lys Glu Gly Glu Pro Arg Lys Ala Ile  
 195 200 205

Ser Asp Leu Lys Ala Ala Ser Lys Leu Lys Asn Asp Asn Thr Glu Ala  
 210 215 220

Phe Tyr Lys Ile Ser Thr Leu Tyr Tyr Gln Leu Gly Asp His Glu Leu  
 225 230 235 240

Ser Leu Ser Glu Val Arg Glu Cys Leu Lys Leu Asp Gln Asp His Lys  
 245 250 255

Arg Cys Phe Ala His Tyr Lys Gln Val Lys Lys Leu Asn Lys Leu Ile  
 260 265 270

Glu Ser Ala Glu Glu Leu Ile Arg Asp Gly Arg Tyr Thr Asp Ala Thr  
 275 280 285

Ser Lys Tyr Glu Ser Val Met Lys Thr Glu Pro Ser Ile Ala Glu Tyr  
 290 295 300

Thr Val Arg Ser Lys Glu Arg Ile Cys His Cys Phe Ser Lys Asp Glu  
 305 310 315 320

# ES 2 534 734 A1

Lys Pro Val Glu Ala Ile Arg Val Cys Ser Glu Val Leu Gln Met Glu  
325 330 335

Pro Asp Asn Val Asn Ala Leu Lys Asp Arg Ala Glu Ala Tyr Leu Ile  
340 345 350

Glu Glu Met Tyr Asp Glu Ala Ile Gln Asp Tyr Glu Thr Ala Gln Glu  
355 360 365

His Asn Glu Asn Asp Gln Gln Ile Arg Glu Gly Leu Glu Lys Ala Gln  
370 375 380

Arg Leu Leu Lys Gln Ser Gln Lys Arg Asp Tyr Tyr Lys Ile Leu Gly  
385 390 395 400

Val Lys Arg Asn Ala Lys Lys Gln Glu Ile Ile Lys Ala Tyr Arg Lys  
405 410 415

Leu Ala Leu Gln Trp His Pro Asp Asn Phe Gln Asn Glu Glu Glu Lys  
420 425 430

Lys Lys Ala Glu Lys Lys Phe Ile Asp Ile Ala Ala Ala Lys Glu Val  
435 440 445

Leu Ser Asp Pro Glu Met Arg Lys Lys Phe Asp Asp Gly Glu Asp Pro  
450 455 460

Leu Asp Ala Glu Ser Gln Gln Gly Gly Gly Gly Asn Pro Phe His Arg  
465 470 475 480

Ser Trp Asn Ser Trp Gln Gly Phe Asn Pro Phe Ser Ser Gly Gly Pro  
485 490 495

Phe Arg Phe Lys Phe His Phe Asn  
500

<210> 133  
<211> 762  
<212> PRT  
<213> Homo sapiens

<400> 133

Met Asn Glu Ala Lys Val Lys Glu Thr Leu Arg Arg Cys Gly Ala Ser  
1 5 10 15

# ES 2 534 734 A1

Gly Asp Glu Cys Gly Arg Leu Gln Tyr Ala Leu Thr Cys Leu Arg Lys  
 20 25 30

Val Thr Gly Leu Gly Gly Glu His Lys Glu Asp Ser Ser Trp Ser Ser  
 35 40 45

Leu Asp Ala Arg Arg Glu Ser Gly Ser Gly Pro Ser Thr Asp Thr Leu  
 50 55 60

Ser Ala Ala Ser Leu Pro Trp Pro Pro Gly Ser Ser Gln Leu Gly Arg  
 65 70 75 80

Ala Gly Asn Ser Ala Gln Gly Pro Arg Ser Ile Ser Val Ser Ala Leu  
 85 90 95

Pro Ala Ser Asp Ser Pro Thr Pro Ser Phe Ser Glu Gly Leu Ser Asp  
 100 105 110

Thr Cys Ile Pro Leu His Ala Ser Gly Arg Leu Thr Pro Arg Ala Leu  
 115 120 125

His Ser Phe Ile Thr Pro Pro Thr Thr Pro Gln Leu Arg Arg His Thr  
 130 135 140

Lys Leu Lys Pro Pro Arg Thr Pro Pro Pro Ser Arg Lys Val Phe  
 145 150 155 160

Gln Leu Leu Pro Ser Phe Pro Thr Leu Thr Arg Ser Lys Ser His Glu  
 165 170 175

Ser Gln Leu Gly Asn Arg Ile Asp Asp Val Ser Ser Met Arg Phe Asp  
 180 185 190

Leu Ser His Gly Ser Pro Gln Met Val Arg Arg Asp Ile Gly Leu Ser  
 195 200 205

Val Thr His Arg Phe Ser Thr Lys Ser Trp Leu Ser Gln Val Cys His  
 210 215 220

Val Cys Gln Lys Ser Met Ile Phe Gly Val Lys Cys Lys His Cys Arg  
 225 230 235 240

Leu Lys Cys His Asn Lys Cys Thr Lys Glu Ala Pro Ala Cys Arg Ile  
 245 250 255

# ES 2 534 734 A1

Ser Phe Leu Pro Leu Thr Arg Leu Arg Arg Thr Glu Ser Val Pro Ser  
 260 265 270

Asp Ile Asn Asn Pro Val Asp Arg Ala Ala Glu Pro His Phe Gly Thr  
 275 280 285

Leu Pro Lys Ala Leu Thr Lys Lys Glu His Pro Pro Ala Met Asn His  
 290 295 300

Leu Asp Ser Ser Ser Asn Pro Ser Ser Thr Thr Ser Ser Thr Pro Ser  
 305 310 315 320

Ser Pro Ala Pro Phe Pro Thr Ser Ser Asn Pro Ser Ser Ala Thr Thr  
 325 330 335

Pro Pro Asn Pro Ser Pro Gly Gln Arg Asp Ser Arg Phe Asn Phe Pro  
 340 345 350

Ala Ala Tyr Phe Ile His His Arg Gln Gln Phe Ile Phe Pro Val Pro  
 355 360 365

Ser Ala Gly His Cys Trp Lys Cys Leu Leu Ile Ala Glu Ser Leu Lys  
 370 375 380

Glu Asn Ala Phe Asn Ile Ser Ala Phe Ala His Ala Ala Pro Leu Pro  
 385 390 395 400

Glu Ala Ala Asp Gly Thr Arg Leu Asp Asp Gln Pro Lys Ala Asp Val  
 405 410 415

Leu Glu Ala His Glu Ala Glu Ala Glu Glu Pro Glu Ala Gly Lys Ser  
 420 425 430

Glu Ala Glu Asp Asp Glu Asp Glu Val Asp Asp Leu Pro Ser Ser Arg  
 435 440 445

Arg Pro Trp Arg Gly Pro Ile Ser Arg Lys Ala Ser Gln Thr Ser Val  
 450 455 460

Tyr Leu Gln Glu Trp Asp Ile Pro Phe Glu Gln Val Glu Leu Gly Glu  
 465 470 475 480

Pro Ile Gly Gln Gly Arg Trp Gly Arg Val His Arg Gly Arg Trp His  
 485 490 495

# ES 2 534 734 A1

Gly Glu Val Ala Ile Arg Leu Leu Glu Met Asp Gly His Asn Gln Asp  
 500 505 510

His Leu Lys Leu Phe Lys Lys Glu Val Met Asn Tyr Arg Gln Thr Arg  
 515 520 525

His Glu Asn Val Val Leu Phe Met Gly Ala Cys Met Asn Pro Pro His  
 530 535 540

Leu Ala Ile Ile Thr Ser Phe Cys Lys Gly Arg Thr Leu His Ser Phe  
 545 550 555 560

Val Arg Asp Pro Lys Thr Ser Leu Asp Ile Asn Lys Thr Arg Gln Ile  
 565 570 575

Ala Gln Glu Ile Ile Lys Gly Met Gly Tyr Leu His Ala Lys Gly Ile  
 580 585 590

Val His Lys Asp Leu Lys Ser Lys Asn Val Phe Tyr Asp Asn Gly Lys  
 595 600 605

Val Val Ile Thr Asp Phe Gly Leu Phe Gly Ile Ser Gly Val Val Arg  
 610 615 620

Glu Gly Arg Arg Glu Asn Gln Leu Lys Leu Ser His Asp Trp Leu Cys  
 625 630 635 640

Tyr Leu Ala Pro Glu Ile Val Arg Glu Met Thr Pro Gly Lys Asp Glu  
 645 650 655

Asp Gln Leu Pro Phe Ser Lys Ala Ala Asp Val Tyr Ala Phe Gly Thr  
 660 665 670

Val Trp Tyr Glu Leu Gln Ala Arg Asp Trp Pro Leu Lys Asn Gln Ala  
 675 680 685

Ala Glu Ala Ser Ile Trp Gln Ile Gly Ser Gly Glu Gly Met Lys Arg  
 690 695 700

Val Leu Thr Ser Val Ser Leu Gly Lys Glu Val Ser Glu Ile Leu Ser  
 705 710 715 720

Ala Cys Trp Ala Phe Asp Leu Gln Glu Arg Pro Ser Phe Ser Leu Leu  
 725 730 735

# ES 2 534 734 A1

Met Asp Met Leu Glu Lys Leu Pro Lys Leu Asn Arg Arg Leu Ser His  
 740 745 750

Pro Gly His Phe Trp Lys Ser Ala Glu Leu  
 755 760

<210> 134  
 <211> 959  
 <212> PRT  
 <213> Homo sapiens

<400> 134

Met Ala Ala Ser Thr Gly Tyr Val Arg Leu Trp Gly Ala Ala Arg Cys  
 1 5 10 15

Trp Val Leu Arg Arg Pro Met Leu Ala Ala Ala Gly Gly Arg Val Pro  
 20 25 30

Thr Ala Ala Gly Ala Trp Leu Leu Arg Gly Gln Arg Thr Cys Asp Ala  
 35 40 45

Ser Pro Pro Trp Ala Leu Trp Gly Arg Gly Pro Ala Ile Gly Gly Gln  
 50 55 60

Trp Arg Gly Phe Trp Glu Ala Ser Ser Arg Gly Gly Gly Ala Phe Ser  
 65 70 75 80

Gly Gly Glu Asp Ala Ser Glu Gly Gly Ala Glu Glu Gly Ala Gly Gly  
 85 90 95

Ala Gly Gly Ser Ala Gly Ala Gly Glu Gly Pro Val Ile Thr Ala Leu  
 100 105 110

Thr Pro Met Thr Ile Pro Asp Val Phe Pro His Leu Pro Leu Ile Ala  
 115 120 125

Ile Thr Arg Asn Pro Val Phe Pro Arg Phe Ile Lys Ile Ile Glu Val  
 130 135 140

Lys Asn Lys Lys Leu Val Glu Leu Leu Arg Arg Lys Val Arg Leu Ala  
 145 150 155 160

Gln Pro Tyr Val Gly Val Phe Leu Lys Arg Asp Asp Ser Asn Glu Ser  
 165 170 175

# ES 2 534 734 A1

Asp Val Val Glu Ser Leu Asp Glu Ile Tyr His Thr Gly Thr Phe Ala  
 180 185 190

Gln Ile His Glu Met Gln Asp Leu Gly Asp Lys Leu Arg Met Ile Val  
 195 200 205

Met Gly His Arg Arg Val His Ile Ser Arg Gln Leu Glu Val Glu Pro  
 210 215 220

Glu Glu Pro Glu Ala Glu Asn Lys His Lys Pro Arg Arg Lys Ser Lys  
 225 230 235 240

Arg Gly Lys Lys Glu Ala Glu Asp Glu Leu Ser Ala Arg His Pro Ala  
 245 250 255

Glu Leu Ala Met Glu Pro Thr Pro Glu Leu Pro Ala Glu Val Leu Met  
 260 265 270

Val Glu Val Glu Asn Val Val His Glu Asp Phe Gln Val Thr Glu Glu  
 275 280 285

Val Lys Ala Leu Thr Ala Glu Ile Val Lys Thr Ile Arg Asp Ile Ile  
 290 295 300

Ala Leu Asn Pro Leu Tyr Arg Glu Ser Val Leu Gln Met Met Gln Ala  
 305 310 315 320

Gly Gln Arg Val Val Asp Asn Pro Ile Tyr Leu Ser Asp Met Gly Ala  
 325 330 335

Ala Leu Thr Gly Ala Glu Ser His Glu Leu Gln Asp Val Leu Glu Glu  
 340 345 350

Thr Asn Ile Pro Lys Arg Leu Tyr Lys Ala Leu Ser Leu Leu Lys Lys  
 355 360 365

Glu Phe Glu Leu Ser Lys Leu Gln Gln Arg Leu Gly Arg Glu Val Glu  
 370 375 380

Glu Lys Ile Lys Gln Thr His Arg Lys Tyr Leu Leu Gln Glu Gln Leu  
 385 390 395 400

Lys Ile Ile Lys Lys Glu Leu Gly Leu Glu Lys Asp Asp Lys Asp Ala  
 405 410 415

# ES 2 534 734 A1

Ile Glu Glu Lys Phe Arg Glu Arg Leu Lys Glu Leu Val Val Pro Lys  
420 425 430

His Val Met Asp Val Val Asp Glu Glu Leu Ser Lys Leu Gly Leu Leu  
435 440 445

Asp Asn His Ser Ser Glu Phe Asn Val Thr Arg Asn Tyr Leu Asp Trp  
450 455 460

Leu Thr Ser Ile Pro Trp Gly Lys Tyr Ser Asn Glu Asn Leu Asp Leu  
465 470 475 480

Ala Arg Ala Gln Ala Val Leu Glu Glu Asp His Tyr Gly Met Glu Asp  
485 490 495

Val Lys Lys Arg Ile Leu Glu Phe Ile Ala Val Ser Gln Leu Arg Gly  
500 505 510

Ser Thr Gln Gly Lys Ile Leu Cys Phe Tyr Gly Pro Pro Gly Val Gly  
515 520 525

Lys Thr Ser Ile Ala Arg Ser Ile Ala Arg Ala Leu Asn Arg Glu Tyr  
530 535 540

Phe Arg Phe Ser Val Gly Gly Met Thr Asp Val Ala Glu Ile Lys Gly  
545 550 555 560

His Arg Arg Thr Tyr Val Gly Ala Met Pro Gly Lys Ile Ile Gln Cys  
565 570 575

Leu Lys Lys Thr Lys Thr Glu Asn Pro Leu Ile Leu Ile Asp Glu Val  
580 585 590

Asp Lys Ile Gly Arg Gly Tyr Gln Gly Asp Pro Ser Ser Ala Leu Leu  
595 600 605

Glu Leu Leu Asp Pro Glu Gln Asn Ala Asn Phe Leu Asp His Tyr Leu  
610 615 620

Asp Val Pro Val Asp Leu Ser Lys Val Leu Phe Ile Cys Thr Ala Asn  
625 630 635 640

Val Thr Asp Thr Ile Pro Glu Pro Leu Arg Asp Arg Met Glu Met Ile  
645 650 655



# ES 2 534 734 A1

Asn Val Ser Gly Tyr Val Ala Gln Glu Lys Leu Ala Ile Ala Glu Arg  
 660 665 670

Tyr Leu Val Pro Gln Ala Arg Ala Leu Cys Gly Leu Asp Glu Ser Lys  
 675 680 685

Ala Lys Leu Ser Ser Asp Val Leu Thr Leu Leu Ile Lys Gln Tyr Cys  
 690 695 700

Arg Glu Ser Gly Val Arg Asn Leu Gln Lys Gln Val Glu Lys Val Leu  
 705 710 715 720

Arg Lys Ser Ala Tyr Lys Ile Val Ser Gly Glu Ala Glu Ser Val Glu  
 725 730 735

Val Thr Pro Glu Asn Leu Gln Asp Phe Val Gly Lys Pro Val Phe Thr  
 740 745 750

Val Glu Arg Met Tyr Asp Val Thr Pro Pro Gly Val Val Met Gly Leu  
 755 760 765

Ala Trp Thr Ala Met Gly Gly Ser Thr Leu Phe Val Glu Thr Ser Leu  
 770 775 780

Arg Arg Pro Gln Asp Lys Asp Ala Lys Gly Asp Lys Asp Gly Ser Leu  
 785 790 795 800

Glu Val Thr Gly Gln Leu Gly Glu Val Met Lys Glu Ser Ala Arg Ile  
 805 810 815

Ala Tyr Thr Phe Ala Arg Ala Phe Leu Met Gln His Ala Pro Ala Asn  
 820 825 830

Asp Tyr Leu Val Thr Ser His Ile His Leu His Val Pro Glu Gly Ala  
 835 840 845

Thr Pro Lys Asp Gly Pro Ser Ala Gly Cys Thr Ile Val Thr Ala Leu  
 850 855 860

Leu Ser Leu Ala Met Gly Arg Pro Val Arg Gln Asn Leu Ala Met Thr  
 865 870 875 880

Gly Glu Val Ser Leu Thr Gly Lys Ile Leu Pro Val Gly Gly Ile Lys  
 885 890 895

# ES 2 534 734 A1

Glu Lys Thr Ile Ala Ala Lys Arg Ala Gly Val Thr Cys Ile Val Leu  
 900 905 910

Pro Ala Glu Asn Lys Lys Asp Phe Tyr Asp Leu Ala Ala Phe Ile Thr  
 915 920 925

Glu Gly Leu Glu Val His Phe Val Glu His Tyr Arg Glu Ile Phe Asp  
 930 935 940

Ile Ala Phe Pro Asp Glu Gln Ala Glu Ala Leu Ala Val Glu Arg  
 945 950 955

<210> 135  
 <211> 979  
 <212> PRT  
 <213> Homo sapiens

<400> 135

Met Gly Thr Arg Leu Pro Leu Val Leu Arg Gln Leu Arg Arg Pro Pro  
 1 5 10 15

Gln Pro Pro Gly Pro Pro Arg Arg Leu Arg Val Pro Cys Arg Ala Ser  
 20 25 30

Ser Gly Gly Gly Gly Gly Gly Gly Gly Arg Glu Gly Leu Leu Gly  
 35 40 45

Gln Arg Arg Pro Gln Asp Gly Gln Ala Arg Ser Ser Cys Ser Pro Gly  
 50 55 60

Gly Arg Thr Pro Ala Ala Arg Asp Ser Ile Val Arg Glu Val Ile Gln  
 65 70 75 80

Asn Ser Lys Glu Val Leu Ser Leu Leu Gln Glu Lys Asn Pro Ala Phe  
 85 90 95

Lys Pro Val Leu Ala Ile Ile Gln Ala Gly Asp Asp Asn Leu Met Gln  
 100 105 110

Glu Ile Asn Gln Asn Leu Ala Glu Glu Ala Gly Leu Asn Ile Thr His  
 115 120 125

Ile Cys Leu Pro Pro Asp Ser Ser Glu Ala Glu Ile Ile Asp Glu Ile  
 130 135 140

# ES 2 534 734 A1

Leu Lys Ile Asn Glu Asp Thr Arg Val His Gly Leu Ala Leu Gln Ile  
 145 150 155 160

Ser Glu Asn Leu Phe Ser Asn Lys Val Leu Asn Ala Leu Lys Pro Glu  
 165 170 175

Lys Asp Val Asp Gly Val Thr Asp Ile Asn Leu Gly Lys Leu Val Arg  
 180 185 190

Gly Asp Ala His Glu Cys Phe Val Ser Pro Val Ala Lys Ala Val Ile  
 195 200 205

Glu Leu Leu Glu Lys Ser Val Gly Val Asn Leu Asp Gly Lys Lys Ile  
 210 215 220

Leu Val Val Gly Ala His Gly Ser Leu Glu Ala Ala Leu Gln Cys Leu  
 225 230 235 240

Phe Gln Arg Lys Gly Ser Met Thr Met Ser Ile Gln Trp Lys Thr Arg  
 245 250 255

Gln Leu Gln Ser Lys Leu His Glu Ala Asp Ile Val Val Leu Gly Ser  
 260 265 270

Pro Lys Pro Glu Glu Ile Pro Leu Thr Trp Ile Gln Pro Gly Thr Thr  
 275 280 285

Val Leu Asn Cys Ser His Asp Phe Leu Ser Gly Lys Val Gly Cys Gly  
 290 295 300

Ser Pro Arg Ile His Phe Gly Gly Leu Ile Glu Glu Asp Asp Val Ile  
 305 310 315 320

Leu Leu Ala Ala Ala Leu Arg Ile Gln Asn Met Val Ser Ser Gly Arg  
 325 330 335

Arg Trp Leu Arg Glu Gln Gln His Arg Arg Trp Arg Leu His Cys Leu  
 340 345 350

Lys Leu Gln Pro Leu Ser Pro Val Pro Ser Asp Ile Glu Ile Ser Arg  
 355 360 365

Gly Gln Thr Pro Lys Ala Val Asp Val Leu Ala Lys Glu Ile Gly Leu  
 370 375 380

# ES 2 534 734 A1

Leu Ala Asp Glu Ile Glu Ile Tyr Gly Lys Ser Lys Ala Lys Val Arg  
 385 390 395 400

Leu Ser Val Leu Glu Arg Leu Lys Asp Gln Ala Asp Gly Lys Tyr Val  
 405 410 415

Leu Val Ala Gly Ile Thr Pro Thr Pro Leu Gly Glu Gly Lys Ser Thr  
 420 425 430

Val Thr Ile Gly Leu Val Gln Ala Leu Thr Ala His Leu Asn Val Asn  
 435 440 445

Ser Phe Ala Cys Leu Arg Gln Pro Ser Gln Gly Pro Thr Phe Gly Val  
 450 455 460

Lys Gly Gly Ala Ala Gly Gly Gly Tyr Ala Gln Val Ile Pro Met Glu  
 465 470 475 480

Glu Phe Asn Leu His Leu Thr Gly Asp Ile His Ala Ile Thr Ala Ala  
 485 490 495

Asn Asn Leu Leu Ala Ala Ala Ile Asp Thr Arg Ile Leu His Glu Asn  
 500 505 510

Thr Gln Thr Asp Lys Ala Leu Tyr Asn Arg Leu Val Pro Leu Val Asn  
 515 520 525

Gly Val Arg Glu Phe Ser Glu Ile Gln Leu Ala Arg Leu Lys Lys Leu  
 530 535 540

Gly Ile Asn Lys Thr Asp Pro Ser Thr Leu Thr Glu Glu Glu Val Ser  
 545 550 555 560 565

Lys Phe Ala Arg Leu Asp Ile Asp Pro Ser Thr Ile Thr Trp Gln Arg  
 565 570 575

Val Leu Asp Thr Asn Asp Arg Phe Leu Arg Lys Ile Thr Ile Gly Gln  
 580 585 590

Gly Asn Thr Glu Lys Gly His Tyr Arg Gln Ala Gln Phe Asp Ile Ala  
 595 600 605

Val Ala Ser Glu Ile Met Ala Val Leu Ala Leu Thr Asp Ser Leu Ala  
 610 615 620

# ES 2 534 734 A1

Asp Met Lys Ala Arg Leu Gly Arg Met Val Val Ala Ser Asp Lys Ser  
 625 630 635 640

Gly Gln Pro Val Thr Ala Asp Asp Leu Gly Val Thr Gly Ala Leu Thr  
 645 650 655

Val Leu Met Lys Asp Ala Ile Lys Pro Asn Leu Met Gln Thr Leu Glu  
 660 665 670

Gly Thr Pro Val Phe Val His Ala Gly Pro Phe Ala Asn Ile Ala His  
 675 680 685

Gly Asn Ser Ser Val Leu Ala Asp Lys Ile Ala Leu Lys Leu Val Gly  
 690 695 700

Glu Glu Gly Phe Val Val Thr Glu Ala Gly Phe Gly Ala Asp Ile Gly  
 705 710 715 720

Met Glu Lys Phe Phe Asn Ile Lys Cys Arg Ala Ser Gly Leu Val Pro  
 725 730 735

Asn Val Val Val Leu Val Ala Thr Val Arg Ala Leu Lys Met His Gly  
 740 745 750

Gly Gly Pro Ser Val Thr Ala Gly Val Pro Leu Lys Lys Glu Tyr Thr  
 755 760 765

Glu Glu Asn Ile Gln Leu Val Ala Asp Gly Cys Cys Asn Leu Gln Lys  
 770 775 780

Gln Ile Gln Ile Thr Gln Leu Phe Gly Val Pro Val Val Val Ala Leu  
 785 790 795 800

Asn Val Phe Lys Thr Asp Thr Arg Ala Glu Ile Asp Leu Val Cys Glu  
 805 810 815

Leu Ala Lys Arg Ala Gly Ala Phe Asp Ala Val Pro Cys Tyr His Trp  
 820 825 830

Ser Val Gly Gly Lys Gly Ser Val Asp Leu Ala Arg Ala Val Arg Glu  
 835 840 845

Ala Ala Ser Lys Arg Ser Arg Phe Gln Phe Leu Tyr Asp Val Gln Val  
 850 855 860

# ES 2 534 734 A1

Pro Ile Val Asp Lys Ile Arg Thr Ile Ala Gln Ala Val Tyr Gly Ala  
865 870 875 880

Lys Asp Ile Glu Leu Ser Pro Glu Ala Gln Ala Lys Ile Asp Arg Tyr  
885 890 895

Thr Gln Gln Gly Phe Gly Asn Leu Pro Ile Cys Met Ala Lys Thr His  
900 905 910

Leu Ser Leu Ser His Gln Pro Asp Lys Lys Gly Val Pro Arg Asp Phe  
915 920 925

Ile Leu Pro Ile Ser Asp Val Arg Ala Ser Ile Gly Ala Gly Phe Ile  
930 935 940

Tyr Pro Leu Val Gly Thr Met Ser Thr Met Pro Gly Leu Pro Thr Arg  
945 950 955 960

Pro Cys Phe Tyr Asp Ile Asp Leu Asp Thr Glu Thr Glu Gln Val Lys  
965 970 975

Gly Leu Phe

<210> 136  
<211> 978  
<212> PRT  
<213> Homo sapiens

<400> 136

Met Gly Thr Arg Leu Pro Leu Val Leu Arg Gln Leu Arg Arg Pro Pro  
1 5 10 15

Gln Pro Pro Gly Pro Pro Arg Arg Leu Arg Val Pro Cys Arg Ala Ser  
20 25 30

Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Arg Glu Gly Leu Leu Gly  
35 40 45

Gln Arg Arg Pro Gln Asp Gly Gln Ala Arg Ser Ser Cys Ser Pro Gly  
50 55 60

Gly Arg Thr Pro Ala Ala Arg Asp Ser Ile Val Arg Glu Val Ile Gln  
65 70 75 80

## ES 2 534 734 A1

Asn	Ser	Lys	Glu	Val	Leu	Ser	Leu	Leu	Gln	Glu	Lys	Asn	Pro	Ala	Phe
				85					90					95	
Lys	Pro	Val	Leu	Ala	Ile	Ile	Gln	Ala	Gly	Asp	Asp	Asn	Leu	Met	Gln
			100					105					110		
Glu	Ile	Asn	Gln	Asn	Leu	Ala	Glu	Glu	Ala	Gly	Leu	Asn	Ile	Thr	His
		115					120					125			
Ile	Cys	Leu	Pro	Pro	Asp	Ser	Ser	Glu	Ala	Glu	Ile	Ile	Asp	Glu	Ile
	130					135					140				
Leu	Lys	Ile	Asn	Glu	Asp	Thr	Arg	Val	His	Gly	Leu	Ala	Leu	Gln	Ile
145					150					155					160
Ser	Glu	Asn	Leu	Phe	Ser	Asn	Lys	Val	Leu	Asn	Ala	Leu	Lys	Pro	Glu
				165					170					175	
Lys	Asp	Val	Asp	Gly	Val	Thr	Asp	Ile	Asn	Leu	Gly	Lys	Leu	Val	Arg
			180					185					190		
Gly	Asp	Ala	His	Glu	Cys	Phe	Val	Ser	Pro	Val	Ala	Lys	Ala	Val	Ile
		195					200					205			
Glu	Leu	Leu	Glu	Lys	Ser	Gly	Val	Asn	Leu	Asp	Gly	Lys	Lys	Ile	Leu
	210					215					220				
Val	Val	Gly	Ala	His	Gly	Ser	Leu	Glu	Ala	Ala	Leu	Gln	Cys	Leu	Phe
225					230					235					240
Gln	Arg	Lys	Gly	Ser	Met	Thr	Met	Ser	Ile	Gln	Trp	Lys	Thr	Arg	Gln
				245					250					255	
Leu	Gln	Ser	Lys	Leu	His	Glu	Ala	Asp	Ile	Val	Val	Leu	Gly	Ser	Pro
			260					265					270		
Lys	Pro	Glu	Glu	Ile	Pro	Leu	Thr	Trp	Ile	Gln	Pro	Gly	Thr	Thr	Val
		275					280					285			
Leu	Asn	Cys	Ser	His	Asp	Phe	Leu	Ser	Gly	Lys	Val	Gly	Cys	Gly	Ser
	290					295					300				
Pro	Arg	Ile	His	Phe	Gly	Gly	Leu	Ile	Glu	Glu	Asp	Asp	Val	Ile	Leu
305					310					315					320

# ES 2 534 734 A1

Leu Ala Ala Ala Leu Arg Ile Gln Asn Met Val Ser Ser Gly Arg Arg  
 325 330 335

Trp Leu Arg Glu Gln Gln His Arg Arg Trp Arg Leu His Cys Leu Lys  
 340 345 350

Leu Gln Pro Leu Ser Pro Val Pro Ser Asp Ile Glu Ile Ser Arg Gly  
 355 360 365

Gln Thr Pro Lys Ala Val Asp Val Leu Ala Lys Glu Ile Gly Leu Leu  
 370 375 380

Ala Asp Glu Ile Glu Ile Tyr Gly Lys Ser Lys Ala Lys Val Arg Leu  
 385 390 395 400

Ser Val Leu Glu Arg Leu Lys Asp Gln Ala Asp Gly Lys Tyr Val Leu  
 405 410 415

Val Ala Gly Ile Thr Pro Thr Pro Leu Gly Glu Gly Lys Ser Thr Val  
 420 425 430

Thr Ile Gly Leu Val Gln Ala Leu Thr Ala His Leu Asn Val Asn Ser  
 435 440 445

Phe Ala Cys Leu Arg Gln Pro Ser Gln Gly Pro Thr Phe Gly Val Lys  
 450 455 460

Gly Gly Ala Ala Gly Gly Gly Tyr Ala Gln Val Ile Pro Met Glu Glu  
 465 470 475 480

Phe Asn Leu His Leu Thr Gly Asp Ile His Ala Ile Thr Ala Ala Asn  
 485 490 495

Asn Leu Leu Ala Ala Ala Ile Asp Thr Arg Ile Leu His Glu Asn Thr  
 500 505 510

Gln Thr Asp Lys Ala Leu Tyr Asn Arg Leu Val Pro Leu Val Asn Gly  
 515 520 525

Val Arg Glu Phe Ser Glu Ile Gln Leu Ala Arg Leu Lys Lys Leu Gly  
 530 535 540

Ile Asn Lys Thr Asp Pro Ser Thr Leu Thr Glu Glu Glu Val Ser Lys  
 545 550 555 560



## ES 2 534 734 A1

Phe Ala Arg Leu Asp Ile Asp Pro Ser Thr Ile Thr Trp Gln Arg Val  
565 570 575

Leu Asp Thr Asn Asp Arg Phe Leu Arg Lys Ile Thr Ile Gly Gln Gly  
580 585 590

Asn Thr Glu Lys Gly His Tyr Arg Gln Ala Gln Phe Asp Ile Ala Val  
595 600 605

Ala Ser Glu Ile Met Ala Val Leu Ala Leu Thr Asp Ser Leu Ala Asp  
610 615 620

Met Lys Ala Arg Leu Gly Arg Met Val Val Ala Ser Asp Lys Ser Gly  
625 630 635 640

Gln Pro Val Thr Ala Asp Asp Leu Gly Val Thr Gly Ala Leu Thr Val  
645 650 655

Leu Met Lys Asp Ala Ile Lys Pro Asn Leu Met Gln Thr Leu Glu Gly  
660 665 670

Thr Pro Val Phe Val His Ala Gly Pro Phe Ala Asn Ile Ala His Gly  
675 680 685

Asn Ser Ser Val Leu Ala Asp Lys Ile Ala Leu Lys Leu Val Gly Glu  
690 695 700

Glu Gly Phe Val Val Thr Glu Ala Gly Phe Gly Ala Asp Ile Gly Met  
705 710 715 720

Glu Lys Phe Phe Asn Ile Lys Cys Arg Ala Ser Gly Leu Val Pro Asn  
725 730 735

Val Val Val Leu Val Ala Thr Val Arg Ala Leu Lys Met His Gly Gly  
740 745 750

Gly Pro Ser Val Thr Ala Gly Val Pro Leu Lys Lys Glu Tyr Thr Glu  
755 760 765

Glu Asn Ile Gln Leu Val Ala Asp Gly Cys Cys Asn Leu Gln Lys Gln  
770 775 780

Ile Gln Ile Thr Gln Leu Phe Gly Val Pro Val Val Val Ala Leu Asn  
785 790 795 800

ES 2 534 734 A1

Val Phe Lys Thr Asp Thr Arg Ala Glu Ile Asp Leu Val Cys Glu Leu  
 805 810 815

Ala Lys Arg Ala Gly Ala Phe Asp Ala Val Pro Cys Tyr His Trp Ser  
 820 825 830

Val Gly Gly Lys Gly Ser Val Asp Leu Ala Arg Ala Val Arg Glu Ala  
 835 840 845

Ala Ser Lys Arg Ser Arg Phe Gln Phe Leu Tyr Asp Val Gln Val Pro  
 850 855 860

Ile Val Asp Lys Ile Arg Thr Ile Ala Gln Ala Val Tyr Gly Ala Lys  
 865 870 875 880

Asp Ile Glu Leu Ser Pro Glu Ala Gln Ala Lys Ile Asp Arg Tyr Thr  
 885 890 895

Gln Gln Gly Phe Gly Asn Leu Pro Ile Cys Met Ala Lys Thr His Leu  
 900 905 910

Ser Leu Ser His Gln Pro Asp Lys Lys Gly Val Pro Arg Asp Phe Ile  
 915 920 925

Leu Pro Ile Ser Asp Val Arg Ala Ser Ile Gly Ala Gly Phe Ile Tyr  
 930 935 940

Pro Leu Val Gly Thr Met Ser Thr Met Pro Gly Leu Pro Thr Arg Pro  
 945 950 955 960

Cys Phe Tyr Asp Ile Asp Leu Asp Thr Glu Thr Glu Gln Val Lys Gly  
 965 970 975

Leu Phe

<210> 137  
 <211> 275  
 <212> PRT  
 <213> Homo sapiens

<400> 137

Met Gly Thr Arg Leu Pro Leu Val Leu Arg Gln Leu Arg Arg Pro Pro  
 1 5 10 15

# ES 2 534 734 A1

Gln Pro Pro Gly Pro Pro Arg Arg Leu Arg Val Pro Cys Arg Ala Ser  
 20 25 30

Ser Gly Gly Gly Gly Gly Gly Gly Gly Gly Arg Glu Gly Leu Leu Gly  
 35 40 45

Gln Arg Arg Pro Gln Asp Gly Gln Ala Arg Ser Ser Cys Ser Pro Gly  
 50 55 60

Gly Arg Thr Pro Ala Ala Arg Asp Ser Ile Val Arg Glu Val Ile Gln  
 65 70 75 80

Asn Ser Lys Glu Val Leu Ser Leu Leu Gln Glu Lys Asn Pro Ala Phe  
 85 90 95

Lys Pro Val Leu Ala Ile Ile Gln Ala Gly Asp Asp Asn Leu Met Gln  
 100 105 110

Glu Ile Asn Gln Asn Leu Ala Glu Glu Ala Gly Leu Asn Ile Thr His  
 115 120 125

Ile Cys Leu Pro Pro Asp Ser Ser Glu Ala Glu Ile Ile Asp Glu Ile  
 130 135 140

Leu Lys Ile Asn Glu Asp Thr Arg Val His Gly Leu Ala Leu Gln Ile  
 145 150 155 160

Ser Glu Asn Leu Phe Ser Asn Lys Val Leu Asn Ala Leu Lys Pro Glu  
 165 170 175

Lys Asp Val Asp Gly Val Thr Asp Ile Asn Leu Gly Lys Leu Val Arg  
 180 185 190

Gly Asp Ala His Glu Cys Phe Val Ser Pro Val Ala Lys Ala Val Ile  
 195 200 205

Glu Leu Leu Glu Lys Ser Gly Val Asn Leu Asp Gly Lys Lys Ile Leu  
 210 215 220

Val Val Gly Ala His Gly Ser Leu Glu Ala Ala Leu Gln Cys Leu Phe  
 225 230 235 240

Gln Arg Lys Gly Ser Met Thr Met Ser Ile Gln Trp Lys Thr Arg Gln  
 245 250 255

# ES 2 534 734 A1

Leu Gln Ser Lys Thr Glu Ser Arg Ser Val Thr Arg Leu Glu Cys Arg  
260 265 270

Arg Val Ile  
275

<210> 138  
<211> 913  
<212> PRT  
<213> Homo sapiens

<400> 138

Met Gln Ser Arg Arg Ala Arg Pro Arg Arg Glu Val Ile Gln Asn Ser  
1 5 10 15

Lys Glu Val Leu Ser Leu Leu Gln Glu Lys Asn Pro Ala Phe Lys Pro  
20 25 30

Val Leu Ala Ile Ile Gln Ala Gly Asp Asp Asn Leu Met Gln Glu Ile  
35 40 45

Asn Gln Asn Leu Ala Glu Glu Ala Gly Leu Asn Ile Thr His Ile Cys  
50 55 60

Leu Pro Pro Asp Ser Ser Glu Ala Glu Ile Ile Asp Glu Ile Leu Lys  
65 70 75 80

Ile Asn Glu Asp Thr Arg Val His Gly Leu Ala Leu Gln Ile Ser Glu  
85 90 95

Asn Leu Phe Ser Asn Lys Val Leu Asn Ala Leu Lys Pro Glu Lys Asp  
100 105 110

Val Asp Gly Val Thr Asp Ile Asn Leu Gly Lys Leu Val Arg Gly Asp  
115 120 125

Ala His Glu Cys Phe Val Ser Pro Val Ala Lys Ala Val Ile Glu Leu  
130 135 140

Leu Glu Lys Ser Val Gly Val Asn Leu Asp Gly Lys Lys Ile Leu Val  
145 150 155 160

Val Gly Ala His Gly Ser Leu Glu Ala Ala Leu Gln Cys Leu Phe Gln  
165 170 175

# ES 2 534 734 A1

Arg Lys Gly Ser Met Thr Met Ser Ile Gln Trp Lys Thr Arg Gln Leu  
 180 185 190

Gln Ser Lys Leu His Glu Ala Asp Ile Val Val Leu Gly Ser Pro Lys  
 195 200 205

Pro Glu Glu Ile Pro Leu Thr Trp Ile Gln Pro Gly Thr Thr Val Leu  
 210 215 220

Asn Cys Ser His Asp Phe Leu Ser Gly Lys Val Gly Cys Gly Ser Pro  
 225 230 235 240

Arg Ile His Phe Gly Gly Leu Ile Glu Glu Asp Asp Val Ile Leu Leu  
 245 250 255

Ala Ala Ala Leu Arg Ile Gln Asn Met Val Ser Ser Gly Arg Arg Trp  
 260 265 270

Leu Arg Glu Gln Gln His Arg Arg Trp Arg Leu His Cys Leu Lys Leu  
 275 280 285

Gln Pro Leu Ser Pro Val Pro Ser Asp Ile Glu Ile Ser Arg Gly Gln  
 290 295 300

Thr Pro Lys Ala Val Asp Val Leu Ala Lys Glu Ile Gly Leu Leu Ala  
 305 310 315 320

Asp Glu Ile Glu Ile Tyr Gly Lys Ser Lys Ala Lys Val Arg Leu Ser  
 325 330 335

Val Leu Glu Arg Leu Lys Asp Gln Ala Asp Gly Lys Tyr Val Leu Val  
 340 345 350

Ala Gly Ile Thr Pro Thr Pro Leu Gly Glu Gly Lys Ser Thr Val Thr  
 355 360 365

Ile Gly Leu Val Gln Ala Leu Thr Ala His Leu Asn Val Asn Ser Phe  
 370 375 380

Ala Cys Leu Arg Gln Pro Ser Gln Gly Pro Thr Phe Gly Val Lys Gly  
 385 390 395 400

Gly Ala Ala Gly Gly Gly Tyr Ala Gln Val Ile Pro Met Glu Glu Phe  
 405 410 415

ES 2 534 734 A1

Asn Leu His Leu Thr Gly Asp Ile His Ala Ile Thr Ala Ala Asn Asn  
 420 425 430

Leu Leu Ala Ala Ala Ile Asp Thr Arg Ile Leu His Glu Asn Thr Gln  
 435 440 445

Thr Asp Lys Ala Leu Tyr Asn Arg Leu Val Pro Leu Val Asn Gly Val  
 450 455 460

Arg Glu Phe Ser Glu Ile Gln Leu Ala Arg Leu Lys Lys Leu Gly Ile  
 465 470 475 480

Asn Lys Thr Asp Pro Ser Thr Leu Thr Glu Glu Glu Val Ser Lys Phe  
 485 490 495

Ala Arg Leu Asp Ile Asp Pro Ser Thr Ile Thr Trp Gln Arg Val Leu  
 500 505 510

Asp Thr Asn Asp Arg Phe Leu Arg Lys Ile Thr Ile Gly Gln Gly Asn  
 515 520 525

Thr Glu Lys Gly His Tyr Arg Gln Ala Gln Phe Asp Ile Ala Val Ala  
 530 535 540

Ser Glu Ile Met Ala Val Leu Ala Leu Thr Asp Ser Leu Ala Asp Met  
 545 550 555 560

Lys Ala Arg Leu Gly Arg Met Val Val Ala Ser Asp Lys Ser Gly Gln  
 565 570 575

Pro Val Thr Ala Asp Asp Leu Gly Val Thr Gly Ala Leu Thr Val Leu  
 580 585 590

Met Lys Asp Ala Ile Lys Pro Asn Leu Met Gln Thr Leu Glu Gly Thr  
 595 600 605

Pro Val Phe Val His Ala Gly Pro Phe Ala Asn Ile Ala His Gly Asn  
 610 615 620

Ser Ser Val Leu Ala Asp Lys Ile Ala Leu Lys Leu Val Gly Glu Glu  
 625 630 635 640

Gly Phe Val Val Thr Glu Ala Gly Phe Gly Ala Asp Ile Gly Met Glu  
 645 650 655

# ES 2 534 734 A1

Lys Phe Phe Asn Ile Lys Cys Arg Ala Ser Gly Leu Val Pro Asn Val  
 660 665 670

Val Val Leu Val Ala Thr Val Arg Ala Leu Lys Met His Gly Gly Gly  
 675 680 685

Pro Ser Val Thr Ala Gly Val Pro Leu Lys Lys Glu Tyr Thr Glu Glu  
 690 695 700

Asn Ile Gln Leu Val Ala Asp Gly Cys Cys Asn Leu Gln Lys Gln Ile  
 705 710 715 720

Gln Ile Thr Gln Leu Phe Gly Val Pro Val Val Val Ala Leu Asn Val  
 725 730 735

Phe Lys Thr Asp Thr Arg Ala Glu Ile Asp Leu Val Cys Glu Leu Ala  
 740 745 750

Lys Arg Ala Gly Ala Phe Asp Ala Val Pro Cys Tyr His Trp Ser Val  
 755 760 765

Gly Gly Lys Gly Ser Val Asp Leu Ala Arg Ala Val Arg Glu Ala Ala  
 770 775 780

Ser Lys Arg Ser Arg Phe Gln Phe Leu Tyr Asp Val Gln Val Pro Ile  
 785 790 795 800

Val Asp Lys Ile Arg Thr Ile Ala Gln Ala Val Tyr Gly Ala Lys Asp  
 805 810 815

Ile Glu Leu Ser Pro Glu Ala Gln Ala Lys Ile Asp Arg Tyr Thr Gln  
 820 825 830

Gln Gly Phe Gly Asn Leu Pro Ile Cys Met Ala Lys Thr His Leu Ser  
 835 840 845

Leu Ser His Gln Pro Asp Lys Lys Gly Val Pro Arg Asp Phe Ile Leu  
 850 855 860

Pro Ile Ser Asp Val Arg Ala Ser Ile Gly Ala Gly Phe Ile Tyr Pro  
 865 870 875 880

Leu Val Gly Thr Met Ser Thr Met Pro Gly Leu Pro Thr Arg Pro Cys  
 885 890 895

# ES 2 534 734 A1

Phe Tyr Asp Ile Asp Leu Asp Thr Glu Thr Glu Gln Val Lys Gly Leu  
 900 905 910

Phe

<210> 139  
 <211> 2697  
 <212> PRT  
 <213> Homo sapiens  
 <400> 139

Met Asn Gly Asp Met Pro His Val Pro Ile Thr Thr Leu Ala Gly Ile  
 1 5 10 15

Ala Ser Leu Thr Asp Leu Leu Asn Gln Leu Pro Leu Pro Ser Pro Leu  
 20 25 30

Pro Ala Thr Thr Thr Lys Ser Leu Leu Phe Asn Ala Arg Ile Ala Glu  
 35 40 45

Glu Val Asn Cys Leu Leu Ala Cys Arg Asp Asp Asn Leu Val Ser Gln  
 50 55 60

Leu Val His Ser Leu Asn Gln Val Ser Thr Asp His Ile Glu Leu Lys  
 65 70 75 80

Asp Asn Leu Gly Ser Asp Asp Pro Glu Gly Asp Ile Pro Val Leu Leu  
 85 90 95

Gln Ala Val Leu Ala Arg Ser Pro Asn Val Phe Arg Glu Lys Ser Met  
 100 105 110

Gln Asn Arg Tyr Val Gln Ser Gly Met Met Met Ser Gln Tyr Lys Leu  
 115 120 125

Ser Gln Asn Ser Met His Ser Ser Pro Ala Ser Ser Asn Tyr Gln Gln  
 130 135 140

Thr Thr Ile Ser His Ser Pro Ser Ser Arg Phe Val Pro Pro Gln Thr  
 145 150 155 160

Ser Ser Gly Asn Arg Phe Met Pro Gln Gln Asn Ser Pro Val Pro Ser  
 165 170 175



# ES 2 534 734 A1

Pro Tyr Ala Pro Gln Ser Pro Ala Gly Tyr Met Pro Tyr Ser His Pro  
 180 185 190

Ser Ser Tyr Thr Thr His Pro Gln Met Gln Gln Ala Ser Val Ser Ser  
 195 200 205

Pro Ile Val Ala Gly Gly Leu Arg Asn Ile His Asp Asn Lys Val Ser  
 210 215 220

Gly Pro Leu Ser Gly Asn Ser Ala Asn His His Ala Asp Asn Pro Arg  
 225 230 235 240

His Gly Ser Ser Glu Asp Tyr Leu His Met Val His Arg Leu Ser Ser  
 245 250 255

Asp Asp Gly Asp Ser Ser Thr Met Arg Asn Ala Ala Ser Phe Pro Leu  
 260 265 270

Arg Ser Pro Gln Pro Val Cys Ser Pro Ala Gly Ser Glu Gly Thr Pro  
 275 280 285

Lys Gly Ser Arg Pro Pro Leu Ile Leu Gln Ser Gln Ser Leu Pro Cys  
 290 295 300

Ser Ser Pro Arg Asp Val Pro Pro Asp Ile Leu Leu Asp Ser Pro Glu  
 305 310 315 320

Arg Lys Gln Lys Lys Gln Lys Lys Met Lys Leu Gly Lys Asp Glu Lys  
 325 330 335

Glu Gln Ser Glu Lys Ala Ala Met Tyr Asp Ile Ile Ser Ser Pro Ser  
 340 345 350

Lys Asp Ser Thr Lys Leu Thr Leu Arg Leu Ser Arg Val Arg Ser Ser  
 355 360 365

Asp Met Asp Gln Gln Glu Asp Met Ile Ser Gly Val Glu Asn Ser Asn  
 370 375 380

Val Ser Glu Asn Asp Ile Pro Phe Asn Val Gln Tyr Pro Gly Gln Thr  
 385 390 395 400

Ser Lys Thr Pro Ile Thr Pro Gln Asp Ile Asn Arg Pro Leu Asn Ala  
 405 410 415

# ES 2 534 734 A1

Ala Gln Cys Leu Ser Gln Gln Glu Gln Thr Ala Phe Leu Pro Ala Asn  
 420 425 430

Gln Val Pro Val Leu Gln Gln Asn Thr Ser Val Ala Ala Lys Gln Pro  
 435 440 445

Gln Thr Ser Val Val Gln Asn Gln Gln Gln Ile Ser Gln Gln Gly Pro  
 450 455 460

Ile Tyr Asp Glu Val Glu Leu Asp Ala Leu Ala Glu Ile Glu Arg Ile  
 465 470 475 480

Glu Arg Glu Ser Ala Ile Glu Arg Glu Arg Phe Ser Lys Glu Val Gln  
 485 490 495

Asp Lys Asp Lys Pro Leu Lys Lys Arg Lys Gln Asp Ser Tyr Pro Gln  
 500 505 510

Glu Ala Gly Gly Ala Thr Gly Gly Asn Arg Pro Ala Ser Gln Glu Thr  
 515 520 525

Gly Ser Thr Gly Asn Gly Ser Arg Pro Ala Leu Met Val Ser Ile Asp  
 530 535 540

Leu His Gln Ala Gly Arg Val Asp Ser Gln Ala Ser Ile Thr Gln Asp  
 545 550 555 560

Ser Asp Ser Ile Lys Lys Pro Glu Glu Ile Lys Gln Cys Asn Asp Ala  
 565 570 575

Pro Val Ser Val Leu Gln Glu Asp Ile Val Gly Ser Leu Lys Ser Thr  
 580 585 590

Pro Glu Asn His Pro Glu Thr Pro Lys Lys Lys Ser Asp Pro Glu Leu  
 595 600 605

Ser Lys Ser Glu Met Lys Gln Ser Glu Ser Arg Leu Ala Glu Ser Lys  
 610 615 620

Pro Asn Glu Asn Arg Leu Val Glu Thr Lys Ser Ser Glu Asn Lys Leu  
 625 630 635 640

Glu Thr Lys Val Glu Thr Gln Thr Glu Glu Leu Lys Gln Asn Glu Ser  
 645 650 655

# ES 2 534 734 A1

Arg Thr Thr Glu Cys Lys Gln Asn Glu Ser Thr Ile Val Glu Pro Lys  
660 665 670

Gln Asn Glu Asn Arg Leu Ser Asp Thr Lys Pro Asn Asp Asn Lys Gln  
675 680 685

Asn Asn Gly Arg Ser Glu Thr Thr Lys Ser Arg Pro Glu Thr Pro Lys  
690 695 700

Gln Lys Gly Glu Ser Arg Pro Glu Thr Pro Lys Gln Lys Ser Asp Gly  
705 710 715 720

His Pro Glu Thr Pro Lys Gln Lys Gly Asp Gly Arg Pro Glu Thr Pro  
725 730 735

Lys Gln Lys Gly Glu Ser Arg Pro Glu Thr Pro Lys Gln Lys Asn Glu  
740 745 750

Gly Arg Pro Glu Thr Pro Lys His Arg His Asp Asn Arg Arg Asp Ser  
755 760 765

Gly Lys Pro Ser Thr Glu Lys Lys Pro Glu Val Ser Lys His Lys Gln  
770 775 780

Asp Thr Lys Ser Asp Ser Pro Arg Leu Lys Ser Glu Arg Ala Glu Ala  
785 790 795 800

Leu Lys Gln Arg Pro Asp Gly Arg Ser Val Ser Glu Ser Leu Arg Arg  
805 810 815

Asp His Asp Asn Lys Gln Lys Ser Asp Asp Arg Gly Glu Ser Glu Arg  
820 825 830

His Arg Gly Asp Gln Ser Arg Val Arg Arg Pro Glu Thr Leu Arg Ser  
835 840 845

Ser Ser Arg Asn Glu His Gly Ile Lys Ser Asp Ser Ser Lys Thr Asp  
850 855 860

Lys Leu Glu Arg Lys His Arg His Glu Ser Gly Asp Ser Arg Glu Arg  
865 870 875 880

Pro Ser Ser Gly Glu Gln Lys Ser Arg Pro Asp Ser Pro Arg Val Lys  
885 890 895

# ES 2 534 734 A1

Gln Gly Asp Ser Asn Lys Ser Arg Ser Asp Lys Leu Gly Phe Lys Ser  
 900 905 910

Pro Thr Ser Lys Asp Asp Lys Arg Thr Glu Gly Asn Lys Ser Lys Val  
 915 920 925

Asp Thr Asn Lys Ala His Pro Asp Asn Lys Ala Glu Phe Pro Ser Tyr  
 930 935 940

Leu Leu Gly Gly Arg Ser Gly Ala Leu Lys Asn Phe Val Ile Pro Lys  
 945 950 955 960

Ile Lys Arg Asp Lys Asp Gly Asn Val Thr Gln Glu Thr Lys Lys Met  
 965 970 975

Glu Met Lys Gly Glu Pro Lys Asp Lys Val Glu Lys Ile Gly Leu Val  
 980 985 990

Glu Asp Leu Asn Lys Gly Ala Lys Pro Val Val Val Leu Gln Lys Leu  
 995 1000 1005

Ser Leu Asp Asp Val Gln Lys Leu Ile Lys Asp Arg Glu Asp Lys  
 1010 1015 1020

Ser Arg Ser Ser Leu Lys Pro Ile Lys Asn Lys Pro Ser Lys Ser  
 1025 1030 1035

Asn Lys Gly Ser Ile Asp Gln Ser Val Leu Lys Glu Leu Pro Pro  
 1040 1045 1050

Glu Leu Leu Ala Glu Ile Glu Ser Thr Met Pro Leu Cys Glu Arg  
 1055 1060 1065

Val Lys Met Asn Lys Arg Lys Arg Ser Thr Val Asn Glu Lys Pro  
 1070 1075 1080

Lys Tyr Ala Glu Ile Ser Ser Asp Glu Asp Asn Asp Ser Asp Glu  
 1085 1090 1095

Ala Phe Glu Ser Ser Arg Lys Arg His Lys Lys Asp Asp Asp Lys  
 1100 1105 1110

Ala Trp Glu Tyr Glu Glu Arg Asp Arg Arg Ser Ser Gly Asp His  
 1115 1120 1125

## ES 2 534 734 A1

Arg	Arg	Ser	Gly	His	Ser	His	Glu	Gly	Arg	Arg	Ser	Ser	Gly	Gly
	1130					1135					1140			
Gly	Arg	Tyr	Arg	Asn	Arg	Ser	Pro	Ser	Asp	Ser	Asp	Met	Glu	Asp
	1145					1150					1155			
Tyr	Ser	Pro	Pro	Pro	Ser	Leu	Ser	Glu	Val	Ala	Arg	Lys	Met	Lys
	1160					1165					1170			
Lys	Lys	Glu	Lys	Gln	Lys	Lys	Arg	Lys	Ala	Tyr	Glu	Pro	Lys	Leu
	1175					1180					1185			
Thr	Pro	Glu	Glu	Met	Met	Asp	Ser	Ser	Thr	Phe	Lys	Arg	Phe	Thr
	1190					1195					1200			
Ala	Ser	Ile	Glu	Asn	Ile	Leu	Asp	Asn	Leu	Glu	Asp	Met	Asp	Phe
	1205					1210					1215			
Thr	Ala	Phe	Gly	Asp	Asp	Asp	Glu	Ile	Pro	Gln	Glu	Leu	Leu	Leu
	1220					1225					1230			
Gly	Lys	His	Gln	Leu	Asn	Glu	Leu	Gly	Ser	Glu	Ser	Ala	Lys	Ile
	1235					1240					1245			
Lys	Ala	Met	Gly	Ile	Met	Asp	Lys	Leu	Ser	Thr	Asp	Lys	Thr	Val
	1250					1255					1260			
Lys	Val	Leu	Asn	Ile	Leu	Glu	Lys	Asn	Ile	Gln	Asp	Gly	Ser	Lys
	1265					1270					1275			
Leu	Ser	Thr	Leu	Leu	Asn	His	Asn	Asn	Asp	Thr	Glu	Glu	Glu	Glu
	1280					1285					1290			
Arg	Leu	Trp	Arg	Asp	Leu	Ile	Met	Glu	Arg	Val	Thr	Lys	Ser	Ala
	1295					1300					1305			
Asp	Ala	Cys	Leu	Thr	Thr	Ile	Asn	Ile	Met	Thr	Ser	Pro	Asn	Met
	1310					1315					1320			
Pro	Lys	Ala	Val	Tyr	Ile	Glu	Asp	Val	Ile	Glu	Arg	Val	Ile	Gln
	1325					1330					1335			
Tyr	Thr	Lys	Phe	His	Leu	Gln	Asn	Thr	Leu	Tyr	Pro	Gln	Tyr	Asp
	1340					1345					1350			

## ES 2 534 734 A1

Pro	Val	Tyr	Arg	Leu	Asp	Pro	His	Gly	Gly	Gly	Leu	Leu	Ser	Ser
	1355					1360					1365			
Lys	Ala	Lys	Arg	Ala	Lys	Cys	Ser	Thr	His	Lys	Gln	Arg	Val	Ile
	1370					1375					1380			
Val	Met	Leu	Tyr	Asn	Lys	Val	Cys	Asp	Ile	Val	Ser	Ser	Leu	Ser
	1385					1390					1395			
Glu	Leu	Leu	Glu	Ile	Gln	Leu	Leu	Thr	Asp	Thr	Thr	Ile	Leu	Gln
	1400					1405					1410			
Val	Ser	Ser	Met	Gly	Ile	Thr	Pro	Phe	Phe	Val	Glu	Asn	Val	Ser
	1415					1420					1425			
Glu	Leu	Gln	Leu	Cys	Ala	Ile	Lys	Leu	Val	Thr	Ala	Val	Phe	Ser
	1430					1435					1440			
Arg	Tyr	Glu	Lys	His	Arg	Gln	Leu	Ile	Leu	Glu	Glu	Ile	Phe	Thr
	1445					1450					1455			
Ser	Leu	Ala	Arg	Leu	Pro	Thr	Ser	Lys	Arg	Ser	Leu	Arg	Asn	Phe
	1460					1465					1470			
Arg	Leu	Asn	Ser	Ser	Asp	Met	Asp	Gly	Glu	Pro	Met	Tyr	Ile	Gln
	1475					1480					1485			
Met	Val	Thr	Ala	Leu	Val	Leu	Gln	Leu	Ile	Gln	Cys	Val	Val	His
	1490					1495					1500			
Leu	Pro	Ser	Ser	Glu	Lys	Asp	Ser	Asn	Ala	Glu	Glu	Asp	Ser	Asn
	1505					1510					1515			
Lys	Lys	Ile	Asp	Gln	Asp	Val	Val	Ile	Thr	Asn	Ser	Tyr	Glu	Thr
	1520					1525					1530			
Ala	Met	Arg	Thr	Ala	Gln	Asn	Phe	Leu	Ser	Ile	Phe	Leu	Lys	Lys
	1535					1540					1545			
Cys	Gly	Ser	Lys	Gln	Gly	Glu	Glu	Asp	Tyr	Arg	Pro	Leu	Phe	Glu
	1550					1555					1560			
Asn	Phe	Val	Gln	Asp	Leu	Leu	Ser	Thr	Val	Asn	Lys	Pro	Glu	Trp
	1565					1570					1575			

## ES 2 534 734 A1

Pro	Ala	Ala	Glu	Leu	Leu	Leu	Ser	Leu	Leu	Gly	Arg	Leu	Leu	Val
	1580					1585					1590			
His	Gln	Phe	Ser	Asn	Lys	Ser	Thr	Glu	Met	Ala	Leu	Arg	Val	Ala
	1595					1600					1605			
Ser	Leu	Asp	Tyr	Leu	Gly	Thr	Val	Ala	Ala	Arg	Leu	Arg	Lys	Asp
	1610					1615					1620			
Ala	Val	Thr	Ser	Lys	Met	Asp	Gln	Gly	Ser	Ile	Glu	Arg	Ile	Leu
	1625					1630					1635			
Lys	Gln	Val	Ser	Gly	Gly	Glu	Asp	Glu	Ile	Gln	Gln	Leu	Gln	Lys
	1640					1645					1650			
Ala	Leu	Leu	Asp	Tyr	Leu	Asp	Glu	Asn	Thr	Glu	Thr	Asp	Pro	Ser
	1655					1660					1665			
Leu	Val	Phe	Ser	Arg	Lys	Phe	Tyr	Ile	Ala	Gln	Trp	Phe	Arg	Asp
	1670					1675					1680			
Thr	Thr	Leu	Glu	Thr	Glu	Lys	Ala	Met	Lys	Ser	Gln	Lys	Asp	Glu
	1685					1690					1695			
Glu	Ser	Ser	Glu	Gly	Thr	His	His	Ala	Lys	Glu	Ile	Glu	Thr	Thr
	1700					1705					1710			
Gly	Gln	Ile	Met	His	Arg	Ala	Glu	Asn	Arg	Lys	Lys	Phe	Leu	Arg
	1715					1720					1725			
Ser	Ile	Ile	Lys	Thr	Thr	Pro	Ser	Gln	Phe	Ser	Thr	Leu	Lys	Met
	1730					1735					1740			
Asn	Ser	Asp	Thr	Val	Asp	Tyr	Asp	Asp	Ala	Cys	Leu	Ile	Val	Arg
	1745					1750					1755			
Tyr	Leu	Ala	Ser	Met	Arg	Pro	Phe	Ala	Gln	Ser	Phe	Asp	Ile	Tyr
	1760					1765					1770			
Leu	Thr	Gln	Ile	Leu	Arg	Val	Leu	Gly	Glu	Asn	Ala	Ile	Ala	Val
	1775					1780					1785			
Arg	Thr	Lys	Ala	Met	Lys	Cys	Leu	Ser	Glu	Val	Val	Ala	Val	Asp
	1790					1795					1800			

## ES 2 534 734 A1

Pro	Ser	Ile	Leu	Ala	Arg	Leu	Asp	Met	Gln	Arg	Gly	Val	His	Gly
	1805					1810					1815			
Arg	Leu	Met	Asp	Asn	Ser	Thr	Ser	Val	Arg	Glu	Ala	Ala	Val	Glu
	1820					1825					1830			
Leu	Leu	Gly	Arg	Phe	Val	Leu	Cys	Arg	Pro	Gln	Leu	Ala	Glu	Gln
	1835					1840					1845			
Tyr	Tyr	Asp	Met	Leu	Ile	Glu	Arg	Ile	Leu	Asp	Thr	Gly	Ile	Ser
	1850					1855					1860			
Val	Arg	Lys	Arg	Val	Ile	Lys	Ile	Leu	Arg	Asp	Ile	Cys	Ile	Glu
	1865					1870					1875			
Gln	Pro	Thr	Phe	Pro	Lys	Ile	Thr	Glu	Met	Cys	Val	Lys	Met	Ile
	1880					1885					1890			
Arg	Arg	Val	Asn	Asp	Glu	Glu	Gly	Ile	Lys	Lys	Leu	Val	Asn	Glu
	1895					1900					1905			
Thr	Phe	Gln	Lys	Leu	Trp	Phe	Thr	Pro	Thr	Pro	His	Asn	Asp	Lys
	1910					1915					1920			
Glu	Ala	Met	Thr	Arg	Lys	Ile	Leu	Asn	Ile	Thr	Asp	Val	Val	Ala
	1925					1930					1935			
Ala	Cys	Arg	Asp	Thr	Gly	Tyr	Asp	Trp	Phe	Glu	Gln	Leu	Leu	Gln
	1940					1945					1950			
Asn	Leu	Leu	Lys	Ser	Glu	Glu	Asp	Ser	Ser	Tyr	Lys	Pro	Val	Lys
	1955					1960					1965			
Lys	Ala	Cys	Thr	Gln	Leu	Val	Asp	Asn	Leu	Val	Glu	His	Ile	Leu
	1970					1975					1980			
Lys	Tyr	Glu	Glu	Ser	Leu	Ala	Asp	Ser	Asp	Asn	Lys	Gly	Val	Asn
	1985					1990					1995			
Ser	Gly	Arg	Leu	Val	Ala	Cys	Ile	Thr	Thr	Leu	Phe	Leu	Phe	Ser
	2000					2005					2010			
Lys	Ile	Arg	Pro	Gln	Leu	Met	Val	Lys	His	Ala	Met	Thr	Met	Gln
	2015					2020					2025			



# ES 2 534 734 A1

Pro Tyr Leu Thr Thr Lys Cys Ser Thr Gln Asn Asp Phe Met Val  
 2030 2035 2040

Ile Cys Asn Val Ala Lys Ile Leu Glu Leu Val Val Pro Leu Met  
 2045 2050 2055

Glu His Pro Ser Glu Thr Phe Leu Ala Thr Ile Glu Glu Asp Leu  
 2060 2065 2070

Met Lys Leu Ile Ile Lys Tyr Gly Met Thr Val Val Gln His Cys  
 2075 2080 2085

Val Ser Cys Leu Gly Ala Val Val Asn Lys Val Thr Gln Asn Phe  
 2090 2095 2100

Lys Phe Val Trp Ala Cys Phe Asn Arg Tyr Tyr Gly Ala Ile Ser  
 2105 2110 2115

Lys Leu Lys Ser Gln His Gln Glu Asp Pro Asn Asn Thr Ser Leu  
 2120 2125 2130

Leu Thr Asn Lys Pro Ala Leu Leu Arg Ser Leu Phe Thr Val Gly  
 2135 2140 2145

Ala Leu Cys Arg His Phe Asp Phe Asp Leu Glu Asp Phe Lys Gly  
 2150 2155 2160

Asn Ser Lys Val Asn Ile Lys Asp Lys Val Leu Glu Leu Leu Met  
 2165 2170 2175

Tyr Phe Thr Lys His Ser Asp Glu Glu Val Gln Thr Lys Ala Ile  
 2180 2185 2190

Ile Gly Leu Gly Phe Ala Phe Ile Gln His Pro Ser Leu Met Phe  
 2195 2200 2205

Glu Gln Glu Val Lys Asn Leu Tyr Asn Asn Ile Leu Ser Asp Lys  
 2210 2215 2220

Asn Ser Ser Val Asn Leu Lys Ile Gln Val Leu Lys Asn Leu Gln  
 2225 2230 2235

Thr Tyr Leu Gln Glu Glu Asp Thr Arg Met Gln Gln Ala Asp Arg  
 2240 2245 2250

# ES 2 534 734 A1

Asp	Trp	Lys	Lys	Val	Ala	Lys	Gln	Glu	Asp	Leu	Lys	Glu	Met	Gly
2255						2260					2265			
Asp	Val	Ser	Ser	Gly	Met	Ser	Ser	Ser	Ile	Met	Gln	Leu	Tyr	Leu
2270						2275					2280			
Lys	Gln	Val	Leu	Glu	Ala	Phe	Phe	His	Thr	Gln	Ser	Ser	Val	Arg
2285						2290					2295			
His	Phe	Ala	Leu	Asn	Val	Ile	Ala	Leu	Thr	Leu	Asn	Gln	Gly	Leu
2300						2305					2310			
Ile	His	Pro	Val	Gln	Cys	Val	Pro	Tyr	Leu	Ile	Ala	Met	Gly	Thr
2315						2320					2325			
Asp	Pro	Glu	Pro	Ala	Met	Arg	Asn	Lys	Ala	Asp	Gln	Gln	Leu	Val
2330						2335					2340			
Glu	Ile	Asp	Lys	Lys	Tyr	Ala	Gly	Phe	Ile	His	Met	Lys	Ala	Val
2345						2350					2355			
Ala	Gly	Met	Lys	Met	Ser	Tyr	Gln	Val	Gln	Gln	Ala	Ile	Asn	Thr
2360						2365					2370			
Cys	Leu	Lys	Asp	Pro	Val	Arg	Gly	Phe	Arg	Gln	Asp	Glu	Ser	Ser
2375						2380					2385			
Ser	Ala	Leu	Cys	Ser	His	Leu	Tyr	Ser	Met	Ile	Arg	Gly	Asn	Arg
2390						2395					2400			
Gln	His	Arg	Arg	Ala	Phe	Leu	Ile	Ser	Leu	Leu	Asn	Leu	Phe	Asp
2405						2410					2415			
Asp	Thr	Ala	Lys	Thr	Asp	Val	Thr	Met	Leu	Leu	Tyr	Ile	Ala	Asp
2420						2425					2430			
Asn	Leu	Ala	Cys	Phe	Pro	Tyr	Gln	Thr	Gln	Glu	Glu	Pro	Leu	Phe
2435						2440					2445			
Ile	Met	His	His	Ile	Asp	Ile	Thr	Leu	Ser	Val	Ser	Gly	Ser	Asn
2450						2455					2460			
Leu	Leu	Gln	Ser	Phe	Lys	Glu	Ser	Met	Val	Lys	Asp	Lys	Arg	Lys
2465						2470					2475			

# ES 2 534 734 A1

Glu Arg Lys Ser Ser Pro Ser Lys Glu Asn Glu Ser Ser Asp Ser  
 2480 2485 2490

Glu Glu Glu Val Ser Arg Pro Arg Lys Ser Arg Lys Arg Val Asp  
 2495 2500 2505

Ser Asp Ser Asp Ser Asp Ser Glu Asp Asp Ile Asn Ser Val Met  
 2510 2515 2520

Lys Cys Leu Pro Glu Asn Ser Ala Pro Leu Ile Glu Phe Ala Asn  
 2525 2530 2535

Val Ser Gln Gly Ile Leu Leu Leu Leu Met Leu Lys Gln His Leu  
 2540 2545 2550

Lys Asn Leu Cys Gly Phe Ser Asp Ser Lys Ile Gln Lys Tyr Ser  
 2555 2560 2565

Pro Ser Glu Ser Ala Lys Val Tyr Asp Lys Ala Ile Asn Arg Lys  
 2570 2575 2580

Thr Gly Val His Phe His Pro Lys Gln Thr Leu Asp Phe Leu Arg  
 2585 2590 2595

Ser Asp Met Ala Asn Ser Lys Ile Thr Glu Glu Val Lys Arg Ser  
 2600 2605 2610

Ile Val Lys Gln Tyr Leu Asp Phe Lys Leu Leu Met Glu His Leu  
 2615 2620 2625

Asp Pro Asp Glu Glu Glu Glu Glu Gly Glu Val Ser Ala Ser Thr  
 2630 2635 2640

Asn Ala Arg Asn Lys Ala Ile Thr Ser Leu Leu Gly Gly Gly Ser  
 2645 2650 2655

Pro Lys Asn Asn Thr Ala Ala Glu Thr Glu Asp Asp Glu Ser Asp  
 2660 2665 2670

Gly Glu Asp Arg Gly Gly Gly Thr Ser Gly Val Arg Arg Arg Arg  
 2675 2680 2685

Ser Gln Arg Ile Ser Gln Arg Ile Thr  
 2690 2695

# ES 2 534 734 A1

<210> 140  
 <211> 2804  
 <212> PRT  
 <213> Homo sapiens

<400> 140

Met Asn Gly Asp Met Pro His Val Pro Ile Thr Thr Leu Ala Gly Ile  
 1 5 10 15

Ala Ser Leu Thr Asp Leu Leu Asn Gln Leu Pro Leu Pro Ser Pro Leu  
 20 25 30

Pro Ala Thr Thr Thr Lys Ser Leu Leu Phe Asn Ala Arg Ile Ala Glu  
 35 40 45

Glu Val Asn Cys Leu Leu Ala Cys Arg Asp Asp Asn Leu Val Ser Gln  
 50 55 60

Leu Val His Ser Leu Asn Gln Val Ser Thr Asp His Ile Glu Leu Lys  
 65 70 75 80

Asp Asn Leu Gly Ser Asp Asp Pro Glu Gly Asp Ile Pro Val Leu Leu  
 85 90 95

Gln Ala Val Leu Ala Arg Ser Pro Asn Val Phe Arg Glu Lys Ser Met  
 100 105 110

Gln Asn Arg Tyr Val Gln Ser Gly Met Met Met Ser Gln Tyr Lys Leu  
 115 120 125

Ser Gln Asn Ser Met His Ser Ser Pro Ala Ser Ser Asn Tyr Gln Gln  
 130 135 140

Thr Thr Ile Ser His Ser Pro Ser Ser Arg Phe Val Pro Pro Gln Thr  
 145 150 155 160

Ser Ser Gly Asn Arg Phe Met Pro Gln Gln Asn Ser Pro Val Pro Ser  
 165 170 175

Pro Tyr Ala Pro Gln Ser Pro Ala Gly Tyr Met Pro Tyr Ser His Pro  
 180 185 190

Ser Ser Tyr Thr Thr His Pro Gln Met Gln Gln Ala Ser Val Ser Ser  
 195 200 205

# ES 2 534 734 A1

Pro Ile Val Ala Gly Gly Leu Arg Asn Ile His Asp Asn Lys Val Ser  
 210 215 220

Gly Pro Leu Ser Gly Asn Ser Ala Asn His His Ala Asp Asn Pro Arg  
 225 230 235 240

His Gly Ser Ser Glu Asp Tyr Leu His Met Val His Arg Leu Ser Ser  
 245 250 255

Asp Asp Gly Asp Ser Ser Thr Met Arg Asn Ala Ala Ser Phe Pro Leu  
 260 265 270

Arg Ser Pro Gln Pro Val Cys Ser Pro Ala Gly Ser Glu Gly Thr Pro  
 275 280 285

Lys Gly Ser Arg Pro Pro Leu Ile Leu Gln Ser Gln Ser Leu Pro Cys  
 290 295 300

Ser Ser Pro Arg Asp Val Pro Pro Asp Ile Leu Leu Asp Ser Pro Glu  
 305 310 315 320

Arg Lys Gln Lys Lys Gln Lys Lys Met Lys Leu Gly Lys Asp Glu Lys  
 325 330 335

Glu Gln Ser Glu Lys Ala Ala Met Tyr Asp Ile Ile Ser Ser Pro Ser  
 340 345 350

Lys Asp Ser Thr Lys Leu Thr Leu Arg Leu Ser Arg Val Arg Ser Ser  
 355 360 365

Asp Met Asp Gln Gln Glu Asp Met Ile Ser Gly Val Glu Asn Ser Asn  
 370 375 380

Val Ser Glu Asn Asp Ile Pro Phe Asn Val Gln Tyr Pro Gly Gln Thr  
 385 390 395 400

Ser Lys Thr Pro Ile Thr Pro Gln Asp Ile Asn Arg Pro Leu Asn Ala  
 405 410 415

Ala Gln Cys Leu Ser Gln Gln Glu Gln Thr Ala Phe Leu Pro Ala Asn  
 420 425 430

Gln Val Pro Val Leu Gln Gln Asn Thr Ser Val Ala Ala Lys Gln Pro  
 435 440 445

# ES 2 534 734 A1

Gln Thr Ser Val Val Gln Asn Gln Gln Gln Ile Ser Gln Gln Gly Pro  
 450 455 460

Ile Tyr Asp Glu Val Glu Leu Asp Ala Leu Ala Glu Ile Glu Arg Ile  
 465 470 475 480

Glu Arg Glu Ser Ala Ile Glu Arg Glu Arg Phe Ser Lys Glu Val Gln  
 485 490 495

Asp Lys Asp Lys Pro Leu Lys Lys Arg Lys Gln Asp Ser Tyr Pro Gln  
 500 505 510

Glu Ala Gly Gly Ala Thr Gly Gly Asn Arg Pro Ala Ser Gln Glu Thr  
 515 520 525

Gly Ser Thr Gly Asn Gly Ser Arg Pro Ala Leu Met Val Ser Ile Asp  
 530 535 540

Leu His Gln Ala Gly Arg Val Asp Ser Gln Ala Ser Ile Thr Gln Asp  
 545 550 555 560

Ser Asp Ser Ile Lys Lys Pro Glu Glu Ile Lys Gln Cys Asn Asp Ala  
 565 570 575

Pro Val Ser Val Leu Gln Glu Asp Ile Val Gly Ser Leu Lys Ser Thr  
 580 585 590

Pro Glu Asn His Pro Glu Thr Pro Lys Lys Lys Ser Asp Pro Glu Leu  
 595 600 605

Ser Lys Ser Glu Met Lys Gln Ser Glu Ser Arg Leu Ala Glu Ser Lys  
 610 615 620

Pro Asn Glu Asn Arg Leu Val Glu Thr Lys Ser Ser Glu Asn Lys Leu  
 625 630 635 640

Glu Thr Lys Val Glu Thr Gln Thr Glu Glu Leu Lys Gln Asn Glu Ser  
 645 650 655

Arg Thr Thr Glu Cys Lys Gln Asn Glu Ser Thr Ile Val Glu Pro Lys  
 660 665 670

Gln Asn Glu Asn Arg Leu Ser Asp Thr Lys Pro Asn Asp Asn Lys Gln  
 675 680 685

# ES 2 534 734 A1

Asn Asn Gly Arg Ser Glu Thr Thr Lys Ser Arg Pro Glu Thr Pro Lys  
 690 695 700

Gln Lys Gly Glu Ser Arg Pro Glu Thr Pro Lys Gln Lys Ser Asp Gly  
 705 710 715 720

His Pro Glu Thr Pro Lys Gln Lys Gly Asp Gly Arg Pro Glu Thr Pro  
 725 730 735

Lys Gln Lys Gly Glu Ser Arg Pro Glu Thr Pro Lys Gln Lys Asn Glu  
 740 745 750

Gly Arg Pro Glu Thr Pro Lys His Arg His Asp Asn Arg Arg Asp Ser  
 755 760 765

Gly Lys Pro Ser Thr Glu Lys Lys Pro Glu Val Ser Lys His Lys Gln  
 770 775 780

Asp Thr Lys Ser Asp Ser Pro Arg Leu Lys Ser Glu Arg Ala Glu Ala  
 785 790 795 800

Leu Lys Gln Arg Pro Asp Gly Arg Ser Val Ser Glu Ser Leu Arg Arg  
 805 810 815

Asp His Asp Asn Lys Gln Lys Ser Asp Asp Arg Gly Glu Ser Glu Arg  
 820 825 830

His Arg Gly Asp Gln Ser Arg Val Arg Arg Pro Glu Thr Leu Arg Ser  
 835 840 845

Ser Ser Arg Asn Glu His Gly Ile Lys Ser Asp Ser Ser Lys Thr Asp  
 850 855 860

Lys Leu Glu Arg Lys His Arg His Glu Ser Gly Asp Ser Arg Glu Arg  
 865 870 875 880

Pro Ser Ser Gly Glu Gln Lys Ser Arg Pro Asp Ser Pro Arg Val Lys  
 885 890 895

Gln Gly Asp Ser Asn Lys Ser Arg Ser Asp Lys Leu Gly Phe Lys Ser  
 900 905 910

Pro Thr Ser Lys Asp Asp Lys Arg Thr Glu Gly Asn Lys Ser Lys Val  
 915 920 925

# ES 2 534 734 A1

Asp Thr Asn Lys Ala His Pro Asp Asn Lys Ala Glu Phe Pro Ser Tyr  
 930 935 940

Leu Leu Gly Gly Arg Ser Gly Ala Leu Lys Asn Phe Val Ile Pro Lys  
 945 950 955 960

Ile Lys Arg Asp Lys Asp Gly Asn Val Thr Gln Glu Thr Lys Lys Met  
 965 970 975

Glu Met Lys Gly Glu Pro Lys Asp Lys Val Glu Lys Ile Gly Leu Val  
 980 985 990

Glu Asp Leu Asn Lys Gly Ala Lys Pro Val Val Val Leu Gln Lys Leu  
 995 1000 1005

Ser Leu Asp Asp Val Gln Lys Leu Ile Lys Asp Arg Glu Asp Lys  
 1010 1015 1020

Ser Arg Ser Ser Leu Lys Pro Ile Lys Asn Lys Pro Ser Lys Ser  
 1025 1030 1035

Asn Lys Gly Ser Ile Asp Gln Ser Val Leu Lys Glu Leu Pro Pro  
 1040 1045 1050

Glu Leu Leu Ala Glu Ile Glu Ser Thr Met Pro Leu Cys Glu Arg  
 1055 1060 1065

Val Lys Met Asn Lys Arg Lys Arg Ser Thr Val Asn Glu Lys Pro  
 1070 1075 1080

Lys Tyr Ala Glu Ile Ser Ser Asp Glu Asp Asn Asp Ser Asp Glu  
 1085 1090 1095

Ala Phe Glu Ser Ser Arg Lys Arg His Lys Lys Asp Asp Asp Lys  
 1100 1105 1110

Ala Trp Glu Tyr Glu Glu Arg Asp Arg Arg Ser Ser Gly Asp His  
 1115 1120 1125

Arg Arg Ser Gly His Ser His Glu Gly Arg Arg Ser Ser Gly Gly  
 1130 1135 1140

Gly Arg Tyr Arg Asn Arg Ser Pro Ser Asp Ser Asp Met Glu Asp  
 1145 1150 1155



## ES 2 534 734 A1

Tyr	Ser	Pro	Pro	Pro	Ser	Leu	Ser	Glu	Val	Ala	Arg	Lys	Met	Lys
	1160					1165					1170			
Lys	Lys	Glu	Lys	Gln	Lys	Lys	Arg	Lys	Ala	Tyr	Glu	Pro	Lys	Leu
	1175					1180					1185			
Thr	Pro	Glu	Glu	Met	Met	Asp	Ser	Ser	Thr	Phe	Lys	Arg	Phe	Thr
	1190					1195					1200			
Ala	Ser	Ile	Glu	Asn	Ile	Leu	Asp	Asn	Leu	Glu	Asp	Met	Asp	Phe
	1205					1210					1215			
Thr	Ala	Phe	Gly	Asp	Asp	Asp	Glu	Ile	Pro	Gln	Glu	Leu	Leu	Leu
	1220					1225					1230			
Gly	Lys	His	Gln	Leu	Asn	Glu	Leu	Gly	Ser	Glu	Ser	Ala	Lys	Ile
	1235					1240					1245			
Lys	Ala	Met	Gly	Ile	Met	Asp	Lys	Leu	Ser	Thr	Asp	Lys	Thr	Val
	1250					1255					1260			
Lys	Val	Leu	Asn	Ile	Leu	Glu	Lys	Asn	Ile	Gln	Asp	Gly	Ser	Lys
	1265					1270					1275			
Leu	Ser	Thr	Leu	Leu	Asn	His	Asn	Asn	Asp	Thr	Glu	Glu	Glu	Glu
	1280					1285					1290			
Arg	Leu	Trp	Arg	Asp	Leu	Ile	Met	Glu	Arg	Val	Thr	Lys	Ser	Ala
	1295					1300					1305			
Asp	Ala	Cys	Leu	Thr	Thr	Ile	Asn	Ile	Met	Thr	Ser	Pro	Asn	Met
	1310					1315					1320			
Pro	Lys	Ala	Val	Tyr	Ile	Glu	Asp	Val	Ile	Glu	Arg	Val	Ile	Gln
	1325					1330					1335			
Tyr	Thr	Lys	Phe	His	Leu	Gln	Asn	Thr	Leu	Tyr	Pro	Gln	Tyr	Asp
	1340					1345					1350			
Pro	Val	Tyr	Arg	Leu	Asp	Pro	His	Gly	Gly	Gly	Leu	Leu	Ser	Ser
	1355					1360					1365			
Lys	Ala	Lys	Arg	Ala	Lys	Cys	Ser	Thr	His	Lys	Gln	Arg	Val	Ile
	1370					1375					1380			

## ES 2 534 734 A1

Val	Met	Leu	Tyr	Asn	Lys	Val	Cys	Asp	Ile	Val	Ser	Ser	Leu	Ser
	1385					1390					1395			
Glu	Leu	Leu	Glu	Ile	Gln	Leu	Leu	Thr	Asp	Thr	Thr	Ile	Leu	Gln
	1400					1405					1410			
Val	Ser	Ser	Met	Gly	Ile	Thr	Pro	Phe	Phe	Val	Glu	Asn	Val	Ser
	1415					1420					1425			
Glu	Leu	Gln	Leu	Cys	Ala	Ile	Lys	Leu	Val	Thr	Ala	Val	Phe	Ser
	1430					1435					1440			
Arg	Tyr	Glu	Lys	His	Arg	Gln	Leu	Ile	Leu	Glu	Glu	Ile	Phe	Thr
	1445					1450					1455			
Ser	Leu	Ala	Arg	Leu	Pro	Thr	Ser	Lys	Arg	Ser	Leu	Arg	Asn	Phe
	1460					1465					1470			
Arg	Leu	Asn	Ser	Ser	Asp	Met	Asp	Gly	Glu	Pro	Met	Tyr	Ile	Gln
	1475					1480					1485			
Met	Val	Thr	Ala	Leu	Val	Leu	Gln	Leu	Ile	Gln	Cys	Val	Val	His
	1490					1495					1500			
Leu	Pro	Ser	Ser	Glu	Lys	Asp	Ser	Asn	Ala	Glu	Glu	Asp	Ser	Asn
	1505					1510					1515			
Lys	Lys	Ile	Asp	Gln	Asp	Val	Val	Ile	Thr	Asn	Ser	Tyr	Glu	Thr
	1520					1525					1530			
Ala	Met	Arg	Thr	Ala	Gln	Asn	Phe	Leu	Ser	Ile	Phe	Leu	Lys	Lys
	1535					1540					1545			
Cys	Gly	Ser	Lys	Gln	Gly	Glu	Glu	Asp	Tyr	Arg	Pro	Leu	Phe	Glu
	1550					1555					1560			
Asn	Phe	Val	Gln	Asp	Leu	Leu	Ser	Thr	Val	Asn	Lys	Pro	Glu	Trp
	1565					1570					1575			
Pro	Ala	Ala	Glu	Leu	Leu	Leu	Ser	Leu	Leu	Gly	Arg	Leu	Leu	Val
	1580					1585					1590			
His	Gln	Phe	Ser	Asn	Lys	Ser	Thr	Glu	Met	Ala	Leu	Arg	Val	Ala
	1595					1600					1605			

# ES 2 534 734 A1

Ser Leu Asp Tyr Leu Gly Thr Val Ala Ala Arg Leu Arg Lys Asp  
 1610 1615 1620

Ala Val Thr Ser Lys Met Asp Gln Gly Ser Ile Glu Arg Ile Leu  
 1625 1630 1635

Lys Gln Val Ser Gly Gly Glu Asp Glu Ile Gln Gln Leu Gln Lys  
 1640 1645 1650

Ala Leu Leu Asp Tyr Leu Asp Glu Asn Thr Glu Thr Asp Pro Ser  
 1655 1660 1665

Leu Val Phe Ser Arg Lys Phe Tyr Ile Ala Gln Trp Phe Arg Asp  
 1670 1675 1680

Thr Thr Leu Glu Thr Glu Lys Ala Met Lys Ser Gln Lys Asp Glu  
 1685 1690 1695

Glu Ser Ser Glu Gly Thr His His Ala Lys Glu Ile Glu Thr Thr  
 1700 1705 1710

Gly Gln Ile Met His Arg Ala Glu Asn Arg Lys Lys Phe Leu Arg  
 1715 1720 1725

Ser Ile Ile Lys Thr Thr Pro Ser Gln Phe Ser Thr Leu Lys Met  
 1730 1735 1740

Asn Ser Asp Thr Val Asp Tyr Asp Asp Ala Cys Leu Ile Val Arg  
 1745 1750 1755

Tyr Leu Ala Ser Met Arg Pro Phe Ala Gln Ser Phe Asp Ile Tyr  
 1760 1765 1770

Leu Thr Gln Ile Leu Arg Val Leu Gly Glu Asn Ala Ile Ala Val  
 1775 1780 1785

Arg Thr Lys Ala Met Lys Cys Leu Ser Glu Val Val Ala Val Asp  
 1790 1795 1800

Pro Ser Ile Leu Ala Arg Leu Asp Met Gln Arg Gly Val His Gly  
 1805 1810 1815

Arg Leu Met Asp Asn Ser Thr Ser Val Arg Glu Ala Ala Val Glu  
 1820 1825 1830

## ES 2 534 734 A1

Leu 1835	Leu	Gly	Arg	Phe	Val	Leu 1840	Cys	Arg	Pro	Gln	Leu 1845	Ala	Glu	Gln
Tyr 1850	Tyr	Asp	Met	Leu	Ile	Glu 1855	Arg	Ile	Leu	Asp	Thr 1860	Gly	Ile	Ser
Val 1865	Arg	Lys	Arg	Val	Ile	Lys 1870	Ile	Leu	Arg	Asp	Ile 1875	Cys	Ile	Glu
Gln 1880	Pro	Thr	Phe	Pro	Lys	Ile 1885	Thr	Glu	Met	Cys	Val 1890	Lys	Met	Ile
Arg 1895	Arg	Val	Asn	Asp	Glu	Glu 1900	Gly	Ile	Lys	Lys	Leu 1905	Val	Asn	Glu
Thr 1910	Phe	Gln	Lys	Leu	Trp	Phe 1915	Thr	Pro	Thr	Pro	His 1920	Asn	Asp	Lys
Glu 1925	Ala	Met	Thr	Arg	Lys	Ile 1930	Leu	Asn	Ile	Thr	Asp 1935	Val	Val	Ala
Ala 1940	Cys	Arg	Asp	Thr	Gly	Tyr 1945	Asp	Trp	Phe	Glu	Gln 1950	Leu	Leu	Gln
Asn 1955	Leu	Leu	Lys	Ser	Glu	Glu 1960	Asp	Ser	Ser	Tyr	Lys 1965	Pro	Val	Lys
Lys 1970	Ala	Cys	Thr	Gln	Leu	Val 1975	Asp	Asn	Leu	Val	Glu 1980	His	Ile	Leu
Lys 1985	Tyr	Glu	Glu	Ser	Leu	Ala 1990	Asp	Ser	Asp	Asn	Lys 1995	Gly	Val	Asn
Ser 2000	Gly	Arg	Leu	Val	Ala	Cys 2005	Ile	Thr	Thr	Leu	Phe 2010	Leu	Phe	Ser
Lys 2015	Ile	Arg	Pro	Gln	Leu	Met 2020	Val	Lys	His	Ala	Met 2025	Thr	Met	Gln
Pro 2030	Tyr	Leu	Thr	Thr	Lys	Cys 2035	Ser	Thr	Gln	Asn	Asp 2040	Phe	Met	Val
Ile 2045	Cys	Asn	Val	Ala	Lys	Ile 2050	Leu	Glu	Leu	Val	Val 2055	Pro	Leu	Met

# ES 2 534 734 A1

Glu	His	Pro	Ser	Glu	Thr	Phe	Leu	Ala	Thr	Ile	Glu	Glu	Asp	Leu
	2060					2065					2070			
Met	Lys	Leu	Ile	Ile	Lys	Tyr	Gly	Met	Thr	Val	Val	Gln	His	Cys
	2075					2080					2085			
Val	Ser	Cys	Leu	Gly	Ala	Val	Val	Asn	Lys	Val	Thr	Gln	Asn	Phe
	2090					2095					2100			
Lys	Phe	Val	Trp	Ala	Cys	Phe	Asn	Arg	Tyr	Tyr	Gly	Ala	Ile	Ser
	2105					2110					2115			
Lys	Leu	Lys	Ser	Gln	His	Gln	Glu	Asp	Pro	Asn	Asn	Thr	Ser	Leu
	2120					2125					2130			
Leu	Thr	Asn	Lys	Pro	Ala	Leu	Leu	Arg	Ser	Leu	Phe	Thr	Val	Gly
	2135					2140					2145			
Ala	Leu	Cys	Arg	His	Phe	Asp	Phe	Asp	Leu	Glu	Asp	Phe	Lys	Gly
	2150					2155					2160			
Asn	Ser	Lys	Val	Asn	Ile	Lys	Asp	Lys	Val	Leu	Glu	Leu	Leu	Met
	2165					2170					2175			
Tyr	Phe	Thr	Lys	His	Ser	Asp	Glu	Glu	Val	Gln	Thr	Lys	Ala	Ile
	2180					2185					2190			
Ile	Gly	Leu	Gly	Phe	Ala	Phe	Ile	Gln	His	Pro	Ser	Leu	Met	Phe
	2195					2200					2205			
Glu	Gln	Glu	Val	Lys	Asn	Leu	Tyr	Asn	Asn	Ile	Leu	Ser	Asp	Lys
	2210					2215					2220			
Asn	Ser	Ser	Val	Asn	Leu	Lys	Ile	Gln	Val	Leu	Lys	Asn	Leu	Gln
	2225					2230					2235			
Thr	Tyr	Leu	Gln	Glu	Glu	Asp	Thr	Arg	Met	Gln	Gln	Ala	Asp	Arg
	2240					2245					2250			
Asp	Trp	Lys	Lys	Val	Ala	Lys	Gln	Glu	Asp	Leu	Lys	Glu	Met	Gly
	2255					2260					2265			
Asp	Val	Ser	Ser	Gly	Met	Ser	Ser	Ser	Ile	Met	Gln	Leu	Tyr	Leu
	2270					2275					2280			

# ES 2 534 734 A1

Lys Gln Val Leu Glu Ala Phe Phe His Thr Gln Ser Ser Val Arg  
 2285 2290 2295

His Phe Ala Leu Asn Val Ile Ala Leu Thr Leu Asn Gln Gly Leu  
 2300 2305 2310

Ile His Pro Val Gln Cys Val Pro Tyr Leu Ile Ala Met Gly Thr  
 2315 2320 2325

Asp Pro Glu Pro Ala Met Arg Asn Lys Ala Asp Gln Gln Leu Val  
 2330 2335 2340

Glu Ile Asp Lys Lys Tyr Ala Gly Phe Ile His Met Lys Ala Val  
 2345 2350 2355

Ala Gly Met Lys Met Ser Tyr Gln Val Gln Gln Ala Ile Asn Thr  
 2360 2365 2370

Cys Leu Lys Asp Pro Val Arg Gly Phe Arg Gln Asp Glu Ser Ser  
 2375 2380 2385

Ser Ala Leu Cys Ser His Leu Tyr Ser Met Ile Arg Gly Asn Arg  
 2390 2395 2400

Gln His Arg Arg Ala Phe Leu Ile Ser Leu Leu Asn Leu Phe Asp  
 2405 2410 2415

Asp Thr Ala Lys Thr Asp Val Thr Met Leu Leu Tyr Ile Ala Asp  
 2420 2425 2430

Asn Leu Ala Cys Phe Pro Tyr Gln Thr Gln Glu Glu Pro Leu Phe  
 2435 2440 2445

Ile Met His His Ile Asp Ile Thr Leu Ser Val Ser Gly Ser Asn  
 2450 2455 2460

Leu Leu Gln Ser Phe Lys Glu Ser Met Val Lys Asp Lys Arg Lys  
 2465 2470 2475

Glu Arg Lys Ser Ser Pro Ser Lys Glu Asn Glu Ser Ser Asp Ser  
 2480 2485 2490

Glu Glu Glu Val Ser Arg Pro Arg Lys Ser Arg Lys Arg Val Asp  
 2495 2500 2505

# ES 2 534 734 A1

Ser	Asp	Ser	Asp	Ser	Asp	Ser	Glu	Asp	Asp	Ile	Asn	Ser	Val	Met
2510						2515					2520			
Lys	Cys	Leu	Pro	Glu	Asn	Ser	Ala	Pro	Leu	Ile	Glu	Phe	Ala	Asn
2525						2530					2535			
Val	Ser	Gln	Gly	Ile	Leu	Leu	Leu	Leu	Met	Leu	Lys	Gln	His	Leu
2540						2545					2550			
Lys	Asn	Leu	Cys	Gly	Phe	Ser	Asp	Ser	Lys	Ile	Gln	Lys	Tyr	Ser
2555						2560					2565			
Pro	Ser	Glu	Ser	Ala	Lys	Val	Tyr	Asp	Lys	Ala	Ile	Asn	Arg	Lys
2570						2575					2580			
Thr	Gly	Val	His	Phe	His	Pro	Lys	Gln	Thr	Leu	Asp	Phe	Leu	Arg
2585						2590					2595			
Ser	Asp	Met	Ala	Asn	Ser	Lys	Ile	Thr	Glu	Glu	Val	Lys	Arg	Ser
2600						2605					2610			
Ile	Val	Lys	Gln	Tyr	Leu	Asp	Phe	Lys	Leu	Leu	Met	Glu	His	Leu
2615						2620					2625			
Asp	Pro	Asp	Glu	Glu	Glu	Glu	Glu	Gly	Glu	Val	Ser	Ala	Ser	Thr
2630						2635					2640			
Asn	Ala	Arg	Asn	Lys	Ala	Ile	Thr	Ser	Leu	Leu	Gly	Gly	Gly	Ser
2645						2650					2655			
Pro	Lys	Asn	Asn	Thr	Ala	Ala	Glu	Thr	Glu	Asp	Asp	Glu	Ser	Asp
2660						2665					2670			
Gly	Glu	Asp	Arg	Gly	Gly	Gly	Thr	Ser	Gly	Ser	Leu	Arg	Arg	Ser
2675						2680					2685			
Lys	Arg	Asn	Ser	Asp	Ser	Thr	Glu	Leu	Ala	Ala	Gln	Met	Asn	Glu
2690						2695					2700			
Ser	Val	Asp	Val	Met	Asp	Val	Ile	Ala	Ile	Cys	Cys	Pro	Lys	Tyr
2705						2710					2715			
Lys	Asp	Arg	Pro	Gln	Ile	Ala	Arg	Val	Val	Gln	Lys	Thr	Ser	Ser
2720						2725					2730			

# ES 2 534 734 A1

Gly Phe Ser Val Gln Trp Met Ala Gly Ser Tyr Ser Gly Ser Trp  
 2735 2740 2745

Thr Glu Ala Lys Arg Arg Asp Gly Arg Lys Leu Val Pro Trp Val  
 2750 2755 2760

Asp Thr Ile Lys Glu Ser Asp Ile Ile Tyr Lys Lys Ile Ala Leu  
 2765 2770 2775

Thr Ser Ala Asn Lys Leu Thr Asn Lys Val Val Gln Thr Leu Arg  
 2780 2785 2790

Ser Leu Tyr Ala Ala Lys Asp Gly Thr Ser Ser  
 2795 2800

<210> 141  
 <211> 379  
 <212> PRT  
 <213> Homo sapiens

<400> 141

Met Glu Met Ala Glu Ala Glu Leu His Lys Glu Arg Leu Gln Ala Ile  
 1 5 10 15

Ala Glu Lys Arg Lys Arg Gln Thr Glu Ile Glu Gly Lys Arg Gln Gln  
 20 25 30

Leu Asp Glu Gln Ile Leu Leu Leu Gln His Ser Lys Ser Lys Val Leu  
 35 40 45

Arg Glu Lys Trp Leu Leu Gln Gly Ile Pro Ala Gly Thr Ala Glu Glu  
 50 55 60

Glu Glu Ala Arg Arg Arg Gln Ser Glu Glu Asp Glu Phe Arg Val Lys  
 65 70 75 80

Gln Leu Glu Asp Asn Ile Gln Arg Leu Glu Gln Glu Ile Gln Thr Leu  
 85 90 95

Glu Ser Glu Glu Ser Gln Ile Ser Ala Lys Glu Gln Ile Ile Leu Glu  
 100 105 110

Lys Leu Lys Glu Thr Glu Lys Ser Phe Lys Asp Phe Gln Lys Gly Phe  
 115 120 125



# ES 2 534 734 A1

Ser Ser Thr Asp Gly Ala Val Tyr Ala Met Glu Ile Asn Val Glu Lys  
 130 135 140

Asp Lys Gln Thr Gly Glu Thr Lys Ile Leu Ser Thr Ser Thr Ile Gly  
 145 150 155 160

Pro Glu Gly Val His Gln Lys Gly Val Lys Val Tyr Asp Asp Gly Thr  
 165 170 175

Lys Val Val Tyr Glu Val Arg Ser Gly Gly Thr Val Val Glu Asn Gly  
 180 185 190

Val His Lys Leu Ser Thr Lys Asp Val Glu Glu Leu Ile Gln Lys Ala  
 195 200 205

Gly Gln Ser Ser Leu Gly Gly Gly His Val Ser Glu Arg Thr Val Ile  
 210 215 220

Ala Asp Gly Ser Leu Ser His Pro Lys Glu His Met Leu Cys Lys Glu  
 225 230 235 240

Ala Lys Leu Glu Met Val His Lys Ser Arg Lys Asp His Ser Ser Gly  
 245 250 255

Asn Pro Gly Gln Gln Ala Gln Ala Pro Ser Ala Ala Gly Pro Glu Ala  
 260 265 270

Asn Leu Asp Gln Pro Val Thr Met Ile Phe Met Gly Tyr Gln Asn Ile  
 275 280 285

Glu Asp Glu Glu Glu Thr Lys Lys Val Leu Gly Tyr Asp Glu Thr Ile  
 290 295 300

Lys Ala Glu Leu Val Leu Ile Asp Glu Asp Asp Glu Lys Ser Leu Arg  
 305 310 315 320

Glu Lys Thr Val Thr Asp Val Ser Thr Ile Asp Gly Asn Ala Ala Glu  
 325 330 335

Leu Val Ser Gly Arg Pro Val Ser Asp Thr Thr Glu Pro Ser Ser Pro  
 340 345 350

Glu Gly Lys Glu Glu Ser Leu Ala Thr Glu Pro Ala Pro Gly Thr Gln  
 355 360 365

# ES 2 534 734 A1

Lys Lys Lys Arg Cys Gln Cys Cys Val Val Met  
 370 375

<210> 142  
 <211> 411  
 <212> PRT  
 <213> Homo sapiens

<400> 142

Met Ala Glu Ala Glu Leu His Lys Glu Arg Leu Gln Ala Ile Ala Glu  
 1 5 10 15

Lys Arg Lys Arg Gln Thr Glu Ile Glu Gly Lys Arg Gln Gln Leu Asp  
 20 25 30

Glu Gln Ile Leu Leu Leu Gln His Ser Lys Ser Lys Val Leu Arg Glu  
 35 40 45

Lys Trp Leu Leu Gln Gly Ile Pro Ala Gly Thr Ala Glu Glu Glu Glu  
 50 55 60

Ala Arg Arg Arg Gln Ser Glu Glu Asp Glu Phe Arg Val Lys Gln Leu  
 65 70 75 80

Glu Asp Asn Ile Gln Arg Leu Glu Gln Glu Ile Gln Thr Leu Glu Ser  
 85 90 95

Glu Glu Ser Gln Ile Ser Ala Lys Glu Gln Ile Ile Leu Glu Lys Leu  
 100 105 110

Lys Glu Thr Glu Lys Ser Phe Lys Asp Phe Gln Lys Gly Phe Ser Ser  
 115 120 125

Thr Asp Gly Asp Ala Val Asn Tyr Ile Ser Ser Gln Leu Pro Asp Leu  
 130 135 140

Pro Ile Leu Cys Ser Arg Thr Ala Glu Pro Ser Pro Gly Gln Asp Gly  
 145 150 155 160

Thr Ser Arg Ala Ala Ala Val Tyr Ala Met Glu Ile Asn Val Glu Lys  
 165 170 175

Asp Lys Gln Thr Gly Glu Thr Lys Ile Leu Ser Thr Ser Thr Ile Gly  
 180 185 190

# ES 2 534 734 A1

Pro Glu Gly Val His Gln Lys Gly Val Lys Val Tyr Asp Asp Gly Thr  
 195 200 205

Lys Val Val Tyr Glu Val Arg Ser Gly Gly Thr Val Val Glu Asn Gly  
 210 215 220

Val His Lys Leu Ser Thr Lys Asp Val Glu Glu Leu Ile Gln Lys Ala  
 225 230 235 240

Gly Gln Ser Ser Leu Gly Gly Gly His Val Ser Glu Arg Thr Val Ile  
 245 250 255

Ala Asp Gly Ser Leu Ser His Pro Lys Glu His Met Leu Cys Lys Glu  
 260 265 270

Ala Lys Leu Glu Met Val His Lys Ser Arg Lys Asp His Ser Ser Gly  
 275 280 285

Asn Pro Gly Gln Gln Ala Gln Ala Pro Ser Ala Ala Gly Pro Glu Ala  
 290 295 300

Asn Leu Asp Gln Pro Val Thr Met Ile Phe Met Gly Tyr Gln Asn Ile  
 305 310 315 320

Glu Asp Glu Glu Glu Thr Lys Lys Val Leu Gly Tyr Asp Glu Thr Ile  
 325 330 335

Lys Ala Glu Leu Val Leu Ile Asp Glu Asp Asp Glu Lys Ser Leu Arg  
 340 345 350

Glu Lys Thr Val Thr Asp Val Ser Thr Ile Asp Gly Asn Ala Ala Glu  
 355 360 365

Leu Val Ser Gly Arg Pro Val Ser Asp Thr Thr Glu Pro Ser Ser Pro  
 370 375 380

Glu Gly Lys Glu Glu Ser Leu Ala Thr Glu Pro Ala Pro Gly Thr Gln  
 385 390 395 400

Lys Lys Lys Arg Cys Gln Cys Cys Val Val Met  
 405 410

<210> 143

<211> 191

ES 2 534 734 A1

<212> PRT

<213> Homo sapiens

<400> 143

Met Gly Lys Gln Asn Ser Lys Leu Ala Pro Glu Val Met Glu Asp Leu  
1 5 10 15

Val Lys Ser Thr Glu Phe Asn Glu His Glu Leu Lys Gln Trp Tyr Lys  
20 25 30

Gly Phe Leu Lys Asp Cys Pro Ser Gly Arg Leu Asn Leu Glu Glu Phe  
35 40 45

Gln Gln Leu Tyr Val Lys Phe Phe Pro Tyr Gly Asp Ala Ser Lys Phe  
50 55 60

Ala Gln His Ala Phe Arg Thr Phe Asp Lys Asn Gly Asp Gly Thr Ile  
65 70 75 80

Asp Phe Arg Glu Phe Ile Cys Ala Leu Ser Ile Thr Ser Arg Gly Ser  
85 90 95

Phe Glu Gln Lys Leu Asn Trp Ala Phe Asn Met Tyr Asp Leu Asp Gly  
100 105 110

Asp Gly Lys Ile Thr Arg Val Glu Met Leu Glu Ile Ile Glu Ala Ile  
115 120 125

Tyr Lys Met Val Gly Thr Val Ile Met Met Lys Met Asn Glu Asp Gly  
130 135 140

Leu Thr Pro Glu Gln Arg Val Asp Lys Ile Phe Ser Lys Met Asp Lys  
145 150 155 160

Asn Lys Asp Asp Gln Ile Thr Leu Asp Glu Phe Lys Glu Ala Ala Lys  
165 170 175

Ser Asp Pro Ser Ile Val Leu Leu Leu Gln Cys Asp Ile Gln Lys  
180 185 190

<210> 144

<211> 1192

<212> PRT

<213> Homo sapiens

# ES 2 534 734 A1

<400> 144

Met	Pro	Arg	Arg	Ala	Gly	Ser	Gly	Gln	Leu	Pro	Leu	Pro	Arg	Gly	Trp
1				5				10						15	
Glu	Glu	Ala	Arg	Asp	Tyr	Asp	Gly	Lys	Val	Phe	Tyr	Ile	Asp	His	Asn
			20					25					30		
Thr	Arg	Arg	Thr	Ser	Trp	Ile	Asp	Pro	Arg	Asp	Arg	Leu	Thr	Lys	Pro
		35					40					45			
Leu	Ser	Phe	Ala	Asp	Cys	Val	Gly	Asp	Glu	Leu	Pro	Trp	Gly	Trp	Glu
	50					55					60				
Ala	Gly	Phe	Asp	Pro	Gln	Ile	Gly	Val	Tyr	Tyr	Ile	Asp	His	Ile	Asn
65					70					75					80
Lys	Thr	Thr	Gln	Ile	Glu	Asp	Pro	Arg	Lys	Gln	Trp	Arg	Gly	Glu	Gln
				85					90					95	
Glu	Lys	Met	Leu	Lys	Asp	Tyr	Leu	Ser	Val	Ala	Gln	Asp	Ala	Leu	Arg
			100					105					110		
Thr	Gln	Lys	Glu	Leu	Tyr	His	Val	Lys	Glu	Gln	Arg	Leu	Ala	Leu	Ala
		115					120					125			
Leu	Asp	Glu	Tyr	Val	Arg	Leu	Asn	Asp	Ala	Tyr	Lys	Glu	Lys	Ser	Ser
	130					135					140				
Ser	His	Thr	Ser	Leu	Phe	Ser	Gly	Ser	Ser	Ser	Ser	Thr	Lys	Tyr	Asp
145					150						155				160
Pro	Asp	Ile	Leu	Lys	Ala	Glu	Ile	Ser	Thr	Thr	Arg	Leu	Arg	Val	Lys
				165					170					175	
Lys	Leu	Lys	Arg	Glu	Leu	Ser	Gln	Met	Lys	Gln	Glu	Leu	Leu	Tyr	Lys
			180					185					190		
Glu	Gln	Gly	Phe	Glu	Thr	Leu	Gln	Gln	Ile	Asp	Lys	Lys	Met	Ser	Gly
		195					200					205			
Gly	Gln	Ser	Gly	Tyr	Glu	Leu	Ser	Glu	Ala	Lys	Ala	Ile	Leu	Thr	Glu
	210					215					220				

# ES 2 534 734 A1

Leu Lys Ser Ile Arg Lys Ala Ile Ser Ser Gly Glu Lys Glu Lys Gln  
 225 230 235 240

Asp Leu Met Gln Ser Leu Ala Lys Leu Gln Glu Arg Phe His Leu Asp  
 245 250 255

Gln Asn Ile Gly Arg Ser Glu Pro Asp Leu Arg Cys Ser Pro Val Asn  
 260 265 270

Ser His Leu Cys Leu Ser Arg Gln Thr Leu Asp Ala Gly Ser Gln Thr  
 275 280 285

Ser Ile Ser Gly Asp Ile Gly Val Arg Ser Arg Ser Asn Leu Ala Glu  
 290 295 300

Lys Val Arg Leu Ser Leu Gln Tyr Glu Glu Ala Lys Arg Ser Met Ala  
 305 310 315 320

Asn Leu Lys Ile Glu Leu Ser Lys Leu Asp Ser Glu Ala Trp Pro Gly  
 325 330 335

Ala Leu Asp Ile Glu Lys Glu Lys Leu Met Leu Ile Asn Glu Lys Glu  
 340 345 350

Glu Leu Leu Lys Glu Leu Gln Phe Val Thr Pro Gln Lys Arg Thr Gln  
 355 360 365

Asp Glu Leu Glu Arg Leu Glu Ala Glu Arg Gln Arg Leu Glu Glu Glu  
 370 375 380

Leu Leu Ser Val Arg Gly Thr Pro Ser Arg Ala Leu Ala Glu Arg Leu  
 385 390 395 400

Arg Leu Glu Glu Arg Arg Lys Glu Leu Leu Gln Lys Leu Glu Glu Thr  
 405 410 415

Thr Lys Leu Thr Thr Tyr Leu His Ser Gln Leu Lys Ser Leu Ser Ala  
 420 425 430

Ser Thr Leu Ser Met Ser Ser Gly Ser Ser Leu Gly Ser Leu Ala Ser  
 435 440 445

Ser Arg Gly Ser Leu Asn Thr Ser Ser Arg Gly Ser Leu Asn Ser Leu  
 450 455 460

# ES 2 534 734 A1

Ser Ser Thr Glu Leu Tyr Tyr Ser Ser Gln Ser Asp Gln Ile Asp Val  
 465 470 475 480

Asp Tyr Gln Tyr Lys Leu Asp Phe Leu Leu Gln Glu Lys Ser Gly Tyr  
 485 490 495

Ile Pro Ser Gly Pro Ile Thr Thr Ile His Glu Asn Glu Val Val Lys  
 500 505 510

Ser Pro Ser Gln Pro Gly Gln Ser Gly Leu Cys Gly Val Ala Ala Ala  
 515 520 525

Ala Thr Gly His Thr Pro Pro Leu Ala Glu Ala Pro Lys Ser Val Ala  
 530 535 540

Ser Leu Ser Ser Arg Ser Ser Leu Ser Ser Leu Ser Pro Pro Gly Ser  
 545 550 555 560

Pro Leu Val Leu Glu Gly Thr Phe Pro Met Ser Ser Ser His Asp Ala  
 565 570 575

Ser Leu His Gln Phe Thr Ala Asp Phe Glu Asp Cys Glu Leu Ser Ser  
 580 585 590

His Phe Ala Asp Ile Ser Leu Ile Glu Asn Gln Ile Leu Leu Asp Ser  
 595 600 605

Asp Ser Gly Gly Ala Ser Gln Ser Leu Ser Glu Asp Lys Asp Leu Asn  
 610 615 620

Glu Cys Ala Arg Glu Pro Leu Tyr Glu Gly Thr Ala Asp Val Glu Lys  
 625 630 635 640

Ser Leu Pro Lys Arg Arg Val Ile His Leu Leu Gly Glu Lys Thr Thr  
 645 650 655

Cys Val Ser Ala Ala Val Ser Asp Glu Ser Val Ala Gly Asp Ser Gly  
 660 665 670

Val Tyr Glu Ala Phe Val Lys Gln Pro Ser Glu Met Glu Asp Val Thr  
 675 680 685

Tyr Ser Glu Glu Asp Val Ala Ile Val Glu Thr Ala Gln Val Gln Ile  
 690 695 700

# ES 2 534 734 A1

Gly Leu Arg Tyr Asn Ala Lys Ser Ser Ser Phe Met Val Ile Ile Ala  
 705 710 715 720

Gln Leu Arg Asn Leu His Ala Phe Leu Ile Pro His Thr Ser Lys Val  
 725 730 735

Tyr Phe Arg Val Ala Val Leu Pro Ser Ser Thr Asp Val Ser Cys Leu  
 740 745 750

Phe Arg Thr Lys Val His Pro Pro Thr Glu Ser Ile Leu Phe Asn Asp  
 755 760 765

Val Phe Arg Val Ala Ile Ser Gln Thr Ala Leu Gln Gln Lys Thr Leu  
 770 775 780

Arg Val Asp Leu Cys Ser Val Ser Lys His Arg Arg Glu Glu Cys Leu  
 785 790 795 800

Ala Gly Thr Gln Ile Ser Leu Ala Asp Leu Pro Phe Ser Ser Glu Val  
 805 810 815

Phe Thr Leu Trp Tyr Asn Leu Leu Pro Ser Lys Gln Met Pro Cys Lys  
 820 825 830

Lys Asn Glu Glu Asn Glu Asp Ser Val Phe Gln Pro Asn Gln Pro Leu  
 835 840 845

Val Asp Ser Ile Asp Leu Asp Ala Val Ser Ala Leu Leu Ala Arg Thr  
 850 855 860

Ser Ala Glu Leu Leu Ala Val Glu Gln Glu Leu Ala Gln Glu Glu Glu  
 865 870 875 880

Glu Glu Ser Gly Gln Glu Glu Pro Arg Gly Pro Asp Gly Asp Trp Leu  
 885 890 895

Thr Met Leu Arg Glu Ala Ser Asp Glu Ile Val Ala Glu Lys Glu Ala  
 900 905 910

Glu Val Lys Leu Pro Glu Asp Ser Ser Cys Thr Glu Asp Leu Ser Ser  
 915 920 925



# ES 2 534 734 A1

Cys Thr Ser Val Pro Glu Met Asn Glu Asp Gly Asn Arg Lys Glu Ser  
 930 935 940

Asn Cys Ala Lys Asp Leu Arg Ser Gln Pro Pro Thr Arg Ile Pro Thr  
 945 950 955 960

Leu Val Asp Lys Glu Thr Asn Thr Asp Glu Ala Ala Asn Asp Asn Met  
 965 970 975

Ala Val Arg Pro Lys Glu Arg Ser Ser Leu Ser Ser Arg Gln His Pro  
 980 985 990

Phe Val Arg Ser Ser Val Ile Val Arg Ser Gln Thr Phe Ser Pro Gly  
 995 1000 1005

Glu Arg Asn Gln Tyr Ile Cys Arg Leu Asn Arg Ser Asp Ser Asp  
 1010 1015 1020

Ser Ser Thr Leu Ala Lys Lys Ser Leu Phe Val Arg Asn Ser Thr  
 1025 1030 1035

Glu Arg Arg Ser Leu Arg Val Lys Arg Thr Val Cys Gln Ser Val  
 1040 1045 1050

Leu Arg Arg Thr Thr Gln Glu Cys Pro Val Arg Thr Ser Leu Asp  
 1055 1060 1065

Leu Glu Leu Asp Leu Gln Ala Ser Leu Thr Arg Gln Ser Arg Leu  
 1070 1075 1080

Asn Asp Glu Leu Gln Ala Leu Arg Asp Leu Arg Gln Lys Leu Glu  
 1085 1090 1095

Glu Leu Lys Ala Gln Gly Glu Thr Asp Leu Pro Pro Gly Val Leu  
 1100 1105 1110

Glu Asp Glu Arg Phe Gln Arg Leu Leu Lys Gln Ala Glu Lys Gln  
 1115 1120 1125

Ala Glu Gln Ser Lys Glu Glu Gln Lys Gln Gly Leu Asn Ala Glu  
 1130 1135 1140

Lys Leu Met Arg Gln Val Ser Lys Asp Val Cys Arg Leu Arg Glu  
 1145 1150 1155

# ES 2 534 734 A1

Gln Ser Gln Lys Val Pro Arg Gln Val Gln Ser Phe Arg Glu Lys  
 1160 1165 1170

Ile Ala Tyr Phe Thr Arg Ala Lys Ile Ser Ile Pro Ser Leu Pro  
 1175 1180 1185

Ala Asp Asp Val  
 1190

<210> 145  
 <211> 650  
 <212> PRT  
 <213> Homo sapiens

<400> 145

Met Ala Ser Asn Met Asp Arg Glu Met Ile Leu Ala Asp Phe Gln Ala  
 1 5 10 15

Cys Thr Gly Ile Glu Asn Ile Asp Glu Ala Ile Thr Leu Leu Glu Gln  
 20 25 30

Asn Asn Trp Asp Leu Val Ala Ala Ile Asn Gly Val Ile Pro Gln Glu  
 35 40 45

Asn Gly Ile Leu Gln Ser Glu Tyr Gly Gly Glu Thr Ile Pro Gly Pro  
 50 55 60

Ala Phe Asn Pro Ala Ser His Pro Ala Ser Ala Pro Thr Ser Ser Ser  
 65 70 75 80

Ser Ser Ala Phe Arg Pro Val Met Pro Ser Arg Gln Ile Val Glu Arg  
 85 90 95

Gln Pro Arg Met Leu Asp Phe Arg Val Glu Tyr Arg Asp Arg Asn Val  
 100 105 110

Asp Val Val Leu Glu Asp Thr Cys Thr Val Gly Glu Ile Lys Gln Ile  
 115 120 125

Leu Glu Asn Glu Leu Gln Ile Pro Val Ser Lys Met Leu Leu Lys Gly  
 130 135 140

Trp Lys Thr Gly Asp Val Glu Asp Ser Thr Val Leu Lys Ser Leu His  
 145 150 155 160

# ES 2 534 734 A1

Leu Pro Lys Asn Asn Ser Leu Tyr Val Leu Thr Pro Asp Leu Pro Pro  
 165 170 175

Pro Ser Ser Ser Ser His Ala Gly Ala Leu Gln Glu Ser Leu Asn Gln  
 180 185 190

Asn Phe Met Leu Ile Ile Thr His Arg Glu Val Gln Arg Glu Tyr Asn  
 195 200 205

Leu Asn Phe Ser Gly Ser Ser Thr Ile Gln Glu Val Lys Arg Asn Val  
 210 215 220

Tyr Asp Leu Thr Ser Ile Pro Val Arg His Gln Leu Trp Glu Gly Trp  
 225 230 235 240

Pro Thr Ser Ala Thr Asp Asp Ser Met Cys Leu Ala Glu Ser Gly Leu  
 245 250 255

Ser Tyr Pro Cys His Arg Leu Thr Val Gly Arg Arg Ser Ser Pro Ala  
 260 265 270

Gln Thr Arg Glu Gln Ser Glu Glu Gln Ile Thr Asp Val His Met Val  
 275 280 285

Ser Asp Ser Asp Gly Asp Asp Phe Glu Asp Ala Thr Glu Phe Gly Val  
 290 295 300

Asp Asp Gly Glu Val Phe Gly Met Ala Ser Ser Ala Leu Arg Lys Ser  
 305 310 315 320

Pro Met Met Pro Glu Asn Ala Glu Asn Glu Gly Asp Ala Leu Leu Gln  
 325 330 335

Phe Thr Ala Glu Phe Ser Ser Arg Tyr Gly Asp Cys His Pro Val Phe  
 340 345 350

Phe Ile Gly Ser Leu Glu Ala Ala Phe Gln Glu Ala Phe Tyr Val Lys  
 355 360 365

Ala Arg Asp Arg Lys Leu Leu Ala Ile Tyr Leu His His Asp Glu Ser  
 370 375 380

Val Leu Thr Asn Val Phe Cys Ser Gln Met Leu Cys Ala Glu Ser Ile  
 385 390 395 400

# ES 2 534 734 A1

Val Ser Tyr Leu Ser Gln Asn Phe Ile Thr Trp Ala Trp Asp Leu Thr  
 405 410 415

Lys Asp Ser Asn Arg Ala Arg Phe Leu Thr Met Cys Asn Arg His Phe  
 420 425 430

Gly Ser Val Val Ala Gln Thr Ile Arg Thr Gln Lys Thr Asp Gln Phe  
 435 440 445

Pro Leu Phe Leu Ile Ile Met Gly Lys Arg Ser Ser Asn Glu Val Leu  
 450 455 460

Asn Val Ile Gln Gly Asn Thr Thr Val Asp Glu Leu Met Met Arg Leu  
 465 470 475 480

Met Ala Ala Met Glu Ile Phe Thr Ala Gln Gln Gln Glu Asp Ile Lys  
 485 490 495

Asp Glu Asp Glu Arg Glu Ala Arg Glu Asn Val Lys Arg Glu Gln Asp  
 500 505 510

Glu Ala Tyr Arg Leu Ser Leu Glu Ala Asp Arg Ala Lys Arg Glu Ala  
 515 520 525

His Glu Arg Glu Met Ala Glu Gln Phe Arg Leu Glu Gln Ile Arg Lys  
 530 535 540

Glu Gln Glu Glu Glu Arg Glu Ala Ile Arg Leu Ser Leu Glu Gln Ala  
 545 550 555 560

Leu Pro Pro Glu Pro Lys Glu Glu Asn Ala Glu Pro Val Ser Lys Leu  
 565 570 575

Arg Ile Arg Thr Pro Ser Gly Glu Phe Leu Glu Arg Arg Phe Leu Ala  
 580 585 590

Ser Asn Lys Leu Gln Ile Val Phe Asp Phe Val Ala Ser Lys Gly Phe  
 595 600 605

Pro Trp Asp Glu Tyr Lys Leu Leu Ser Thr Phe Pro Arg Arg Asp Val  
 610 615 620

Thr Gln Leu Asp Pro Asn Lys Ser Leu Leu Glu Val Lys Leu Phe Pro  
 625 630 635 640

## ES 2 534 734 A1

Gln Glu Thr Leu Phe Leu Glu Ala Lys Glu  
 645 650

<210> 146  
 <211> 403  
 <212> PRT  
 <213> Homo sapiens

<400> 146

Met Phe Arg Ala Gln Trp Met Phe Glu Leu Ala Pro Gly Val Ser Ser  
 1 5 10 15

Ser Asn Leu Glu Asn Arg Pro Cys Arg Ala Ala Arg Gly Ser Leu Gln  
 20 25 30

Lys Thr Ser Ala Asp Thr Lys Gly Lys Gln Glu Gln Ala Lys Glu Glu  
 35 40 45

Lys Ala Arg Glu Leu Phe Leu Lys Ala Val Glu Glu Glu Gln Asn Gly  
 50 55 60

Ala Leu Tyr Glu Ala Ile Lys Phe Tyr Arg Arg Ala Met Gln Leu Val  
 65 70 75 80

Pro Asp Ile Glu Phe Lys Ile Thr Tyr Thr Arg Ser Pro Asp Gly Asp  
 85 90 95

Gly Val Gly Asn Ser Tyr Ile Glu Asp Asn Asp Asp Asp Ser Lys Met  
 100 105 110

Ala Asp Leu Leu Ser Tyr Phe Gln Gln Gln Leu Thr Phe Gln Glu Ser  
 115 120 125

Val Leu Lys Leu Cys Gln Pro Glu Leu Glu Ser Ser Gln Ile His Ile  
 130 135 140

Ser Val Leu Pro Met Glu Val Leu Met Tyr Ile Phe Arg Trp Val Val  
 145 150 155 160

Ser Ser Asp Leu Asp Leu Arg Ser Leu Glu Gln Leu Ser Leu Val Cys  
 165 170 175

Arg Gly Phe Tyr Ile Cys Ala Arg Asp Pro Glu Ile Trp Arg Leu Ala  
 180 185 190

# ES 2 534 734 A1

Cys Leu Lys Val Trp Gly Arg Ser Cys Ile Lys Leu Val Pro Tyr Thr  
 195 200 205

Ser Trp Arg Glu Met Phe Leu Glu Arg Pro Arg Val Arg Phe Asp Gly  
 210 215 220

Val Tyr Ile Ser Lys Thr Thr Tyr Ile Arg Gln Gly Glu Gln Ser Leu  
 225 230 235 240

Asp Gly Phe Tyr Arg Ala Trp His Gln Val Glu Tyr Tyr Arg Tyr Ile  
 245 250 255

Arg Phe Phe Pro Asp Gly His Val Met Met Leu Thr Thr Pro Glu Glu  
 260 265 270

Pro Gln Ser Ile Val Pro Arg Leu Arg Thr Arg Asn Thr Arg Thr Asp  
 275 280 285

Ala Ile Leu Leu Gly His Tyr Arg Leu Ser Gln Asp Thr Asp Asn Gln  
 290 295 300

Thr Lys Val Phe Ala Val Ile Thr Lys Lys Lys Glu Glu Lys Pro Leu  
 305 310 315 320

Asp Tyr Lys Tyr Arg Tyr Phe Arg Arg Val Pro Val Gln Glu Ala Asp  
 325 330 335

Gln Ser Phe His Val Gly Leu Gln Leu Cys Ser Ser Gly His Gln Arg  
 340 345 350

Phe Asn Lys Leu Ile Trp Ile His His Ser Cys His Ile Thr Tyr Lys  
 355 360 365

Ser Thr Gly Glu Thr Ala Val Ser Ala Phe Glu Ile Asp Lys Met Tyr  
 370 375 380

Thr Pro Leu Phe Phe Ala Arg Val Arg Ser Tyr Thr Ala Phe Ser Glu  
 385 390 395 400

Arg Pro Leu

<210> 147  
 <211> 437  
 <212> PRT

# ES 2 534 734 A1

<213> Homo sapiens

<400> 147

Met Ala Glu Ala Glu Glu Asp Cys His Ser Asp Thr Val Arg Ala Asp  
 1 5 10 15

Asp Asp Glu Glu Asn Glu Ser Pro Ala Glu Thr Asp Leu Gln Ala Gln  
 20 25 30

Leu Gln Met Phe Arg Ala Gln Trp Met Phe Glu Leu Ala Pro Gly Val  
 35 40 45

Ser Ser Ser Asn Leu Glu Asn Arg Pro Cys Arg Ala Ala Arg Gly Ser  
 50 55 60

Leu Gln Lys Thr Ser Ala Asp Thr Lys Gly Lys Gln Glu Gln Ala Lys  
 65 70 75 80

Glu Glu Lys Ala Arg Glu Leu Phe Leu Lys Ala Val Glu Glu Glu Gln  
 85 90 95

Asn Gly Ala Leu Tyr Glu Ala Ile Lys Phe Tyr Arg Arg Ala Met Gln  
 100 105 110

Leu Val Pro Asp Ile Glu Phe Lys Ile Thr Tyr Thr Arg Ser Pro Asp  
 115 120 125

Gly Asp Gly Val Gly Asn Ser Tyr Ile Glu Asp Asn Asp Asp Asp Ser  
 130 135 140

Lys Met Ala Asp Leu Leu Ser Tyr Phe Gln Gln Gln Leu Thr Phe Gln  
 145 150 155 160

Glu Ser Val Leu Lys Leu Cys Gln Pro Glu Leu Glu Ser Ser Gln Ile  
 165 170 175

His Ile Ser Val Leu Pro Met Glu Val Leu Met Tyr Ile Phe Arg Trp  
 180 185 190

Val Val Ser Ser Asp Leu Asp Leu Arg Ser Leu Glu Gln Leu Ser Leu  
 195 200 205

Val Cys Arg Gly Phe Tyr Ile Cys Ala Arg Asp Pro Glu Ile Trp Arg  
 210 215 220

# ES 2 534 734 A1

Leu Ala Cys Leu Lys Val Trp Gly Arg Ser Cys Ile Lys Leu Val Pro  
 225 230 235 240

Tyr Thr Ser Trp Arg Glu Met Phe Leu Glu Arg Pro Arg Val Arg Phe  
 245 250 255

Asp Gly Val Tyr Ile Ser Lys Thr Thr Tyr Ile Arg Gln Gly Glu Gln  
 260 265 270

Ser Leu Asp Gly Phe Tyr Arg Ala Trp His Gln Val Glu Tyr Tyr Arg  
 275 280 285

Tyr Ile Arg Phe Phe Pro Asp Gly His Val Met Met Leu Thr Thr Pro  
 290 295 300

Glu Glu Pro Gln Ser Ile Val Pro Arg Leu Arg Thr Arg Asn Thr Arg  
 305 310 315 320

Thr Asp Ala Ile Leu Leu Gly His Tyr Arg Leu Ser Gln Asp Thr Asp  
 325 330 335

Asn Gln Thr Lys Val Phe Ala Val Ile Thr Lys Lys Lys Glu Glu Lys  
 340 345 350

Pro Leu Asp Tyr Lys Tyr Arg Tyr Phe Arg Arg Val Pro Val Gln Glu  
 355 360 365

Ala Asp Gln Ser Phe His Val Gly Leu Gln Leu Cys Ser Ser Gly His  
 370 375 380

Gln Arg Phe Asn Lys Leu Ile Trp Ile His His Ser Cys His Ile Thr  
 385 390 395 400

Tyr Lys Ser Thr Gly Glu Thr Ala Val Ser Ala Phe Glu Ile Asp Lys  
 405 410 415

Met Tyr Thr Pro Leu Phe Phe Ala Arg Val Arg Ser Tyr Thr Ala Phe  
 420 425 430

Ser Glu Arg Pro Leu  
 435

<210> 148

<211> 447



ES 2 534 734 A1

<212> PRT

<213> Homo sapiens

<400> 148

Met Pro Asp Ile Ile Trp Val Phe Pro Pro Gln Ala Glu Ala Glu Glu  
1 5 10 15

Asp Cys His Ser Asp Thr Val Arg Ala Asp Asp Asp Glu Glu Asn Glu  
20 25 30

Ser Pro Ala Glu Thr Asp Leu Gln Ala Gln Leu Gln Met Phe Arg Ala  
35 40 45

Gln Trp Met Phe Glu Leu Ala Pro Gly Val Ser Ser Ser Asn Leu Glu  
50 55 60

Asn Arg Pro Cys Arg Ala Ala Arg Gly Ser Leu Gln Lys Thr Ser Ala  
65 70 75 80

Asp Thr Lys Gly Lys Gln Glu Gln Ala Lys Glu Glu Lys Ala Arg Glu  
85 90 95

Leu Phe Leu Lys Ala Val Glu Glu Glu Gln Asn Gly Ala Leu Tyr Glu  
100 105 110

Ala Ile Lys Phe Tyr Arg Arg Ala Met Gln Leu Val Pro Asp Ile Glu  
115 120 125

Phe Lys Ile Thr Tyr Thr Arg Ser Pro Asp Gly Asp Gly Val Gly Asn  
130 135 140

Ser Tyr Ile Glu Asp Asn Asp Asp Asp Ser Lys Met Ala Asp Leu Leu  
145 150 155 160

Ser Tyr Phe Gln Gln Gln Leu Thr Phe Gln Glu Ser Val Leu Lys Leu  
165 170 175

Cys Gln Pro Glu Leu Glu Ser Ser Gln Ile His Ile Ser Val Leu Pro  
180 185 190

Met Glu Val Leu Met Tyr Ile Phe Arg Trp Val Val Ser Ser Asp Leu  
195 200 205

# ES 2 534 734 A1

Asp Leu Arg Ser Leu Glu Gln Leu Ser Leu Val Cys Arg Gly Phe Tyr  
 210 215 220

Ile Cys Ala Arg Asp Pro Glu Ile Trp Arg Leu Ala Cys Leu Lys Val  
 225 230 235 240

Trp Gly Arg Ser Cys Ile Lys Leu Val Pro Tyr Thr Ser Trp Arg Glu  
 245 250 255

Met Phe Leu Glu Arg Pro Arg Val Arg Phe Asp Gly Val Tyr Ile Ser  
 260 265 270

Lys Thr Thr Tyr Ile Arg Gln Gly Glu Gln Ser Leu Asp Gly Phe Tyr  
 275 280 285

Arg Ala Trp His Gln Val Glu Tyr Tyr Arg Tyr Ile Arg Phe Phe Pro  
 290 295 300

Asp Gly His Val Met Met Leu Thr Thr Pro Glu Glu Pro Gln Ser Ile  
 305 310 315 320

Val Pro Arg Leu Arg Thr Arg Asn Thr Arg Thr Asp Ala Ile Leu Leu  
 325 330 335

Gly His Tyr Arg Leu Ser Gln Asp Thr Asp Asn Gln Thr Lys Val Phe  
 340 345 350

Ala Val Ile Thr Lys Lys Lys Glu Glu Lys Pro Leu Asp Tyr Lys Tyr  
 355 360 365

Arg Tyr Phe Arg Arg Val Pro Val Gln Glu Ala Asp Gln Ser Phe His  
 370 375 380

Val Gly Leu Gln Leu Cys Ser Ser Gly His Gln Arg Phe Asn Lys Leu  
 385 390 395 400

Ile Trp Ile His His Ser Cys His Ile Thr Tyr Lys Ser Thr Gly Glu  
 405 410 415

Thr Ala Val Ser Ala Phe Glu Ile Asp Lys Met Tyr Thr Pro Leu Phe  
 420 425 430

Phe Ala Arg Val Arg Ser Tyr Thr Ala Phe Ser Glu Arg Pro Leu  
 435 440 445

# ES 2 534 734 A1

<210> 149  
 <211> 1173  
 <212> PRT  
 <213> Homo sapiens

<400> 149

Met Ala Val Glu Thr Leu Ser Pro Asp Trp Glu Phe Asp Arg Val Asp  
 1 5 10 15

Asp Gly Ser Gln Lys Ile His Ala Glu Val Gln Leu Lys Asn Tyr Gly  
 20 25 30

Lys Phe Leu Glu Glu Tyr Thr Ser Gln Leu Arg Arg Ile Glu Asp Ala  
 35 40 45

Leu Asp Asp Ser Ile Gly Asp Val Trp Asp Phe Asn Leu Asp Pro Ile  
 50 55 60

Ala Leu Lys Leu Leu Pro Tyr Glu Gln Ser Ser Leu Leu Glu Leu Ile  
 65 70 75 80

Lys Thr Glu Asn Lys Val Leu Asn Lys Val Ile Thr Val Tyr Ala Ala  
 85 90 95

Leu Cys Cys Glu Ile Lys Lys Leu Lys Tyr Glu Ala Glu Thr Lys Phe  
 100 105 110

Tyr Asn Gly Leu Leu Phe Tyr Gly Glu Gly Ala Thr Asp Ala Ser Met  
 115 120 125

Val Glu Gly Asp Cys Gln Ile Gln Met Gly Arg Phe Ile Ser Phe Leu  
 130 135 140

Gln Glu Leu Ser Cys Phe Val Thr Arg Cys Tyr Glu Val Val Met Asn  
 145 150 155 160

Val Val His Gln Leu Ala Ala Leu Tyr Ile Ser Asn Lys Ile Ala Pro  
 165 170 175

Lys Ile Ile Glu Thr Thr Gly Val His Phe Gln Thr Met Tyr Glu His  
 180 185 190

Leu Gly Glu Leu Leu Thr Val Leu Leu Thr Leu Asp Glu Ile Ile Asp  
 195 200 205

# ES 2 534 734 A1

Asn His Ile Thr Leu Lys Asp His Trp Thr Met Tyr Lys Arg Leu Leu  
 210 215 220

Lys Ser Val His His Asn Pro Ser Lys Phe Gly Ile Gln Glu Glu Lys  
 225 230 235 240

Leu Lys Pro Phe Glu Lys Phe Leu Leu Lys Leu Glu Gly Gln Leu Leu  
 245 250 255

Asp Gly Met Ile Phe Gln Ala Cys Ile Glu Gln Gln Phe Asp Ser Leu  
 260 265 270

Asn Gly Gly Val Ser Val Ser Lys Asn Ser Thr Phe Ala Glu Glu Phe  
 275 280 285

Ala His Ser Ile Arg Ser Ile Phe Ala Asn Val Glu Ala Lys Leu Gly  
 290 295 300

Glu Pro Ser Glu Ile Asp Gln Arg Asp Lys Tyr Val Gly Ile Cys Gly  
 305 310 315 320

Leu Phe Val Leu His Phe Gln Ile Phe Arg Thr Ile Asp Lys Lys Phe  
 325 330 335

Tyr Lys Ser Leu Leu Asp Ile Cys Lys Lys Val Pro Ala Ile Thr Leu  
 340 345 350

Thr Ala Asn Ile Ile Trp Phe Pro Asp Asn Phe Leu Ile Gln Lys Ile  
 355 360 365

Pro Ala Ala Ala Lys Leu Leu Asp Arg Lys Ser Leu Gln Ala Ile Lys  
 370 375 380

Ile His Arg Asp Thr Phe Leu Gln Gln Lys Ala Gln Ser Leu Thr Lys  
 385 390 395 400

Asp Val Gln Ser Tyr Tyr Val Phe Val Ser Ser Trp Met Met Lys Met  
 405 410 415

Glu Ser Ile Leu Ser Lys Glu Gln Arg Met Asp Lys Phe Ala Glu Asp  
 420 425 430

Leu Thr Asn Arg Cys Asn Val Phe Ile Gln Gly Phe Leu Tyr Ala Tyr  
 435 440 445

# ES 2 534 734 A1

Ser Ile Ser Thr Ile Ile Lys Thr Thr Met Asn Leu Tyr Met Ser Met  
 450 455 460

Gln Lys Pro Met Thr Lys Thr Ser Val Lys Ala Leu Cys Arg Leu Val  
 465 470 475 480

Glu Leu Leu Lys Ala Ile Glu His Met Phe Tyr Arg Arg Ser Met Val  
 485 490 495

Val Ala Asp Ser Val Ser His Ile Thr Gln His Leu Gln His Gln Ala  
 500 505 510

Leu His Ser Ile Ser Val Ala Lys Lys Arg Val Ile Ser Asp Lys Lys  
 515 520 525

Tyr Ser Glu Gln Arg Leu Asp Val Leu Ser Ala Leu Val Leu Ala Glu  
 530 535 540

Asn Thr Leu Asn Gly Pro Ser Thr Lys Gln Arg Arg Leu Ile Val Ser  
 545 550 555 560

Leu Ala Leu Ser Val Gly Thr Gln Met Lys Thr Phe Lys Asp Glu Glu  
 565 570 575

Leu Phe Pro Leu Gln Val Val Met Lys Lys Leu Asp Leu Ile Ser Glu  
 580 585 590

Leu Arg Glu Arg Val Gln Thr Gln Cys Asp Cys Cys Phe Leu Tyr Trp  
 595 600 605

His Arg Ala Val Phe Pro Ile Tyr Leu Asp Asp Val Tyr Glu Asn Ala  
 610 615 620

Val Asp Ala Ala Arg Leu His Tyr Met Phe Ser Ala Leu Arg Asp Cys  
 625 630 635 640

Val Pro Ala Met Met His Ala Arg His Leu Glu Ser Tyr Glu Ile Leu  
 645 650 655

Leu Asp Cys Tyr Asp Lys Glu Ile Met Glu Ile Leu Asn Glu His Leu  
 660 665 670

Leu Asp Lys Leu Cys Lys Glu Ile Glu Lys Asp Leu Arg Leu Ser Val  
 675 680 685

# ES 2 534 734 A1

His Thr His Leu Lys Leu Asp Asp Arg Asn Pro Phe Lys Val Gly Met  
 690 695 700

Lys Asp Leu Ala Leu Phe Phe Ser Leu Asn Pro Ile Arg Phe Phe Asn  
 705 710 715 720

Arg Phe Ile Asp Ile Arg Ala Tyr Val Thr His Tyr Leu Asp Lys Thr  
 725 730 735

Phe Tyr Asn Leu Thr Thr Val Ala Leu His Asp Trp Ala Thr Tyr Ser  
 740 745 750

Glu Met Arg Asn Leu Ala Thr Gln Arg Tyr Gly Leu Val Met Thr Glu  
 755 760 765

Ala His Leu Pro Ser Gln Thr Leu Glu Gln Gly Leu Asp Val Leu Glu  
 770 775 780

Ile Met Arg Asn Ile His Ile Phe Val Ser Arg Tyr Leu Tyr Asn Leu  
 785 790 795 800

Asn Asn Gln Ile Phe Ile Glu Arg Thr Ser Asn Asn Lys His Leu Asn  
 805 810 815

Thr Ile Asn Ile Arg His Ile Ala Asn Ser Ile Arg Thr His Gly Thr  
 820 825 830

Gly Ile Met Asn Thr Thr Val Asn Phe Thr Tyr Gln Phe Leu Lys Lys  
 835 840 845

Lys Phe Tyr Ile Phe Ser Gln Phe Met Tyr Asp Glu His Ile Lys Ser  
 850 855 860

Arg Leu Ile Lys Asp Ile Arg Phe Phe Arg Glu Ile Lys Asp Gln Asn  
 865 870 875 880

Asp His Lys Tyr Pro Phe Asp Arg Ala Glu Lys Phe Asn Arg Gly Ile  
 885 890 895

Arg Lys Leu Gly Val Thr Pro Glu Gly Gln Ser Tyr Leu Asp Gln Phe  
 900 905 910

Arg Gln Leu Ile Ser Gln Ile Gly Asn Ala Met Gly Tyr Val Arg Met  
 915 920 925

# ES 2 534 734 A1

Ile Arg Ser Gly Gly Leu His Cys Ser Ser Asn Ala Ile Arg Phe Val  
 930 935 940

Pro Asp Leu Glu Asp Ile Val Asn Phe Glu Glu Leu Val Lys Glu Glu  
 945 950 955 960

Gly Leu Ala Glu Glu Thr Leu Lys Ala Ala Arg His Leu Asp Ser Val  
 965 970 975

Leu Ser Asp His Thr Arg Asn Ser Ala Glu Gly Thr Glu Tyr Phe Lys  
 980 985 990

Met Leu Val Asp Val Phe Ala Pro Glu Phe Arg Arg Pro Lys Asn Ile  
 995 1000 1005

His Leu Arg Asn Phe Tyr Ile Ile Val Pro Pro Leu Thr Leu Asn  
 1010 1015 1020

Phe Val Glu His Ser Ile Ser Cys Lys Glu Lys Leu Asn Lys Lys  
 1025 1030 1035

Asn Lys Ile Gly Ala Ala Phe Thr Asp Asp Gly Phe Ala Met Gly  
 1040 1045 1050

Val Ala Tyr Ile Leu Lys Leu Leu Asp Gln Tyr Arg Glu Phe Asp  
 1055 1060 1065

Ser Leu His Trp Phe Gln Ser Val Arg Glu Lys Tyr Leu Lys Glu  
 1070 1075 1080

Ile Arg Ala Val Ala Lys Gln Gln Asn Val Gln Ser Ala Ser Gln  
 1085 1090 1095

Asp Glu Lys Leu Leu Gln Thr Met Asn Leu Thr Gln Lys Arg Leu  
 1100 1105 1110

Asp Val Tyr Leu Gln Glu Phe Glu Leu Leu Tyr Phe Ser Leu Ser  
 1115 1120 1125

Ser Ala Arg Ile Phe Phe Arg Ala Asp Lys Thr Ala Ala Glu Glu  
 1130 1135 1140

Asn Gln Glu Lys Lys Glu Lys Glu Glu Glu Thr Lys Thr Ser Asn  
 1145 1150 1155

# ES 2 534 734 A1

Gly Asp Leu Ser Asp Ser Thr Val Ser Ala Asp Pro Val Val Lys  
 1160 1165 1170

<210> 150  
 <211> 173  
 <212> PRT  
 <213> Homo sapiens

<400> 150

Met Glu Asp Ser Phe Leu Gln Ser Phe Gly Arg Leu Ser Leu Gln Pro  
 1 5 10 15

Gln Gln Gln Gln Gln Arg Gln Arg Pro Pro Arg Pro Pro Pro Arg Gly  
 20 25 30

Thr Pro Pro Arg Arg His Ser Phe Arg Lys His Leu Tyr Leu Leu Arg  
 35 40 45

Gly Leu Pro Gly Ser Gly Lys Thr Thr Leu Ala Arg Gln Leu Gln His  
 50 55 60

Asp Phe Pro Arg Ala Leu Ile Phe Ser Thr Asp Asp Phe Phe Phe Arg  
 65 70 75 80

Glu Asp Gly Ala Tyr Glu Phe Asn Pro Asp Phe Leu Glu Glu Ala His  
 85 90 95

Glu Trp Asn Gln Lys Arg Ala Arg Lys Ala Met Arg Asn Gly Ile Ser  
 100 105 110

Pro Ile Ile Ile Asp Asn Thr Asn Leu His Ala Trp Glu Met Lys Pro  
 115 120 125

Tyr Ala Val Met Val Phe Gln Thr Glu Gln Lys Asn Leu Phe Arg Leu  
 130 135 140

Glu Met Asp Met Val Val Phe Arg Pro Glu Met Lys Lys His Ser Trp  
 145 150 155 160

Cys Leu Lys Arg Lys Asn Pro Pro Asn Glu Arg Thr Val  
 165 170

<210> 151  
 <211> 243  
 <212> PRT



# ES 2 534 734 A1

<213> Homo sapiens

<400> 151

Met Glu Asp Ser Phe Leu Gln Ser Phe Gly Arg Leu Ser Leu Gln Pro  
 1 5 10 15

Gln Gln Gln Gln Gln Arg Gln Arg Pro Pro Arg Pro Pro Pro Arg Gly  
 20 25 30

Thr Pro Pro Arg Arg His Ser Phe Arg Lys His Leu Tyr Leu Leu Arg  
 35 40 45

Gly Leu Pro Gly Ser Gly Lys Thr Thr Leu Ala Arg Gln Leu Gln His  
 50 55 60

Asp Phe Pro Arg Ala Leu Ile Phe Ser Thr Asp Asp Phe Phe Phe Arg  
 65 70 75 80

Glu Asp Gly Ala Tyr Glu Phe Asn Pro Asp Phe Leu Glu Glu Ala His  
 85 90 95

Glu Trp Asn Gln Lys Arg Ala Arg Lys Ala Met Arg Asn Gly Ile Ser  
 100 105 110

Pro Ile Ile Ile Asp Asn Thr Asn Leu His Ala Trp Glu Met Lys Pro  
 115 120 125

Tyr Ala Val Met Ala Leu Glu Asn Asn Tyr Glu Val Ile Phe Arg Glu  
 130 135 140

Pro Asp Thr Arg Trp Lys Phe Asn Val Gln Glu Leu Ala Arg Arg Asn  
 145 150 155 160

Ile His Gly Val Ser Arg Glu Lys Ile His Arg Met Lys Glu Arg Tyr  
 165 170 175

Glu His Asp Val Thr Phe His Ser Val Leu His Ala Glu Lys Pro Ser  
 180 185 190

Arg Met Asn Arg Asn Gln Asp Arg Asn Asn Ala Leu Pro Ser Asn Asn  
 195 200 205

Ala Arg Tyr Trp Asn Ser Tyr Thr Glu Phe Pro Asn Arg Arg Ala His  
 210 215 220

# ES 2 534 734 A1

Gly Gly Phe Thr Asn Glu Ser Ser Tyr His Arg Arg Gly Gly Cys His  
 225 230 235 240

His Gly Tyr

<210> 152  
 <211> 1087  
 <212> PRT  
 <213> Homo sapiens

<400> 152

Met Arg Ala Gly Gly Ala Cys Arg Pro Gly Ala Ala Gly Thr Ala Ala  
 1 5 10 15

Gly Thr Ala Ala Gly Gly Trp Asp Gly Gly Cys Gly Gly Ala Glu Pro  
 20 25 30

Ala Arg Cys Leu Thr Ser Pro Trp Cys Gln Trp Thr Gly Arg Gly Ala  
 35 40 45

Ala Thr Met Thr Thr Ser Arg Gly Ser Val Gly Trp Thr Thr Gly Ser  
 50 55 60

Ala Pro Ser Trp Met Thr Arg Thr Glu Glu Leu Asp Ile Arg Pro Lys  
 65 70 75 80

Val Ser Ser Leu Leu Gly Lys Leu Val Ser Tyr Thr Asn Leu Thr Gln  
 85 90 95

Gly Ala Lys Glu His Glu Glu Ala Glu Ser Gly Glu Gly Thr Arg Arg  
 100 105 110

Arg Ala Ala Glu Ala Pro Ser Met Gly Thr Leu Met Gly Val Tyr Leu  
 115 120 125

Pro Cys Leu Gln Asn Ile Phe Gly Val Ile Leu Phe Leu Arg Leu Thr  
 130 135 140

Trp Met Val Gly Thr Ala Gly Val Leu Gln Ala Leu Leu Ile Val Leu  
 145 150 155 160

Ile Cys Cys Cys Cys Thr Leu Leu Thr Ala Ile Ser Met Ser Ala Ile  
 165 170 175

# ES 2 534 734 A1

Ala Thr Asn Gly Val Val Pro Ala Gly Gly Ser Tyr Phe Met Ile Ser  
180 185 190

Arg Ser Leu Gly Pro Glu Phe Gly Gly Ala Val Gly Leu Cys Phe Tyr  
195 200 205

Leu Gly Thr Thr Phe Ala Ala Ala Met Tyr Ile Leu Gly Ala Ile Glu  
210 215 220

Ile Leu Leu Thr Tyr Ile Ala Pro Pro Ala Ala Ile Phe Tyr Pro Ser  
225 230 235 240

Gly Ala His Asp Thr Ser Asn Ala Thr Leu Asn Asn Met Arg Val Tyr  
245 250 255

Gly Thr Ile Phe Leu Thr Phe Met Thr Leu Val Val Phe Val Gly Val  
260 265 270

Lys Tyr Val Asn Lys Phe Ala Ser Leu Phe Leu Ala Cys Val Ile Ile  
275 280 285

Ser Ile Leu Ser Ile Tyr Ala Gly Gly Ile Lys Ser Ile Phe Asp Pro  
290 295 300

Pro Val Phe Pro Val Cys Met Leu Gly Asn Arg Thr Leu Ser Arg Asp  
305 310 315 320

Gln Phe Asp Ile Cys Ala Lys Thr Ala Val Val Asp Asn Glu Thr Val  
325 330 335

Ala Thr Gln Leu Trp Ser Phe Phe Cys His Ser Pro Asn Leu Thr Thr  
340 345 350

Asp Ser Cys Asp Pro Tyr Phe Met Leu Asn Asn Val Thr Glu Ile Pro  
355 360 365

Gly Ile Pro Gly Ala Ala Ala Gly Val Leu Gln Glu Asn Leu Trp Ser  
370 375 380

Ala Tyr Leu Glu Lys Gly Asp Ile Val Glu Lys His Gly Leu Pro Ser  
385 390 395 400

Ala Asp Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu Tyr Val Val Ala  
405 410 415

# ES 2 534 734 A1

Asp Ile Ala Thr Ser Phe Thr Val Leu Val Gly Ile Phe Phe Pro Ser  
 420 425 430

Val Thr Gly Ile Met Ala Gly Ser Asn Arg Ser Gly Asp Leu Arg Asp  
 435 440 445

Ala Gln Lys Ser Ile Pro Val Gly Thr Ile Leu Ala Ile Ile Thr Thr  
 450 455 460

Ser Leu Val Tyr Phe Ser Ser Val Val Leu Phe Gly Ala Cys Ile Glu  
 465 470 475 480

Gly Val Val Leu Arg Asp Lys Tyr Gly Asp Gly Val Ser Arg Asn Leu  
 485 490 495

Val Val Gly Thr Leu Ala Trp Pro Ser Pro Trp Val Ile Val Ile Gly  
 500 505 510

Ser Phe Phe Ser Thr Cys Gly Ala Gly Leu Gln Ser Leu Thr Gly Ala  
 515 520 525

Pro Arg Leu Leu Gln Ala Ile Ala Lys Asp Asn Ile Ile Pro Phe Leu  
 530 535 540

Arg Val Phe Gly His Gly Lys Val Asn Gly Glu Pro Thr Trp Ala Leu  
 545 550 555 560

Leu Leu Thr Ala Leu Ile Ala Glu Leu Gly Ile Leu Ile Ala Ser Leu  
 565 570 575

Asp Met Val Ala Pro Ile Leu Ser Met Phe Phe Leu Met Cys Tyr Leu  
 580 585 590

Phe Val Asn Leu Ala Cys Ala Val Gln Thr Leu Leu Arg Thr Pro Asn  
 595 600 605

Trp Arg Pro Arg Phe Lys Tyr Tyr His Trp Ala Leu Ser Phe Leu Gly  
 610 615 620

Met Ser Leu Cys Leu Ala Leu Met Phe Val Ser Ser Trp Tyr Tyr Ala  
 625 630 635 640

Leu Val Ala Met Leu Ile Ala Gly Met Ile Tyr Lys Tyr Ile Glu Tyr  
 645 650 655

# ES 2 534 734 A1

Gln Gly Ala Glu Lys Glu Trp Gly Asp Gly Ile Arg Gly Leu Ser Leu  
 660 665 670

Ser Ala Ala Arg Tyr Ala Leu Leu Arg Leu Glu Glu Gly Pro Pro His  
 675 680 685

Thr Lys Asn Trp Arg Pro Gln Leu Leu Val Leu Leu Lys Leu Asp Glu  
 690 695 700

Asp Leu His Val Lys Tyr Pro Arg Leu Leu Thr Phe Ala Ser Gln Leu  
 705 710 715 720

Lys Ala Gly Lys Gly Leu Thr Ile Val Gly Ser Val Ile Gln Gly Ser  
 725 730 735

Phe Leu Glu Ser Tyr Gly Glu Ala Gln Ala Ala Glu Gln Thr Ile Lys  
 740 745 750

Asn Met Met Glu Ile Glu Lys Val Lys Gly Phe Cys Gln Val Val Val  
 755 760 765

Ala Ser Lys Val Arg Glu Gly Leu Ala His Leu Ile Gln Ser Cys Gly  
 770 775 780

Leu Gly Gly Met Arg His Asn Ser Val Val Leu Gly Trp Pro Tyr Gly  
 785 790 795 800

Trp Arg Gln Ser Glu Asp Pro Arg Ala Trp Lys Thr Phe Ile Asp Thr  
 805 810 815

Val Arg Cys Thr Thr Ala Ala His Leu Ala Leu Leu Val Pro Lys Asn  
 820 825 830

Ile Ala Phe Tyr Pro Ser Asn His Glu Arg Tyr Leu Glu Gly His Ile  
 835 840 845

Asp Val Trp Trp Ile Val His Asp Gly Gly Met Leu Met Leu Leu Pro  
 850 855 860

Phe Leu Leu Arg Gln His Lys Val Trp Arg Lys Cys Arg Met Arg Ile  
 865 870 875 880

Phe Thr Val Ala Gln Met Asp Asp Asn Ser Ile Gln Met Lys Lys Asp  
 885 890 895

# ES 2 534 734 A1

Leu Ala Val Phe Leu Tyr His Leu Arg Leu Glu Ala Glu Val Glu Val  
900 905 910

Val Glu Met His Asn Ser Asp Ile Ser Ala Tyr Thr Tyr Glu Arg Thr  
915 920 925

Leu Met Met Glu Gln Arg Ser Gln Met Leu Arg Gln Met Arg Leu Thr  
930 935 940

Lys Thr Glu Arg Glu Arg Glu Ala Gln Leu Val Lys Asp Arg His Ser  
945 950 955 960

Ala Leu Arg Leu Glu Ser Leu Tyr Ser Asp Glu Glu Asp Glu Ser Ala  
965 970 975

Val Gly Ala Asp Lys Ile Gln Met Thr Trp Thr Arg Asp Lys Tyr Met  
980 985 990

Thr Glu Thr Trp Asp Pro Ser His Ala Pro Asp Asn Phe Arg Glu Leu  
995 1000 1005

Val His Ile Lys Pro Asp Gln Ser Asn Val Arg Arg Met His Thr  
1010 1015 1020

Ala Val Lys Leu Asn Glu Val Ile Val Thr Arg Ser His Asp Ala  
1025 1030 1035

Arg Leu Val Leu Leu Asn Met Pro Gly Pro Pro Arg Asn Ser Glu  
1040 1045 1050

Gly Asp Glu Asn Tyr Met Glu Phe Leu Glu Val Leu Thr Glu Gly  
1055 1060 1065

Leu Glu Arg Val Leu Leu Val Arg Gly Gly Gly Arg Glu Val Ile  
1070 1075 1080

Thr Ile Tyr Ser  
1085

<210> 153

<211> 1079

<212> PRT

<213> Homo sapiens

<400> 153

# ES 2 534 734 A1

Met	Pro	His	Phe	Thr	Val	Val	Pro	Val	Asp	Gly	Pro	Arg	Arg	Gly	Asp
1				5					10					15	
Tyr	Asp	Asn	Leu	Glu	Gly	Leu	Ser	Trp	Val	Asp	Tyr	Gly	Glu	Arg	Ala
			20					25					30		
Glu	Leu	Asp	Asp	Ser	Asp	Gly	His	Gly	Asn	His	Arg	Glu	Ser	Ser	Pro
		35					40					45			
Phe	Leu	Ser	Pro	Leu	Glu	Ala	Ser	Arg	Gly	Ile	Asp	Tyr	Tyr	Asp	Arg
	50					55					60				
Asn	Leu	Ala	Leu	Phe	Glu	Glu	Glu	Leu	Asp	Ile	Arg	Pro	Lys	Val	Ser
65					70					75					80
Ser	Leu	Leu	Gly	Lys	Leu	Val	Ser	Tyr	Thr	Asn	Leu	Thr	Gln	Gly	Ala
				85					90					95	
Lys	Glu	His	Glu	Glu	Ala	Glu	Ser	Gly	Glu	Gly	Thr	Arg	Arg	Arg	Ala
			100					105					110		
Ala	Glu	Ala	Pro	Ser	Met	Gly	Thr	Leu	Met	Gly	Val	Tyr	Leu	Pro	Cys
		115					120					125			
Leu	Gln	Asn	Ile	Phe	Gly	Val	Ile	Leu	Phe	Leu	Arg	Leu	Thr	Trp	Met
	130					135					140				
Val	Gly	Thr	Ala	Gly	Val	Leu	Gln	Ala	Leu	Leu	Ile	Val	Leu	Ile	Cys
145					150					155					160
Cys	Cys	Cys	Thr	Leu	Leu	Thr	Ala	Ile	Ser	Met	Ser	Ala	Ile	Ala	Thr
				165					170					175	
Asn	Gly	Val	Val	Pro	Ala	Gly	Gly	Ser	Tyr	Phe	Met	Ile	Ser	Arg	Ser
			180					185					190		
Leu	Gly	Pro	Glu	Phe	Gly	Gly	Ala	Val	Gly	Leu	Cys	Phe	Tyr	Leu	Gly
		195					200					205			
Thr	Thr	Phe	Ala	Ala	Ala	Met	Tyr	Ile	Leu	Gly	Ala	Ile	Glu	Ile	Leu
	210					215					220				
Leu	Thr	Tyr	Ile	Ala	Pro	Pro	Ala	Ala	Ile	Phe	Tyr	Pro	Ser	Gly	Ala
225					230					235					240

# ES 2 534 734 A1

His Asp Thr Ser Asn Ala Thr Leu Asn Asn Met Arg Val Tyr Gly Thr  
245 250 255

Ile Phe Leu Thr Phe Met Thr Leu Val Val Phe Val Gly Val Lys Tyr  
260 265 270

Val Asn Lys Phe Ala Ser Leu Phe Leu Ala Cys Val Ile Ile Ser Ile  
275 280 285

Leu Ser Ile Tyr Ala Gly Gly Ile Lys Ser Ile Phe Asp Pro Pro Val  
290 295 300

Phe Pro Val Cys Met Leu Gly Asn Arg Thr Leu Ser Arg Asp Gln Phe  
305 310 315 320

Asp Ile Cys Ala Lys Thr Ala Val Val Asp Asn Glu Thr Val Ala Thr  
325 330 335

Gln Leu Trp Ser Phe Phe Cys His Ser Pro Asn Leu Thr Thr Asp Ser  
340 345 350

Cys Asp Pro Tyr Phe Met Leu Asn Asn Val Thr Glu Ile Pro Gly Ile  
355 360 365

Pro Gly Ala Ala Ala Gly Val Leu Gln Glu Asn Leu Trp Ser Ala Tyr  
370 375 380

Leu Glu Lys Gly Asp Ile Val Glu Lys His Gly Leu Pro Ser Ala Asp  
385 390 395 400

Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu Tyr Val Val Ala Asp Ile  
405 410 415

Ala Thr Ser Phe Thr Val Leu Val Gly Ile Phe Phe Pro Ser Val Thr  
420 425 430

Gly Ile Met Ala Gly Ser Asn Arg Ser Gly Asp Leu Arg Asp Ala Gln  
435 440 445

Lys Ser Ile Pro Val Gly Thr Ile Leu Ala Ile Ile Thr Thr Ser Leu  
450 455 460

Val Tyr Phe Ser Ser Val Val Leu Phe Gly Ala Cys Ile Glu Gly Val  
465 470 475 480



# ES 2 534 734 A1

Val Leu Arg Asp Lys Tyr Gly Asp Gly Val Ser Arg Asn Leu Val Val  
 485 490 495

Gly Thr Leu Ala Trp Pro Ser Pro Trp Val Ile Val Ile Gly Ser Phe  
 500 505 510

Phe Ser Thr Cys Gly Ala Gly Leu Gln Ser Leu Thr Gly Ala Pro Arg  
 515 520 525

Leu Leu Gln Ala Ile Ala Lys Asp Asn Ile Ile Pro Phe Leu Arg Val  
 530 535 540

Phe Gly His Gly Lys Val Asn Gly Glu Pro Thr Trp Ala Leu Leu Leu  
 545 550 555 560

Thr Ala Leu Ile Ala Glu Leu Gly Ile Leu Ile Ala Ser Leu Asp Met  
 565 570 575

Val Ala Pro Ile Leu Ser Met Phe Phe Leu Met Cys Tyr Leu Phe Val  
 580 585 590

Asn Leu Ala Cys Ala Val Gln Thr Leu Leu Arg Thr Pro Asn Trp Arg  
 595 600 605

Pro Arg Phe Lys Tyr Tyr His Trp Ala Leu Ser Phe Leu Gly Met Ser  
 610 615 620

Leu Cys Leu Ala Leu Met Phe Val Ser Ser Trp Tyr Tyr Ala Leu Val  
 625 630 635 640

Ala Met Leu Ile Ala Gly Met Ile Tyr Lys Tyr Ile Glu Tyr Gln Gly  
 645 650 655

Ala Glu Lys Glu Trp Gly Asp Gly Ile Arg Gly Leu Ser Leu Ser Ala  
 660 665 670

Ala Arg Tyr Ala Leu Leu Arg Leu Glu Glu Gly Pro Pro His Thr Lys  
 675 680 685

Asn Trp Arg Pro Gln Leu Leu Val Leu Leu Lys Leu Asp Glu Asp Leu  
 690 695 700

His Val Lys Tyr Pro Arg Leu Leu Thr Phe Ala Ser Gln Leu Lys Ala  
 705 710 715 720

# ES 2 534 734 A1

Gly Lys Gly Leu Thr Ile Val Gly Ser Val Ile Gln Gly Ser Phe Leu  
725 730 735

Glu Ser Tyr Gly Glu Ala Gln Ala Ala Glu Gln Thr Ile Lys Asn Met  
740 745 750

Met Glu Ile Glu Lys Val Lys Gly Phe Cys Gln Val Val Val Ala Ser  
755 760 765

Lys Val Arg Glu Gly Leu Ala His Leu Ile Gln Ser Cys Gly Leu Gly  
770 775 780

Gly Met Arg His Asn Ser Val Val Leu Gly Trp Pro Tyr Gly Trp Arg  
785 790 795 800

Gln Ser Glu Asp Pro Arg Ala Trp Lys Thr Phe Ile Asp Thr Val Arg  
805 810 815

Cys Thr Thr Ala Ala His Leu Ala Leu Leu Val Pro Lys Asn Ile Ala  
820 825 830

Phe Tyr Pro Ser Asn His Glu Arg Tyr Leu Glu Gly His Ile Asp Val  
835 840 845

Trp Trp Ile Val His Asp Gly Gly Met Leu Met Leu Leu Pro Phe Leu  
850 855 860

Leu Arg Gln His Lys Val Trp Arg Lys Cys Arg Met Arg Ile Phe Thr  
865 870 875 880

Val Ala Gln Met Asp Asp Asn Ser Ile Gln Met Lys Lys Asp Leu Ala  
885 890 895

Val Phe Leu Tyr His Leu Arg Leu Glu Ala Glu His Asn Ser Asp Ile  
900 905 910

Ser Ala Tyr Thr Tyr Glu Arg Thr Leu Met Met Glu Gln Arg Ser Gln  
915 920 925

Met Leu Arg Gln Met Arg Leu Thr Lys Thr Glu Arg Glu Arg Glu Ala  
930 935 940

Gln Leu Val Lys Asp Arg His Ser Ala Leu Arg Leu Glu Ser Leu Tyr  
945 950 955 960

# ES 2 534 734 A1

Ser Asp Glu Glu Asp Glu Ser Ala Val Gly Ala Asp Lys Ile Gln Met  
                                   965                                  970                                  975

Thr Trp Thr Arg Asp Lys Tyr Met Thr Glu Thr Trp Asp Pro Ser His  
                                   980                                  985                                  990

Ala Pro Asp Asn Phe Arg Glu Leu Val His Ile Lys Pro Asp Gln Ser  
                                   995                                  1000                                  1005

Asn Val Arg Arg Met His Thr Ala Val Lys Leu Asn Glu Val Ile  
                                   1010                                  1015                                  1020

Val Thr Arg Ser His Asp Ala Arg Leu Val Leu Leu Asn Met Pro  
                                   1025                                  1030                                  1035

Gly Pro Pro Arg Asn Ser Glu Gly Asp Glu Asn Tyr Met Glu Phe  
                                   1040                                  1045                                  1050

Leu Glu Val Leu Thr Glu Gly Leu Glu Arg Val Leu Leu Val Arg  
                                   1055                                  1060                                  1065

Gly Gly Gly Arg Glu Val Ile Thr Ile Tyr Ser  
                                   1070                                  1075

<210> 154  
 <211> 1085  
 <212> PRT  
 <213> Homo sapiens

<400> 154

Met Pro His Phe Thr Val Val Pro Val Asp Gly Pro Arg Arg Gly Asp  
 1                                  5                                  10                                  15

Tyr Asp Asn Leu Glu Gly Leu Ser Trp Val Asp Tyr Gly Glu Arg Ala  
                                   20                                  25                                  30

Glu Leu Asp Asp Ser Asp Gly His Gly Asn His Arg Glu Ser Ser Pro  
                                   35                                  40                                  45

Phe Leu Ser Pro Leu Glu Ala Ser Arg Gly Ile Asp Tyr Tyr Asp Arg  
                                   50                                  55                                  60

Asn Leu Ala Leu Phe Glu Glu Glu Leu Asp Ile Arg Pro Lys Val Ser  
 65                                  70                                  75                                  80

# ES 2 534 734 A1

Ser Leu Leu Gly Lys Leu Val Ser Tyr Thr Asn Leu Thr Gln Gly Ala  
 85 90 95

Lys Glu His Glu Glu Ala Glu Ser Gly Glu Gly Thr Arg Arg Arg Ala  
 100 105 110

Ala Glu Ala Pro Ser Met Gly Thr Leu Met Gly Val Tyr Leu Pro Cys  
 115 120 125

Leu Gln Asn Ile Phe Gly Val Ile Leu Phe Leu Arg Leu Thr Trp Met  
 130 135 140

Val Gly Thr Ala Gly Val Leu Gln Ala Leu Leu Ile Val Leu Ile Cys  
 145 150 155 160

Cys Cys Cys Thr Leu Leu Thr Ala Ile Ser Met Ser Ala Ile Ala Thr  
 165 170 175

Asn Gly Val Val Pro Ala Gly Gly Ser Tyr Phe Met Ile Ser Arg Ser  
 180 185 190

Leu Gly Pro Glu Phe Gly Gly Ala Val Gly Leu Cys Phe Tyr Leu Gly  
 195 200 205

Thr Thr Phe Ala Ala Ala Met Tyr Ile Leu Gly Ala Ile Glu Ile Leu  
 210 215 220

Leu Thr Tyr Ile Ala Pro Pro Ala Ala Ile Phe Tyr Pro Ser Gly Ala  
 225 230 235 240

His Asp Thr Ser Asn Ala Thr Leu Asn Asn Met Arg Val Tyr Gly Thr  
 245 250 255

Ile Phe Leu Thr Phe Met Thr Leu Val Val Phe Val Gly Val Lys Tyr  
 260 265 270

Val Asn Lys Phe Ala Ser Leu Phe Leu Ala Cys Val Ile Ile Ser Ile  
 275 280 285

Leu Ser Ile Tyr Ala Gly Gly Ile Lys Ser Ile Phe Asp Pro Pro Val  
 290 295 300

Phe Pro Val Cys Met Leu Gly Asn Arg Thr Leu Ser Arg Asp Gln Phe  
 305 310 315 320

## ES 2 534 734 A1

Asp Ile Cys Ala Lys Thr Ala Val Val Asp Asn Glu Thr Val Ala Thr  
325 330 335

Gln Leu Trp Ser Phe Phe Cys His Ser Pro Asn Leu Thr Thr Asp Ser  
340 345 350

Cys Asp Pro Tyr Phe Met Leu Asn Asn Val Thr Glu Ile Pro Gly Ile  
355 360 365

Pro Gly Ala Ala Ala Gly Val Leu Gln Glu Asn Leu Trp Ser Ala Tyr  
370 375 380

Leu Glu Lys Gly Asp Ile Val Glu Lys His Gly Leu Pro Ser Ala Asp  
385 390 395 400

Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu Tyr Val Val Ala Asp Ile  
405 410 415

Ala Thr Ser Phe Thr Val Leu Val Gly Ile Phe Phe Pro Ser Val Thr  
420 425 430

Gly Ile Met Ala Gly Ser Asn Arg Ser Gly Asp Leu Arg Asp Ala Gln  
435 440 445

Lys Ser Ile Pro Val Gly Thr Ile Leu Ala Ile Ile Thr Thr Ser Leu  
450 455 460

Val Tyr Phe Ser Ser Val Val Leu Phe Gly Ala Cys Ile Glu Gly Val  
465 470 475 480

Val Leu Arg Asp Lys Tyr Gly Asp Gly Val Ser Arg Asn Leu Val Val  
485 490 495

Gly Thr Leu Ala Trp Pro Ser Pro Trp Val Ile Val Ile Gly Ser Phe  
500 505 510

Phe Ser Thr Cys Gly Ala Gly Leu Gln Ser Leu Thr Gly Ala Pro Arg  
515 520 525

Leu Leu Gln Ala Ile Ala Lys Asp Asn Ile Ile Pro Phe Leu Arg Val  
530 535 540

Phe Gly His Gly Lys Val Asn Gly Glu Pro Thr Trp Ala Leu Leu Leu  
545 550 555 560

# ES 2 534 734 A1

Thr Ala Leu Ile Ala Glu Leu Gly Ile Leu Ile Ala Ser Leu Asp Met  
 565 570 575

Val Ala Pro Ile Leu Ser Met Phe Phe Leu Met Cys Tyr Leu Phe Val  
 580 585 590

Asn Leu Ala Cys Ala Val Gln Thr Leu Leu Arg Thr Pro Asn Trp Arg  
 595 600 605

Pro Arg Phe Lys Tyr Tyr His Trp Ala Leu Ser Phe Leu Gly Met Ser  
 610 615 620

Leu Cys Leu Ala Leu Met Phe Val Ser Ser Trp Tyr Tyr Ala Leu Val  
 625 630 635 640

Ala Met Leu Ile Ala Gly Met Ile Tyr Lys Tyr Ile Glu Tyr Gln Gly  
 645 650 655

Ala Glu Lys Glu Trp Gly Asp Gly Ile Arg Gly Leu Ser Leu Ser Ala  
 660 665 670

Ala Arg Tyr Ala Leu Leu Arg Leu Glu Glu Gly Pro Pro His Thr Lys  
 675 680 685

Asn Trp Arg Pro Gln Leu Leu Val Leu Leu Lys Leu Asp Glu Asp Leu  
 690 695 700

His Val Lys Tyr Pro Arg Leu Leu Thr Phe Ala Ser Gln Leu Lys Ala  
 705 710 715 720

Gly Lys Gly Leu Thr Ile Val Gly Ser Val Ile Gln Gly Ser Phe Leu  
 725 730 735

Glu Ser Tyr Gly Glu Ala Gln Ala Ala Glu Gln Thr Ile Lys Asn Met  
 740 745 750

Met Glu Ile Glu Lys Val Lys Gly Phe Cys Gln Val Val Val Ala Ser  
 755 760 765

Lys Val Arg Glu Gly Leu Ala His Leu Ile Gln Ser Cys Gly Leu Gly  
 770 775 780

Gly Met Arg His Asn Ser Val Val Leu Gly Trp Pro Tyr Gly Trp Arg  
 785 790 795 800

# ES 2 534 734 A1

Gln Ser Glu Asp Pro Arg Ala Trp Lys Thr Phe Ile Asp Thr Val Arg  
 805 810 815

Cys Thr Thr Ala Ala His Leu Ala Leu Leu Val Pro Lys Asn Ile Ala  
 820 825 830

Phe Tyr Pro Ser Asn His Glu Arg Tyr Leu Glu Gly His Ile Asp Val  
 835 840 845

Trp Trp Ile Val His Asp Gly Gly Met Leu Met Leu Leu Pro Phe Leu  
 850 855 860

Leu Arg Gln His Lys Val Trp Arg Lys Cys Arg Met Arg Ile Phe Thr  
 865 870 875 880

Val Ala Gln Met Asp Asp Asn Ser Ile Gln Met Lys Lys Asp Leu Ala  
 885 890 895

Val Phe Leu Tyr His Leu Arg Leu Glu Ala Glu Val Glu Val Val Glu  
 900 905 910

Met His Asn Ser Asp Ile Ser Ala Tyr Thr Tyr Glu Arg Thr Leu Met  
 915 920 925

Met Glu Gln Arg Ser Gln Met Leu Arg Gln Met Arg Leu Thr Lys Thr  
 930 935 940

Glu Arg Glu Arg Glu Ala Gln Leu Val Lys Asp Arg His Ser Ala Leu  
 945 950 955 960

Arg Leu Glu Ser Leu Tyr Ser Asp Glu Glu Asp Glu Ser Ala Val Gly  
 965 970 975

Ala Asp Lys Ile Gln Met Thr Trp Thr Arg Asp Lys Tyr Met Thr Glu  
 980 985 990

Thr Trp Asp Pro Ser His Ala Pro Asp Asn Phe Arg Glu Leu Val His  
 995 1000 1005

Ile Lys Pro Asp Gln Ser Asn Val Arg Arg Met His Thr Ala Val  
 1010 1015 1020

Lys Leu Asn Glu Val Ile Val Thr Arg Ser His Asp Ala Arg Leu  
 1025 1030 1035

# ES 2 534 734 A1

Val Leu Leu Asn Met Pro Gly Pro Pro Arg Asn Ser Glu Gly Asp  
 1040 1045 1050

Glu Asn Tyr Met Glu Phe Leu Glu Val Leu Thr Glu Gly Leu Glu  
 1055 1060 1065

Arg Val Leu Leu Val Arg Gly Gly Gly Arg Glu Val Ile Thr Ile  
 1070 1075 1080

Tyr Ser  
 1085

<210> 155  
 <211> 1054  
 <212> PRT  
 <213> Homo sapiens

<400> 155

Met Gly Asp Thr Leu Ser Pro Gly His Gly Asn His Arg Glu Ser Ser  
 1 5 10 15

Pro Phe Leu Ser Pro Leu Glu Ala Ser Arg Gly Ile Asp Tyr Tyr Asp  
 20 25 30

Arg Asn Leu Ala Leu Phe Glu Glu Glu Leu Asp Ile Arg Pro Lys Val  
 35 40 45

Ser Ser Leu Leu Gly Lys Leu Val Ser Tyr Thr Asn Leu Thr Gln Gly  
 50 55 60

Ala Lys Glu His Glu Glu Ala Glu Ser Gly Glu Gly Thr Arg Arg Arg  
 65 70 75 80

Ala Ala Glu Ala Pro Ser Met Gly Thr Leu Met Gly Val Tyr Leu Pro  
 85 90 95

Cys Leu Gln Asn Ile Phe Gly Val Ile Leu Phe Leu Arg Leu Thr Trp  
 100 105 110

Met Val Gly Thr Ala Gly Val Leu Gln Ala Leu Leu Ile Val Leu Ile  
 115 120 125

Cys Cys Cys Cys Thr Leu Leu Thr Ala Ile Ser Met Ser Ala Ile Ala  
 130 135 140



# ES 2 534 734 A1

Thr Asn Gly Val Val Pro Ala Gly Gly Ser Tyr Phe Met Ile Ser Arg  
 145 150 155 160

Ser Leu Gly Pro Glu Phe Gly Gly Ala Val Gly Leu Cys Phe Tyr Leu  
 165 170 175

Gly Thr Thr Phe Ala Ala Ala Met Tyr Ile Leu Gly Ala Ile Glu Ile  
 180 185 190

Leu Leu Thr Tyr Ile Ala Pro Pro Ala Ala Ile Phe Tyr Pro Ser Gly  
 195 200 205

Ala His Asp Thr Ser Asn Ala Thr Leu Asn Asn Met Arg Val Tyr Gly  
 210 215 220

Thr Ile Phe Leu Thr Phe Met Thr Leu Val Val Phe Val Gly Val Lys  
 225 230 235 240

Tyr Val Asn Lys Phe Ala Ser Leu Phe Leu Ala Cys Val Ile Ile Ser  
 245 250 255

Ile Leu Ser Ile Tyr Ala Gly Gly Ile Lys Ser Ile Phe Asp Pro Pro  
 260 265 270

Val Phe Pro Val Cys Met Leu Gly Asn Arg Thr Leu Ser Arg Asp Gln  
 275 280 285

Phe Asp Ile Cys Ala Lys Thr Ala Val Val Asp Asn Glu Thr Val Ala  
 290 295 300

Thr Gln Leu Trp Ser Phe Phe Cys His Ser Pro Asn Leu Thr Thr Asp  
 305 310 315 320

Ser Cys Asp Pro Tyr Phe Met Leu Asn Asn Val Thr Glu Ile Pro Gly  
 325 330 335

Ile Pro Gly Ala Ala Ala Gly Val Leu Gln Glu Asn Leu Trp Ser Ala  
 340 345 350

Tyr Leu Glu Lys Gly Asp Ile Val Glu Lys His Gly Leu Pro Ser Ala  
 355 360 365

Asp Ala Pro Ser Leu Lys Glu Ser Leu Pro Leu Tyr Val Val Ala Asp  
 370 375 380

# ES 2 534 734 A1

Ile Ala Thr Ser Phe Thr Val Leu Val Gly Ile Phe Phe Pro Ser Val  
 385 390 395 400

Thr Gly Ile Met Ala Gly Ser Asn Arg Ser Gly Asp Leu Arg Asp Ala  
 405 410 415

Gln Lys Ser Ile Pro Val Gly Thr Ile Leu Ala Ile Ile Thr Thr Ser  
 420 425 430

Leu Val Tyr Phe Ser Ser Val Val Leu Phe Gly Ala Cys Ile Glu Gly  
 435 440 445

Val Val Leu Arg Asp Lys Tyr Gly Asp Gly Val Ser Arg Asn Leu Val  
 450 455 460

Val Gly Thr Leu Ala Trp Pro Ser Pro Trp Val Ile Val Ile Gly Ser  
 465 470 475 480

Phe Phe Ser Thr Cys Gly Ala Gly Leu Gln Ser Leu Thr Gly Ala Pro  
 485 490 495

Arg Leu Leu Gln Ala Ile Ala Lys Asp Asn Ile Ile Pro Phe Leu Arg  
 500 505 510

Val Phe Gly His Gly Lys Val Asn Gly Glu Pro Thr Trp Ala Leu Leu  
 515 520 525

Leu Thr Ala Leu Ile Ala Glu Leu Gly Ile Leu Ile Ala Ser Leu Asp  
 530 535 540

Met Val Ala Pro Ile Leu Ser Met Phe Phe Leu Met Cys Tyr Leu Phe  
 545 550 555 560

Val Asn Leu Ala Cys Ala Val Gln Thr Leu Leu Arg Thr Pro Asn Trp  
 565 570 575

Arg Pro Arg Phe Lys Tyr Tyr His Trp Ala Leu Ser Phe Leu Gly Met  
 580 585 590

Ser Leu Cys Leu Ala Leu Met Phe Val Ser Ser Trp Tyr Tyr Ala Leu  
 595 600 605

Val Ala Met Leu Ile Ala Gly Met Ile Tyr Lys Tyr Ile Glu Tyr Gln  
 610 615 620

# ES 2 534 734 A1

Gly Ala Glu Lys Glu Trp Gly Asp Gly Ile Arg Gly Leu Ser Leu Ser  
 625 630 635 640

Ala Ala Arg Tyr Ala Leu Leu Arg Leu Glu Glu Gly Pro Pro His Thr  
 645 650 655

Lys Asn Trp Arg Pro Gln Leu Leu Val Leu Leu Lys Leu Asp Glu Asp  
 660 665 670

Leu His Val Lys Tyr Pro Arg Leu Leu Thr Phe Ala Ser Gln Leu Lys  
 675 680 685

Ala Gly Lys Gly Leu Thr Ile Val Gly Ser Val Ile Gln Gly Ser Phe  
 690 695 700

Leu Glu Ser Tyr Gly Glu Ala Gln Ala Ala Glu Gln Thr Ile Lys Asn  
 705 710 715 720

Met Met Glu Ile Glu Lys Val Lys Gly Phe Cys Gln Val Val Val Ala  
 725 730 735

Ser Lys Val Arg Glu Gly Leu Ala His Leu Ile Gln Ser Cys Gly Leu  
 740 745 750

Gly Gly Met Arg His Asn Ser Val Val Leu Gly Trp Pro Tyr Gly Trp  
 755 760 765

Arg Gln Ser Glu Asp Pro Arg Ala Trp Lys Thr Phe Ile Asp Thr Val  
 770 775 780

Arg Cys Thr Thr Ala Ala His Leu Ala Leu Leu Val Pro Lys Asn Ile  
 785 790 795 800

Ala Phe Tyr Pro Ser Asn His Glu Arg Tyr Leu Glu Gly His Ile Asp  
 805 810 815

Val Trp Trp Ile Val His Asp Gly Gly Met Leu Met Leu Leu Pro Phe  
 820 825 830

Leu Leu Arg Gln His Lys Val Trp Arg Lys Cys Arg Met Arg Ile Phe  
 835 840 845

Thr Val Ala Gln Met Asp Asp Asn Ser Ile Gln Met Lys Lys Asp Leu  
 850 855 860

# ES 2 534 734 A1

Ala Val Phe Leu Tyr His Leu Arg Leu Glu Ala Glu Val Glu Val Val  
 865 870 875 880

Glu Met His Asn Ser Asp Ile Ser Ala Tyr Thr Tyr Glu Arg Thr Leu  
 885 890 895

Met Met Glu Gln Arg Ser Gln Met Leu Arg Gln Met Arg Leu Thr Lys  
 900 905 910

Thr Glu Arg Glu Arg Glu Ala Gln Leu Val Lys Asp Arg His Ser Ala  
 915 920 925

Leu Arg Leu Glu Ser Leu Tyr Ser Asp Glu Glu Asp Glu Ser Ala Val  
 930 935 940

Gly Ala Asp Lys Ile Gln Met Thr Trp Thr Arg Asp Lys Tyr Met Thr  
 945 950 955 960

Glu Thr Trp Asp Pro Ser His Ala Pro Asp Asn Phe Arg Glu Leu Val  
 965 970 975

His Ile Lys Pro Asp Gln Ser Asn Val Arg Arg Met His Thr Ala Val  
 980 985 990

Lys Leu Asn Glu Val Ile Val Thr Arg Ser His Asp Ala Arg Leu Val  
 995 1000 1005

Leu Leu Asn Met Pro Gly Pro Pro Arg Asn Ser Glu Gly Asp Glu  
 1010 1015 1020

Asn Tyr Met Glu Phe Leu Glu Val Leu Thr Glu Gly Leu Glu Arg  
 1025 1030 1035

Val Leu Leu Val Arg Gly Gly Gly Arg Glu Val Ile Thr Ile Tyr  
 1040 1045 1050

Ser

<210> 156  
 <211> 1079  
 <212> PRT  
 <213> Homo sapiens

<400> 156

# ES 2 534 734 A1

Met Ala Ala Glu Gly Ala Val Cys Gly Phe Val Tyr Leu Glu Gly Thr  
 1 5 10 15  
 Ala Trp Ala Val Pro Glu Asp Thr Glu Pro Leu Ala Ser Cys Thr Leu  
 20 25 30  
 Gly His Gly Asn His Arg Glu Ser Ser Pro Phe Leu Ser Pro Leu Glu  
 35 40 45  
 Ala Ser Arg Gly Ile Asp Tyr Tyr Asp Arg Asn Leu Ala Leu Phe Glu  
 50 55 60  
 Glu Glu Leu Asp Ile Arg Pro Lys Val Ser Ser Leu Leu Gly Lys Leu  
 65 70 75 80  
 Val Ser Tyr Thr Asn Leu Thr Gln Gly Ala Lys Glu His Glu Glu Ala  
 85 90 95  
 Glu Ser Gly Glu Gly Thr Arg Arg Arg Ala Ala Glu Ala Pro Ser Met  
 100 105 110  
 Gly Thr Leu Met Gly Val Tyr Leu Pro Cys Leu Gln Asn Ile Phe Gly  
 115 120 125  
 Val Ile Leu Phe Leu Arg Leu Thr Trp Met Val Gly Thr Ala Gly Val  
 130 135 140  
 Leu Gln Ala Leu Leu Ile Val Leu Ile Cys Cys Cys Cys Thr Leu Leu  
 145 150 155 160  
 Thr Ala Ile Ser Met Ser Ala Ile Ala Thr Asn Gly Val Val Pro Ala  
 165 170 175  
 Gly Gly Ser Tyr Phe Met Ile Ser Arg Ser Leu Gly Pro Glu Phe Gly  
 180 185 190  
 Gly Ala Val Gly Leu Cys Phe Tyr Leu Gly Thr Thr Phe Ala Ala Ala  
 195 200 205  
 Met Tyr Ile Leu Gly Ala Ile Glu Ile Leu Leu Thr Tyr Ile Ala Pro  
 210 215 220  
 Pro Ala Ala Ile Phe Tyr Pro Ser Gly Ala His Asp Thr Ser Asn Ala  
 225 230 235 240

# ES 2 534 734 A1

Thr Leu Asn Asn Met Arg Val Tyr Gly Thr Ile Phe Leu Thr Phe Met  
 245 250 255

Thr Leu Val Val Phe Val Gly Val Lys Tyr Val Asn Lys Phe Ala Ser  
 260 265 270

Leu Phe Leu Ala Cys Val Ile Ile Ser Ile Leu Ser Ile Tyr Ala Gly  
 275 280 285

Gly Ile Lys Ser Ile Phe Asp Pro Pro Val Phe Pro Val Cys Met Leu  
 290 295 300

Gly Asn Arg Thr Leu Ser Arg Asp Gln Phe Asp Ile Cys Ala Lys Thr  
 305 310 315 320

Ala Val Val Asp Asn Glu Thr Val Ala Thr Gln Leu Trp Ser Phe Phe  
 325 330 335

Cys His Ser Pro Asn Leu Thr Thr Asp Ser Cys Asp Pro Tyr Phe Met  
 340 345 350

Leu Asn Asn Val Thr Glu Ile Pro Gly Ile Pro Gly Ala Ala Ala Gly  
 355 360 365

Val Leu Gln Glu Asn Leu Trp Ser Ala Tyr Leu Glu Lys Gly Asp Ile  
 370 375 380

Val Glu Lys His Gly Leu Pro Ser Ala Asp Ala Pro Ser Leu Lys Glu  
 385 390 395 400

Ser Leu Pro Leu Tyr Val Val Ala Asp Ile Ala Thr Ser Phe Thr Val  
 405 410 415

Leu Val Gly Ile Phe Phe Pro Ser Val Thr Gly Ile Met Ala Gly Ser  
 420 425 430

Asn Arg Ser Gly Asp Leu Arg Asp Ala Gln Lys Ser Ile Pro Val Gly  
 435 440 445

Thr Ile Leu Ala Ile Ile Thr Thr Ser Leu Val Tyr Phe Ser Ser Val  
 450 455 460

Val Leu Phe Gly Ala Cys Ile Glu Gly Val Val Leu Arg Asp Lys Tyr  
 465 470 475 480

# ES 2 534 734 A1

Gly Asp Gly Val Ser Arg Asn Leu Val Val Gly Thr Leu Ala Trp Pro  
 485 490 495

Ser Pro Trp Val Ile Val Ile Gly Ser Phe Phe Ser Thr Cys Gly Ala  
 500 505 510

Gly Leu Gln Ser Leu Thr Gly Ala Pro Arg Leu Leu Gln Ala Ile Ala  
 515 520 525

Lys Asp Asn Ile Ile Pro Phe Leu Arg Val Phe Gly His Gly Lys Val  
 530 535 540

Asn Gly Glu Pro Thr Trp Ala Leu Leu Leu Thr Ala Leu Ile Ala Glu  
 545 550 555 560

Leu Gly Ile Leu Ile Ala Ser Leu Asp Met Val Ala Pro Ile Leu Ser  
 565 570 575

Met Phe Phe Leu Met Cys Tyr Leu Phe Val Asn Leu Ala Cys Ala Val  
 580 585 590

Gln Thr Leu Leu Arg Thr Pro Asn Trp Arg Pro Arg Phe Lys Tyr Tyr  
 595 600 605

His Trp Ala Leu Ser Phe Leu Gly Met Ser Leu Cys Leu Ala Leu Met  
 610 615 620

Phe Val Ser Ser Trp Tyr Tyr Ala Leu Val Ala Met Leu Ile Ala Gly  
 625 630 635 640

Met Ile Tyr Lys Tyr Ile Glu Tyr Gln Gly Ala Glu Lys Glu Trp Gly  
 645 650 655

Asp Gly Ile Arg Gly Leu Ser Leu Ser Ala Ala Arg Tyr Ala Leu Leu  
 660 665 670

Arg Leu Glu Glu Gly Pro Pro His Thr Lys Asn Trp Arg Pro Gln Leu  
 675 680 685

Leu Val Leu Leu Lys Leu Asp Glu Asp Leu His Val Lys Tyr Pro Arg  
 690 695 700

Leu Leu Thr Phe Ala Ser Gln Leu Lys Ala Gly Lys Gly Leu Thr Ile  
 705 710 715 720

ES 2 534 734 A1

Val Gly Ser Val Ile Gln Gly Ser Phe Leu Glu Ser Tyr Gly Glu Ala  
 725 730 735

Gln Ala Ala Glu Gln Thr Ile Lys Asn Met Met Glu Ile Glu Lys Val  
 740 745 750

Lys Gly Phe Cys Gln Val Val Val Ala Ser Lys Val Arg Glu Gly Leu  
 755 760 765

Ala His Leu Ile Gln Ser Cys Gly Leu Gly Gly Met Arg His Asn Ser  
 770 775 780

Val Val Leu Gly Trp Pro Tyr Gly Trp Arg Gln Ser Glu Asp Pro Arg  
 785 790 795 800

Ala Trp Lys Thr Phe Ile Asp Thr Val Arg Cys Thr Thr Ala Ala His  
 805 810 815

Leu Ala Leu Leu Val Pro Lys Asn Ile Ala Phe Tyr Pro Ser Asn His  
 820 825 830

Glu Arg Tyr Leu Glu Gly His Ile Asp Val Trp Trp Ile Val His Asp  
 835 840 845

Gly Gly Met Leu Met Leu Leu Pro Phe Leu Leu Arg Gln His Lys Val  
 850 855 860

Trp Arg Lys Cys Arg Met Arg Ile Phe Thr Val Ala Gln Met Asp Asp  
 865 870 875 880

Asn Ser Ile Gln Met Lys Lys Asp Leu Ala Val Phe Leu Tyr His Leu  
 885 890 895

Arg Leu Glu Ala Glu Val Glu Val Val Glu Met His Asn Ser Asp Ile  
 900 905 910

Ser Ala Tyr Thr Tyr Glu Arg Thr Leu Met Met Glu Gln Arg Ser Gln  
 915 920 925

Met Leu Arg Gln Met Arg Leu Thr Lys Thr Glu Arg Glu Arg Glu Ala  
 930 935 940

Gln Leu Val Lys Asp Arg His Ser Ala Leu Arg Leu Glu Ser Leu Tyr  
 945 950 955 960



# ES 2 534 734 A1

Ser Asp Glu Glu Asp Glu Ser Ala Val Gly Ala Asp Lys Ile Gln Met  
                                   965                                  970                                  975

Thr Trp Thr Arg Asp Lys Tyr Met Thr Glu Thr Trp Asp Pro Ser His  
                                   980                                  985                                  990

Ala Pro Asp Asn Phe Arg Glu Leu Val His Ile Lys Pro Asp Gln Ser  
                                   995                                  1000                                  1005

Asn Val Arg Arg Met His Thr Ala Val Lys Leu Asn Glu Val Ile  
                                   1010                                  1015                                  1020

Val Thr Arg Ser His Asp Ala Arg Leu Val Leu Leu Asn Met Pro  
                                   1025                                  1030                                  1035

Gly Pro Pro Arg Asn Ser Glu Gly Asp Glu Asn Tyr Met Glu Phe  
                                   1040                                  1045                                  1050

Leu Glu Val Leu Thr Glu Gly Leu Glu Arg Val Leu Leu Val Arg  
                                   1055                                  1060                                  1065

Gly Gly Gly Arg Glu Val Ile Thr Ile Tyr Ser  
                                   1070                                  1075

<210> 157  
 <211> 1078  
 <212> PRT  
 <213> Homo sapiens

<400> 157

Met Ser Thr Gly Thr Gln Pro Lys Thr Lys Val Leu Ser Asp Asn Arg  
 1                                  5                                  10                                  15

Pro Lys Glu Arg Val Glu Ile Glu Ala Lys Glu Ala Cys Asp Trp Leu  
                                   20                                  25                                  30

Arg Ala Ala Gly Phe Pro Gln Tyr Ala Gln Leu Tyr Glu Asp Ser Gln  
                                   35                                  40                                  45

Phe Pro Ile Asn Ile Val Ala Val Lys Asn Asp His Asp Phe Leu Glu  
                                   50                                  55                                  60

Lys Asp Leu Val Glu Pro Leu Cys Arg Arg Leu Asn Thr Leu Asn Lys  
 65                                  70                                  75                                  80

# ES 2 534 734 A1

Cys Ala Ser Met Lys Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp  
85 90 95

Asp Ser Asp Glu Glu Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln  
100 105 110

Arg Thr Ser Arg Arg Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu  
115 120 125

Pro Arg Gly Asp Arg Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn  
130 135 140

Thr Thr Ser Ser Glu Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val  
145 150 155 160

Cys Ser Ile His Ser Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln  
165 170 175

Pro Gly Gln Cys Cys Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu  
180 185 190

Val Ser Ser Ser Leu Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro  
195 200 205

Phe His Pro Lys Asn Glu Lys Pro Thr Arg Ala Arg Ala Lys Ser Phe  
210 215 220

Leu Lys Arg Met Glu Thr Leu Arg Gly Lys Gly Ala His Gly Arg His  
225 230 235 240

Lys Gly Ser Gly Arg Thr Gly Gly Leu Val Ile Ser Gly Pro Met Leu  
245 250 255

Gln Gln Glu Pro Glu Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro  
260 265 270

Asn Gly Asp Leu Gln Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu  
275 280 285

Pro Cys Ser Gly Lys Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser  
290 295 300

Ser Ser Gly Val Ser Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu  
305 310 315 320

# ES 2 534 734 A1

Ala Asn Lys Arg Gly Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala  
 325 330 335

Gly Thr Ala Leu Pro Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe  
 340 345 350

His Ser Gln Glu Asn Leu Val Val His Ile Pro Lys Asp His Lys Pro  
 355 360 365

Gly Thr Phe Pro Lys Ala Leu Ser Ile Glu Ser Leu Ser Pro Thr Asp  
 370 375 380

Ser Ser Asn Gly Val Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg  
 385 390 395 400

Glu Gln Val Pro Gly Ala Arg Glu Pro Arg Leu Met Ala Ser Cys His  
 405 410 415

Arg Ala Ser Arg Val Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu  
 420 425 430

Tyr Ala Ser Thr Gly Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe  
 435 440 445

Pro His Leu Asp Asp Ile Leu Gln His Val Asn Gly Leu Gln Glu Val  
 450 455 460

Val Asp Asp Trp Ser Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp  
 465 470 475 480

Thr Leu Val Gly Glu Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln  
 485 490 495

Ile Thr Leu Asp Phe Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr  
 500 505 510

Pro Ser Asp Val Glu Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro  
 515 520 525

Pro Gly Val Arg Asp Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr  
 530 535 540

Arg Pro Asn Arg Arg Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln  
 545 550 555 560

# ES 2 534 734 A1

Pro Arg Pro Ala Pro Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser  
 565 570 575

Gln Leu Ser Leu Leu Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile  
 580 585 590

Met Glu Lys His Ser Met Ser Asn Lys His Gly Trp Thr Trp Ser Val  
 595 600 605

Pro Lys Phe Met Lys Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala  
 610 615 620

Val Phe Gly Val Pro Leu Ile Val His Val Gln Arg Thr Gly Gln Pro  
 625 630 635

Leu Pro Gln Ser Ile Gln Gln Ala Leu Arg Tyr Leu Arg Ser Asn Cys  
 645 650 655

Leu Asp Gln Val Gly Leu Phe Arg Lys Ser Gly Val Lys Ser Arg Ile  
 660 665 670

His Ala Leu Arg Gln Met Asn Glu Asn Phe Pro Glu Asn Val Asn Tyr  
 675 680 685

Glu Asp Gln Ser Ala Tyr Asp Val Ala Asp Met Val Lys Gln Phe Phe  
 690 695 700

Arg Asp Leu Pro Glu Pro Leu Phe Thr Asn Lys Leu Ser Glu Thr Phe  
 705 710 715 720

Leu His Ile Tyr Gln Tyr Val Ser Lys Glu Gln Arg Leu Gln Ala Val  
 725 730 735

Gln Ala Ala Ile Leu Leu Leu Ala Asp Glu Asn Arg Glu Val Leu Gln  
 740 745 750

Thr Leu Leu Cys Phe Leu Asn Asp Val Val Asn Leu Val Glu Glu Asn  
 755 760 765

Gln Met Thr Pro Met Asn Leu Ala Val Cys Leu Ala Pro Ser Leu Phe  
 770 775 780

His Leu Asn Leu Leu Lys Lys Glu Ser Ser Pro Arg Val Ile Gln Lys  
 785 790 795 800

# ES 2 534 734 A1

Lys Tyr Ala Thr Gly Lys Pro Asp Gln Lys Asp Leu Asn Glu Asn Leu  
 805 810 815

Ala Ala Ala Gln Gly Leu Ala His Met Ile Met Glu Cys Asp Arg Leu  
 820 825 830

Phe Glu Val Pro His Glu Leu Val Ala Gln Ser Arg Asn Ser Tyr Val  
 835 840 845

Glu Ala Glu Ile His Val Pro Thr Leu Glu Glu Leu Gly Thr Gln Leu  
 850 855 860

Glu Glu Ser Gly Ala Thr Phe His Thr Tyr Leu Asn His Leu Ile Gln  
 865 870 875 880

Gly Leu Gln Lys Glu Ala Lys Glu Lys Phe Lys Gly Trp Val Thr Cys  
 885 890 895

Ser Ser Thr Asp Asn Thr Asp Leu Ala Phe Lys Lys Val Gly Asp Gly  
 900 905 910

Asn Pro Leu Lys Leu Trp Lys Ala Ser Val Glu Val Glu Ala Pro Pro  
 915 920 925

Ser Val Val Leu Asn Arg Val Leu Arg Glu Arg His Leu Trp Asp Glu  
 930 935 940

Asp Phe Val Gln Trp Lys Val Val Glu Thr Leu Asp Arg Gln Thr Glu  
 945 950 955 960

Ile Tyr Gln Tyr Val Leu Asn Ser Met Ala Pro His Pro Ser Arg Asp  
 965 970 975

Phe Val Val Leu Arg Thr Trp Lys Thr Asp Leu Pro Lys Gly Met Cys  
 980 985 990

Thr Leu Val Ser Leu Ser Val Glu His Glu Glu Ala Gln Leu Leu Gly  
 995 1000 1005

Gly Val Arg Ala Val Val Met Asp Ser Gln Tyr Leu Ile Glu Pro  
 1010 1015 1020

Cys Gly Ser Gly Lys Ser Arg Leu Thr His Ile Cys Arg Ile Asp  
 1025 1030 1035

# ES 2 534 734 A1

Leu Lys Gly His Ser Pro Glu Trp Tyr Ser Lys Gly Phe Gly His  
 1040 1045 1050

Leu Cys Ala Ala Glu Val Ala Arg Ile Arg Asn Ser Phe Gln Pro  
 1055 1060 1065

Leu Ile Ala Glu Gly Pro Glu Thr Lys Ile  
 1070 1075

<210> 158  
 <211> 1113  
 <212> PRT  
 <213> Homo sapiens

<400> 158

Met Phe Ser Gln Val Pro Arg Thr Pro Ala Ser Gly Cys Tyr Tyr Leu  
 1 5 10 15

Asn Ser Met Thr Pro Glu Gly Gln Glu Met Tyr Leu Arg Phe Asp Gln  
 20 25 30

Thr Thr Arg Arg Ser Pro Tyr Arg Met Ser Arg Ile Leu Ala Arg His  
 35 40 45

Gln Leu Val Thr Lys Ile Gln Gln Glu Ile Glu Ala Lys Glu Ala Cys  
 50 55 60

Asp Trp Leu Arg Ala Ala Gly Phe Pro Gln Tyr Ala Gln Leu Tyr Glu  
 65 70 75 80

Asp Ser Gln Phe Pro Ile Asn Ile Val Ala Val Lys Asn Asp His Asp  
 85 90 95

Phe Leu Glu Lys Asp Leu Val Glu Pro Leu Cys Arg Arg Leu Asn Thr  
 100 105 110

Leu Asn Lys Cys Ala Ser Met Lys Leu Asp Val Asn Phe Gln Arg Lys  
 115 120 125

Lys Gly Asp Asp Ser Asp Glu Glu Asp Leu Cys Ile Ser Asn Lys Trp  
 130 135 140

Thr Phe Gln Arg Thr Ser Arg Arg Trp Ser Arg Val Asp Asp Leu Tyr  
 145 150 155 160

# ES 2 534 734 A1

Thr Leu Leu Pro Arg Gly Asp Arg Asn Gly Ser Pro Gly Gly Thr Gly  
 165 170 175

Met Arg Asn Thr Thr Ser Ser Glu Ser Val Leu Thr Asp Leu Ser Glu  
 180 185 190

Pro Glu Val Cys Ser Ile His Ser Glu Ser Ser Gly Gly Ser Asp Ser  
 195 200 205

Arg Ser Gln Pro Gly Gln Cys Cys Thr Asp Asn Pro Val Met Leu Asp  
 210 215 220

Ala Pro Leu Val Ser Ser Ser Leu Pro Gln Pro Pro Arg Asp Val Leu  
 225 230 235 240

Asn His Pro Phe His Pro Lys Asn Glu Lys Pro Thr Arg Ala Arg Ala  
 245 250 255

Lys Ser Phe Leu Lys Arg Met Glu Thr Leu Arg Gly Lys Gly Ala His  
 260 265 270

Gly Arg His Lys Gly Ser Gly Arg Thr Gly Gly Leu Val Ile Ser Gly  
 275 280 285

Pro Met Leu Gln Gln Glu Pro Glu Ser Phe Lys Ala Met Gln Cys Ile  
 290 295 300

Gln Ile Pro Asn Gly Asp Leu Gln Asn Ser Pro Pro Ala Cys Arg  
 305 310 315 320

Lys Gly Leu Pro Cys Ser Gly Lys Ser Ser Gly Glu Ser Ser Pro Ser  
 325 330 335

Glu His Ser Ser Ser Gly Val Ser Thr Pro Cys Leu Lys Glu Arg Lys  
 340 345 350

Cys His Glu Ala Asn Lys Arg Gly Gly Met Tyr Leu Glu Asp Leu Asp  
 355 360 365

Val Leu Ala Gly Thr Ala Leu Pro Asp Ala Gly Asp Gln Ser Arg Met  
 370 375 380

His Glu Phe His Ser Gln Glu Asn Leu Val Val His Ile Pro Lys Asp  
 385 390 395 400

# ES 2 534 734 A1

His Lys Pro Gly Thr Phe Pro Lys Ala Leu Ser Ile Glu Ser Leu Ser  
 405 410 415

Pro Thr Asp Ser Ser Asn Gly Val Asn Trp Arg Thr Gly Ser Ile Ser  
 420 425 430

Leu Gly Arg Glu Gln Val Pro Gly Ala Arg Glu Pro Arg Leu Met Ala  
 435 440 445

Ser Cys His Arg Ala Ser Arg Val Ser Ile Tyr Asp Asn Val Pro Gly  
 450 455 460

Ser His Leu Tyr Ala Ser Thr Gly Asp Leu Leu Asp Leu Glu Lys Asp  
 465 470 475 480

Asp Leu Phe Pro His Leu Asp Asp Ile Leu Gln His Val Asn Gly Leu  
 485 490 495

Gln Glu Val Val Asp Asp Trp Ser Lys Asp Val Leu Pro Glu Leu Gln  
 500 505 510

Thr His Asp Thr Leu Val Gly Glu Pro Gly Leu Ser Thr Phe Pro Ser  
 515 520 525

Pro Asn Gln Ile Thr Leu Asp Phe Glu Gly Asn Ser Val Ser Glu Gly  
 530 535 540

Arg Thr Thr Pro Ser Asp Val Glu Arg Asp Val Thr Ser Leu Asn Glu  
 545 550 555 560

Ser Glu Pro Pro Gly Val Arg Asp Arg Arg Asp Ser Gly Val Gly Ala  
 565 570 575

Ser Leu Thr Arg Pro Asn Arg Arg Leu Arg Trp Asn Ser Phe Gln Leu  
 580 585 590

Ser His Gln Pro Arg Pro Ala Pro Ala Ser Pro His Ile Ser Ser Gln  
 595 600 605

Thr Ala Ser Gln Leu Ser Leu Leu Gln Arg Phe Ser Leu Leu Arg Leu  
 610 615 620

Thr Ala Ile Met Glu Lys His Ser Met Ser Asn Lys His Gly Trp Thr  
 625 630 635 640



# ES 2 534 734 A1

Trp Ser Val Pro Lys Phe Met Lys Arg Met Lys Val Pro Asp Tyr Lys  
                                 645  650  655

Asp Lys Ala Val Phe Gly Val Pro Leu Ile Val His Val Gln Arg Thr  
                                 660  665  670

Gly Gln Pro Leu Pro Gln Ser Ile Gln Gln Ala Leu Arg Tyr Leu Arg  
                                 675  680  685

Ser Asn Cys Leu Asp Gln Val Gly Leu Phe Arg Lys Ser Gly Val Lys  
                                 690  695  700

Ser Arg Ile His Ala Leu Arg Gln Met Asn Glu Asn Phe Pro Glu Asn  
 705  710  715  720

Val Asn Tyr Glu Asp Gln Ser Ala Tyr Asp Val Ala Asp Met Val Lys  
                                 725  730  735

Gln Phe Phe Arg Asp Leu Pro Glu Pro Leu Phe Thr Asn Lys Leu Ser  
                                 740  745  750

Glu Thr Phe Leu His Ile Tyr Gln Tyr Val Ser Lys Glu Gln Arg Leu  
                                 755  760  765

Gln Ala Val Gln Ala Ala Ile Leu Leu Leu Ala Asp Glu Asn Arg Glu  
                                 770  775  780

Val Leu Gln Thr Leu Leu Cys Phe Leu Asn Asp Val Val Asn Leu Val  
 785  790  795  800

Glu Glu Asn Gln Met Thr Pro Met Asn Leu Ala Val Cys Leu Ala Pro  
                                 805  810  815

Ser Leu Phe His Leu Asn Leu Leu Lys Lys Glu Ser Ser Pro Arg Val  
                                 820  825  830

Ile Gln Lys Lys Tyr Ala Thr Gly Lys Pro Asp Gln Lys Asp Leu Asn  
                                 835  840  845

Glu Asn Leu Ala Ala Ala Gln Gly Leu Ala His Met Ile Met Glu Cys  
                                 850  855  860

Asp Arg Leu Phe Glu Val Pro His Glu Leu Val Ala Gln Ser Arg Asn  
 865  870  875  880

# ES 2 534 734 A1

Ser Tyr Val Glu Ala Glu Ile His Val Pro Thr Leu Glu Glu Leu Gly  
 885 890 895

Thr Gln Leu Glu Glu Ser Gly Ala Thr Phe His Thr Tyr Leu Asn His  
 900 905 910

Leu Ile Gln Gly Leu Gln Lys Glu Ala Lys Glu Lys Phe Lys Gly Trp  
 915 920 925

Val Thr Cys Ser Ser Thr Asp Asn Thr Asp Leu Ala Phe Lys Lys Val  
 930 935 940

Gly Asp Gly Asn Pro Leu Lys Leu Trp Lys Ala Ser Val Glu Val Glu  
 945 950 955 960

Ala Pro Pro Ser Val Val Leu Asn Arg Val Leu Arg Glu Arg His Leu  
 965 970 975

Trp Asp Glu Asp Phe Val Gln Trp Lys Val Val Glu Thr Leu Asp Arg  
 980 985 990

Gln Thr Glu Ile Tyr Gln Tyr Val Leu Asn Ser Met Ala Pro His Pro  
 995 1000 1005

Ser Arg Asp Phe Val Val Leu Arg Thr Trp Lys Thr Asp Leu Pro  
 1010 1015 1020

Lys Gly Met Cys Thr Leu Val Ser Leu Ser Val Glu His Glu Glu  
 1025 1030 1035

Ala Gln Leu Leu Gly Gly Val Arg Ala Val Val Met Asp Ser Gln  
 1040 1045 1050

Tyr Leu Ile Glu Pro Cys Gly Ser Gly Lys Ser Arg Leu Thr His  
 1055 1060 1065

Ile Cys Arg Ile Asp Leu Lys Gly His Ser Pro Glu Trp Tyr Ser  
 1070 1075 1080

Lys Gly Phe Gly His Leu Cys Ala Ala Glu Val Ala Arg Ile Arg  
 1085 1090 1095

Asn Ser Phe Gln Pro Leu Ile Ala Glu Gly Pro Glu Thr Lys Ile  
 1100 1105 1110

# ES 2 534 734 A1

<210> 159  
 <211> 995  
 <212> PRT  
 <213> Homo sapiens

<400> 159

Met Lys Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp Asp Ser Asp  
 1 5 10 15

Glu Glu Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln Arg Thr Ser  
 20 25 30

Arg Arg Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu Pro Arg Gly  
 35 40 45

Asp Arg Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn Thr Thr Ser  
 50 55 60

Ser Glu Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val Cys Ser Ile  
 65 70 75 80

His Ser Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln Pro Gly Gln  
 85 90 95

Cys Cys Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu Val Ser Ser  
 100 105 110

Ser Leu Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro Phe His Pro  
 115 120 125

Lys Asn Glu Lys Pro Thr Arg Ala Arg Ala Lys Ser Phe Leu Lys Arg  
 130 135 140

Met Glu Thr Leu Arg Gly Lys Gly Ala His Gly Arg His Lys Gly Ser  
 145 150 155 160

Gly Arg Thr Gly Gly Leu Val Ile Ser Gly Pro Met Leu Gln Gln Glu  
 165 170 175

Pro Glu Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro Asn Gly Asp  
 180 185 190

Leu Gln Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu Pro Cys Ser  
 195 200 205

# ES 2 534 734 A1

Gly Lys Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser Ser Ser Gly  
 210 215 220

Val Ser Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu Ala Asn Lys  
 225 230 235 240

Arg Gly Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala Gly Thr Ala  
 245 250 255

Leu Pro Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe His Ser Gln  
 260 265 270

Glu Asn Leu Val Val His Ile Pro Lys Asp His Lys Pro Gly Thr Phe  
 275 280 285

Pro Lys Ala Leu Ser Ile Glu Ser Leu Ser Pro Thr Asp Ser Ser Asn  
 290 295 300

Gly Val Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg Glu Gln Val  
 305 310 315 320

Pro Gly Ala Arg Glu Pro Arg Leu Met Ala Ser Cys His Arg Ala Ser  
 325 330 335

Arg Val Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu Tyr Ala Ser  
 340 345 350

Thr Gly Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe Pro His Leu  
 355 360 365

Asp Asp Ile Leu Gln His Val Asn Gly Leu Gln Glu Val Val Asp Asp  
 370 375 380

Trp Ser Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp Thr Leu Val  
 385 390 395 400

Gly Glu Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln Ile Thr Leu  
 405 410 415

Asp Phe Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr Pro Ser Asp  
 420 425 430

Val Glu Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro Pro Gly Val  
 435 440 445

# ES 2 534 734 A1

Arg Asp Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr Arg Pro Asn  
 450 455 460

Arg Arg Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln Pro Arg Pro  
 465 470 475 480

Ala Pro Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser Gln Leu Ser  
 485 490 495

Leu Leu Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile Met Glu Lys  
 500 505 510

His Ser Met Ser Asn Lys His Gly Trp Thr Trp Ser Val Pro Lys Phe  
 515 520 525

Met Lys Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala Val Phe Gly  
 530 535 540

Val Pro Leu Ile Val His Val Gln Arg Thr Gly Gln Pro Leu Pro Gln  
 545 550 555

Ser Ile Gln Gln Ala Leu Arg Tyr Leu Arg Ser Asn Cys Leu Asp Gln  
 565 570 575

Val Gly Leu Phe Arg Lys Ser Gly Val Lys Ser Arg Ile His Ala Leu  
 580 585 590

Arg Gln Met Asn Glu Asn Phe Pro Glu Asn Val Asn Tyr Glu Asp Gln  
 595 600 605

Ser Ala Tyr Asp Val Ala Asp Met Val Lys Gln Phe Phe Arg Asp Leu  
 610 615 620

Pro Glu Pro Leu Phe Thr Asn Lys Leu Ser Glu Thr Phe Leu His Ile  
 625 630 635 640

Tyr Gln Tyr Val Ser Lys Glu Gln Arg Leu Gln Ala Val Gln Ala Ala  
 645 650 655

Ile Leu Leu Leu Ala Asp Glu Asn Arg Glu Val Leu Gln Thr Leu Leu  
 660 665 670

Cys Phe Leu Asn Asp Val Val Asn Leu Val Glu Glu Asn Gln Met Thr  
 675 680 685

# ES 2 534 734 A1

Pro Met Asn Leu Ala Val Cys Leu Ala Pro Ser Leu Phe His Leu Asn  
 690 695 700

Leu Leu Lys Lys Glu Ser Ser Pro Arg Val Ile Gln Lys Lys Tyr Ala  
 705 710 715 720

Thr Gly Lys Pro Asp Gln Lys Asp Leu Asn Glu Asn Leu Ala Ala Ala  
 725 730 735

Gln Gly Leu Ala His Met Ile Met Glu Cys Asp Arg Leu Phe Glu Val  
 740 745 750

Pro His Glu Leu Val Ala Gln Ser Arg Asn Ser Tyr Val Glu Ala Glu  
 755 760 765

Ile His Val Pro Thr Leu Glu Glu Leu Gly Thr Gln Leu Glu Glu Ser  
 770 775 780

Gly Ala Thr Phe His Thr Tyr Leu Asn His Leu Ile Gln Gly Leu Gln  
 785 790 795 800

Lys Glu Ala Lys Glu Lys Phe Lys Gly Trp Val Thr Cys Ser Ser Thr  
 805 810 815

Asp Asn Thr Asp Leu Ala Phe Lys Lys Val Gly Asp Gly Asn Pro Leu  
 820 825 830

Lys Leu Trp Lys Ala Ser Val Glu Val Glu Ala Pro Pro Ser Val Val  
 835 840 845

Leu Asn Arg Val Leu Arg Glu Arg His Leu Trp Asp Glu Asp Phe Val  
 850 855 860

Gln Trp Lys Val Val Glu Thr Leu Asp Arg Gln Thr Glu Ile Tyr Gln  
 865 870 875 880

Tyr Val Leu Asn Ser Met Ala Pro His Pro Ser Arg Asp Phe Val Val  
 885 890 895

Leu Arg Thr Trp Lys Thr Asp Leu Pro Lys Gly Met Cys Thr Leu Val  
 900 905 910

Ser Leu Ser Val Glu His Glu Glu Ala Gln Leu Leu Gly Gly Val Arg  
 915 920 925

# ES 2 534 734 A1

Ala Val Val Met Asp Ser Gln Tyr Leu Ile Glu Pro Cys Gly Ser Gly  
 930 935 940

Lys Ser Arg Leu Thr His Ile Cys Arg Ile Asp Leu Lys Gly His Ser  
 945 950 955 960

Pro Glu Trp Tyr Ser Lys Gly Phe Gly His Leu Cys Ala Ala Glu Val  
 965 970 975

Ala Arg Ile Arg Asn Ser Phe Gln Pro Leu Ile Ala Glu Gly Pro Glu  
 980 985 990

Thr Lys Ile  
 995

<210> 160  
 <211> 1105  
 <212> PRT  
 <213> Homo sapiens

<400> 160

Met Leu Glu Pro Ser Ser Val Leu His Ala Asn Val Asn Gln Ala Pro  
 1 5 10 15

Leu Trp Cys Leu Val Leu Arg Trp Cys Arg Glu Cys Lys Asp Thr Val  
 20 25 30

Cys Gly Gly Lys Gln Lys Ser Arg Val Asn His Thr Phe Gln Arg Arg  
 35 40 45

Glu Ile Glu Ala Lys Glu Ala Cys Asp Trp Leu Arg Ala Ala Gly Phe  
 50 55 60

Pro Gln Tyr Ala Gln Leu Tyr Glu Asp Ser Gln Phe Pro Ile Asn Ile  
 65 70 75 80

Val Ala Val Lys Asn Asp His Asp Phe Leu Glu Lys Asp Leu Val Glu  
 85 90 95

Pro Leu Cys Arg Arg Leu Asn Thr Leu Asn Lys Cys Ala Ser Met Lys  
 100 105 110

Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp Asp Ser Asp Glu Glu  
 115 120 125

# ES 2 534 734 A1

Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln Arg Thr Ser Arg Arg  
 130 135 140

Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu Pro Arg Gly Asp Arg  
 145 150 155 160

Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn Thr Thr Ser Ser Glu  
 165 170 175

Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val Cys Ser Ile His Ser  
 180 185 190

Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln Pro Gly Gln Cys Cys  
 195 200 205

Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu Val Ser Ser Ser Leu  
 210 215 220

Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro Phe His Pro Lys Asn  
 225 230 235 240

Glu Lys Pro Thr Arg Ala Arg Ala Lys Ser Phe Leu Lys Arg Met Glu  
 245 250 255

Thr Leu Arg Gly Lys Gly Ala His Gly Arg His Lys Gly Ser Gly Arg  
 260 265 270

Thr Gly Gly Leu Val Ile Ser Gly Pro Met Leu Gln Gln Glu Pro Glu  
 275 280 285

Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro Asn Gly Asp Leu Gln  
 290 295 300

Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu Pro Cys Ser Gly Lys  
 305 310 315 320

Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser Ser Ser Gly Val Ser  
 325 330 335

Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu Ala Asn Lys Arg Gly  
 340 345 350

Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala Gly Thr Ala Leu Pro  
 355 360 365



# ES 2 534 734 A1

Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe His Ser Gln Glu Asn  
 370 375 380

Leu Val Val His Ile Pro Lys Asp His Lys Pro Gly Thr Phe Pro Lys  
 385 390 395 400

Ala Leu Ser Ile Glu Ser Leu Ser Pro Thr Asp Ser Ser Asn Gly Val  
 405 410 415

Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg Glu Gln Val Pro Gly  
 420 425 430

Ala Arg Glu Pro Arg Leu Met Ala Ser Cys His Arg Ala Ser Arg Val  
 435 440 445

Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu Tyr Ala Ser Thr Gly  
 450 455 460

Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe Pro His Leu Asp Asp  
 465 470 475 480

Ile Leu Gln His Val Asn Gly Leu Gln Glu Val Val Asp Asp Trp Ser  
 485 490 495

Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp Thr Leu Val Gly Glu  
 500 505 510

Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln Ile Thr Leu Asp Phe  
 515 520 525

Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr Pro Ser Asp Val Glu  
 530 535 540

Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro Pro Gly Val Arg Asp  
 545 550 555 560

Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr Arg Pro Asn Arg Arg  
 565 570 575

Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln Pro Arg Pro Ala Pro  
 580 585 590

Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser Gln Leu Ser Leu Leu  
 595 600 605

# ES 2 534 734 A1

Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile Met Glu Lys His Ser  
 610 615 620

Met Ser Asn Lys His Gly Trp Thr Trp Ser Val Pro Lys Phe Met Lys  
 625 630 635 640

Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala Val Phe Gly Val Pro  
 645 650 655

Leu Ile Val His Val Gln Arg Thr Gly Gln Pro Leu Pro Gln Ser Ile  
 660 665 670

Gln Gln Ala Leu Arg Tyr Leu Arg Ser Asn Cys Leu Asp Gln Val Gly  
 675 680 685

Leu Phe Arg Lys Ser Gly Val Lys Ser Arg Ile His Ala Leu Arg Gln  
 690 695 700

Met Asn Glu Asn Phe Pro Glu Asn Val Asn Tyr Glu Asp Gln Ser Ala  
 705 710 715 720

Tyr Asp Val Ala Asp Met Val Lys Gln Phe Phe Arg Asp Leu Pro Glu  
 725 730 735

Pro Leu Phe Thr Asn Lys Leu Ser Glu Thr Phe Leu His Ile Tyr Gln  
 740 745 750

Tyr Val Ser Lys Glu Gln Arg Leu Gln Ala Val Gln Ala Ala Ile Leu  
 755 760 765

Leu Leu Ala Asp Glu Asn Arg Glu Val Leu Gln Thr Leu Leu Cys Phe  
 770 775 780

Leu Asn Asp Val Val Asn Leu Val Glu Glu Asn Gln Met Thr Pro Met  
 785 790 795 800

Asn Leu Ala Val Cys Leu Ala Pro Ser Leu Phe His Leu Asn Leu Leu  
 805 810 815

Lys Lys Glu Ser Ser Pro Arg Val Ile Gln Lys Lys Tyr Ala Thr Gly  
 820 825 830

Lys Pro Asp Gln Lys Asp Leu Asn Glu Asn Leu Ala Ala Ala Gln Gly  
 835 840 845

# ES 2 534 734 A1

Leu Ala His Met Ile Met Glu Cys Asp Arg Leu Phe Glu Val Pro His  
 850 855 860

Glu Leu Val Ala Gln Ser Arg Asn Ser Tyr Val Glu Ala Glu Ile His  
 865 870 875 880

Val Pro Thr Leu Glu Glu Leu Gly Thr Gln Leu Glu Glu Ser Gly Ala  
 885 890 895

Thr Phe His Thr Tyr Leu Asn His Leu Ile Gln Gly Leu Gln Lys Glu  
 900 905 910

Ala Lys Glu Lys Phe Lys Gly Trp Val Thr Cys Ser Ser Thr Asp Asn  
 915 920 925

Thr Asp Leu Ala Phe Lys Lys Val Gly Asp Gly Asn Pro Leu Lys Leu  
 930 935 940

Trp Lys Ala Ser Val Glu Val Glu Ala Pro Pro Ser Val Val Leu Asn  
 945 950 955 960

Arg Val Leu Arg Glu Arg His Leu Trp Asp Glu Asp Phe Val Gln Trp  
 965 970 975

Lys Val Val Glu Thr Leu Asp Arg Gln Thr Glu Ile Tyr Gln Tyr Val  
 980 985 990

Leu Asn Ser Met Ala Pro His Pro Ser Arg Asp Phe Val Val Leu Arg  
 995 1000 1005

Thr Trp Lys Thr Asp Leu Pro Lys Gly Met Cys Thr Leu Val Ser  
 1010 1015 1020

Leu Ser Val Glu His Glu Glu Ala Gln Leu Leu Gly Gly Val Arg  
 1025 1030 1035

Ala Val Val Met Asp Ser Gln Tyr Leu Ile Glu Pro Cys Gly Ser  
 1040 1045 1050

Gly Lys Ser Arg Leu Thr His Ile Cys Arg Ile Asp Leu Lys Gly  
 1055 1060 1065

His Ser Pro Glu Trp Tyr Ser Lys Gly Phe Gly His Leu Cys Ala  
 1070 1075 1080

# ES 2 534 734 A1

Ala Glu Val Ala Arg Ile Arg Asn Ser Phe Gln Pro Leu Ile Ala  
 1085 1090 1095

Glu Gly Pro Glu Thr Lys Ile  
 1100 1105

<210> 161  
 <211> 646  
 <212> PRT  
 <213> Homo sapiens

<400> 161

Met Lys Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp Asp Ser Asp  
 1 5 10 15

Glu Glu Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln Arg Thr Ser  
 20 25 30

Arg Arg Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu Pro Arg Gly  
 35 40 45

Asp Arg Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn Thr Thr Ser  
 50 55 60

Ser Glu Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val Cys Ser Ile  
 65 70 75 80

His Ser Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln Pro Gly Gln  
 85 90 95

Cys Cys Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu Val Ser Ser  
 100 105 110

Ser Leu Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro Phe His Pro  
 115 120 125

Lys Asn Glu Lys Pro Thr Arg Ala Arg Ala Lys Ser Phe Leu Lys Arg  
 130 135 140

Met Glu Thr Leu Arg Gly Lys Gly Ala His Gly Arg His Lys Gly Ser  
 145 150 155 160

Gly Arg Thr Gly Gly Leu Val Ile Ser Gly Pro Met Leu Gln Gln Glu  
 165 170 175

# ES 2 534 734 A1

Pro Glu Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro Asn Gly Asp  
 180 185 190

Leu Gln Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu Pro Cys Ser  
 195 200 205

Gly Lys Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser Ser Ser Gly  
 210 215 220

Val Ser Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu Ala Asn Lys  
 225 230 235 240

Arg Gly Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala Gly Thr Ala  
 245 250 255

Leu Pro Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe His Ser Gln  
 260 265 270

Glu Asn Leu Val Val His Ile Pro Lys Asp His Lys Pro Gly Thr Phe  
 275 280 285

Pro Lys Ala Leu Ser Ile Glu Ser Leu Ser Pro Thr Asp Ser Ser Asn  
 290 295 300

Gly Val Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg Glu Gln Val  
 305 310 315 320

Pro Gly Ala Arg Glu Pro Arg Leu Met Ala Ser Cys His Arg Ala Ser  
 325 330 335

Arg Val Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu Tyr Ala Ser  
 340 345 350

Thr Gly Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe Pro His Leu  
 355 360 365

Asp Asp Ile Leu Gln His Val Asn Gly Leu Gln Glu Val Val Asp Asp  
 370 375 380

Trp Ser Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp Thr Leu Val  
 385 390 395 400

Gly Glu Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln Ile Thr Leu  
 405 410 415

# ES 2 534 734 A1

Asp Phe Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr Pro Ser Asp  
 420 425 430

Val Glu Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro Pro Gly Val  
 435 440 445

Arg Asp Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr Arg Pro Asn  
 450 455 460

Arg Arg Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln Pro Arg Pro  
 465 470 475 480

Ala Pro Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser Gln Leu Ser  
 485 490 495

Leu Leu Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile Met Glu Lys  
 500 505 510

His Ser Met Ser Asn Lys His Gly Trp Thr Trp Ser Val Pro Lys Phe  
 515 520 525

Met Lys Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala Val Phe Gly  
 530 535 540

Val Pro Leu Ile Val His Val Gln Arg Thr Gly Gln Pro Leu Pro Gln  
 545 550 555 560

Ser Ile Gln Gln Ala Leu Arg Tyr Leu Arg Ser Asn Cys Leu Asp Gln  
 565 570 575

Val Gly Leu Phe Arg Lys Ser Gly Val Lys Ser Arg Ile His Ala Leu  
 580 585 590

Arg Gln Met Asn Glu Asn Phe Pro Glu Asn Val Asn Tyr Glu Asp Gln  
 595 600 605

Ser Ala Tyr Asp Val Ala Asp Met Val Lys Gln Phe Phe Arg Asp Leu  
 610 615 620

Pro Glu Pro Leu Phe Thr Asn Lys Leu Ser Glu Thr Phe Leu His Ile  
 625 630 635 640

Tyr Gln Cys Lys Trp Lys  
 645

# ES 2 534 734 A1

<210> 162  
 <211> 687  
 <212> PRT  
 <213> Homo sapiens

<400> 162

Met Leu Glu Pro Ser Ser Val Leu His Ala Asn Val Asn Gln Ala Pro  
 1 5 10 15

Leu Trp Cys Leu Val Leu Arg Trp Cys Arg Glu Cys Lys Asp Thr Val  
 20 25 30

Cys Gly Gly Lys Gln Lys Ser Arg Val Asn His Thr Phe Gln Arg Arg  
 35 40 45

Glu Ile Glu Ala Lys Glu Ala Cys Asp Trp Leu Arg Ala Ala Gly Phe  
 50 55 60

Pro Gln Tyr Ala Gln Leu Tyr Glu Asp Ser Gln Phe Pro Ile Asn Ile  
 65 70 75 80

Val Ala Val Lys Asn Asp His Asp Phe Leu Glu Lys Asp Leu Val Glu  
 85 90 95

Pro Leu Cys Arg Arg Leu Asn Thr Leu Asn Lys Cys Ala Ser Met Lys  
 100 105 110

Leu Asp Val Asn Phe Gln Arg Lys Lys Gly Asp Asp Ser Asp Glu Glu  
 115 120 125

Asp Leu Cys Ile Ser Asn Lys Trp Thr Phe Gln Arg Thr Ser Arg Arg  
 130 135 140

Trp Ser Arg Val Asp Asp Leu Tyr Thr Leu Leu Pro Arg Gly Asp Arg  
 145 150 155 160

Asn Gly Ser Pro Gly Gly Thr Gly Met Arg Asn Thr Thr Ser Ser Glu  
 165 170 175

Ser Val Leu Thr Asp Leu Ser Glu Pro Glu Val Cys Ser Ile His Ser  
 180 185 190

Glu Ser Ser Gly Gly Ser Asp Ser Arg Ser Gln Pro Gly Gln Cys Cys  
 195 200 205

# ES 2 534 734 A1

Thr Asp Asn Pro Val Met Leu Asp Ala Pro Leu Val Ser Ser Ser Leu  
 210 215 220

Pro Gln Pro Pro Arg Asp Val Leu Asn His Pro Phe His Pro Lys Asn  
 225 230 235 240

Glu Lys Pro Thr Arg Ala Arg Ala Lys Ser Phe Leu Lys Arg Met Glu  
 245 250 255

Thr Leu Arg Gly Lys Gly Ala His Gly Arg His Lys Gly Ser Gly Arg  
 260 265 270

Thr Gly Gly Leu Val Ile Ser Gly Pro Met Leu Gln Gln Glu Pro Glu  
 275 280 285

Ser Phe Lys Ala Met Gln Cys Ile Gln Ile Pro Asn Gly Asp Leu Gln  
 290 295 300

Asn Ser Pro Pro Pro Ala Cys Arg Lys Gly Leu Pro Cys Ser Gly Lys  
 305 310 315 320

Ser Ser Gly Glu Ser Ser Pro Ser Glu His Ser Ser Ser Gly Val Ser  
 325 330 335

Thr Pro Cys Leu Lys Glu Arg Lys Cys His Glu Ala Asn Lys Arg Gly  
 340 345 350

Gly Met Tyr Leu Glu Asp Leu Asp Val Leu Ala Gly Thr Ala Leu Pro  
 355 360 365

Asp Ala Gly Asp Gln Ser Arg Met His Glu Phe His Ser Gln Glu Asn  
 370 375 380

Leu Val Val His Ile Pro Lys Asp His Lys Pro Gly Thr Phe Pro Lys  
 385 390 395 400

Ala Leu Ser Ile Glu Ser Leu Ser Pro Thr Asp Ser Ser Asn Gly Val  
 405 410 415

Asn Trp Arg Thr Gly Ser Ile Ser Leu Gly Arg Glu Gln Val Pro Gly  
 420 425 430

Ala Arg Glu Pro Arg Leu Met Ala Ser Cys His Arg Ala Ser Arg Val  
 435 440 445



# ES 2 534 734 A1

Ser Ile Tyr Asp Asn Val Pro Gly Ser His Leu Tyr Ala Ser Thr Gly  
 450 455 460

Asp Leu Leu Asp Leu Glu Lys Asp Asp Leu Phe Pro His Leu Asp Asp  
 465 470 475 480

Ile Leu Gln His Val Asn Gly Leu Gln Glu Val Val Asp Asp Trp Ser  
 485 490 495

Lys Asp Val Leu Pro Glu Leu Gln Thr His Asp Thr Leu Val Gly Glu  
 500 505 510

Pro Gly Leu Ser Thr Phe Pro Ser Pro Asn Gln Ile Thr Leu Asp Phe  
 515 520 525

Glu Gly Asn Ser Val Ser Glu Gly Arg Thr Thr Pro Ser Asp Val Glu  
 530 535 540

Arg Asp Val Thr Ser Leu Asn Glu Ser Glu Pro Pro Gly Val Arg Asp  
 545 550 555 560

Arg Arg Asp Ser Gly Val Gly Ala Ser Leu Thr Arg Pro Asn Arg Arg  
 565 570 575

Leu Arg Trp Asn Ser Phe Gln Leu Ser His Gln Pro Arg Pro Ala Pro  
 580 585 590

Ala Ser Pro His Ile Ser Ser Gln Thr Ala Ser Gln Leu Ser Leu Leu  
 595 600 605

Gln Arg Phe Ser Leu Leu Arg Leu Thr Ala Ile Met Glu Lys His Ser  
 610 615 620

Met Ser Asn Lys His Gly Trp Thr Trp Ser Val Pro Lys Phe Met Lys  
 625 630 635 640

Arg Met Lys Val Pro Asp Tyr Lys Asp Lys Ala Val Phe Gly Val Pro  
 645 650 655

Leu Ile Val His Val Gln Arg Thr Gly Gln Pro Leu Pro Gln Ser Ile  
 660 665 670

Gln Gln Ala Leu Arg Tyr Leu Arg Ser Asn Cys Leu Asp Gln Glu  
 675 680 685

# ES 2 534 734 A1

<210> 163  
 <211> 1591  
 <212> PRT  
 <213> Homo sapiens

<400> 163

Met Lys Leu Tyr Val Phe Leu Val Asn Thr Gly Thr Thr Leu Thr Phe  
 1 5 10 15

Asp Thr Glu Leu Thr Val Gln Thr Val Ala Asp Leu Lys His Ala Ile  
 20 25 30

Gln Ser Lys Tyr Lys Ile Ala Ile Gln His Gln Val Leu Val Val Asn  
 35 40 45

Gly Gly Glu Cys Met Ala Ala Asp Arg Arg Val Cys Thr Tyr Ser Ala  
 50 55 60

Gly Thr Asp Thr Asn Pro Ile Phe Leu Phe Asn Lys Glu Met Ile Leu  
 65 70 75 80

Cys Asp Arg Pro Pro Ala Ile Pro Lys Thr Thr Phe Ser Thr Glu Asn  
 85 90 95

Asp Met Glu Ile Lys Val Glu Glu Ser Leu Met Met Pro Ala Val Phe  
 100 105 110

His Thr Val Ala Ser Arg Thr Gln Leu Ala Leu Glu Met Tyr Glu Val  
 115 120 125

Ala Lys Lys Leu Cys Ser Phe Cys Glu Gly Leu Val His Asp Glu His  
 130 135 140

Leu Gln His Gln Gly Trp Ala Ala Ile Met Ala Asn Leu Glu Asp Cys  
 145 150 155 160

Ser Asn Ser Tyr Gln Lys Leu Leu Phe Lys Phe Glu Ser Ile Tyr Ser  
 165 170 175

Asn Tyr Leu Gln Ser Ile Glu Asp Ile Lys Leu Lys Leu Thr His Leu  
 180 185 190

Gly Thr Ala Val Ser Val Met Ala Lys Ile Pro Leu Leu Glu Cys Leu  
 195 200 205

# ES 2 534 734 A1

Thr Arg His Ser Tyr Arg Glu Cys Leu Gly Arg Leu Asp Ser Leu Pro  
 210 215 220

Glu His Glu Asp Ser Glu Lys Ala Glu Met Lys Arg Ser Thr Glu Leu  
 225 230 235 240

Val Leu Ser Pro Asp Met Pro Arg Thr Thr Asn Glu Ser Leu Leu Thr  
 245 250 255

Ser Phe Pro Lys Ser Val Glu His Val Ser Pro Asp Thr Ala Asp Ala  
 260 265 270

Glu Ser Gly Lys Glu Ile Arg Glu Ser Cys Gln Ser Thr Val His Gln  
 275 280 285

Gln Asp Glu Thr Thr Ile Asp Thr Lys Asp Gly Asp Leu Pro Phe Phe  
 290 295 300

Asn Val Ser Leu Leu Asp Trp Ile Asn Val Gln Asp Arg Pro Asn Asp  
 305 310 315 320

Val Glu Ser Leu Val Arg Lys Cys Phe Asp Ser Met Ser Arg Leu Asp  
 325 330 335

Pro Arg Ile Ile Arg Pro Phe Ile Ala Glu Cys Arg Gln Thr Ile Ala  
 340 345 350

Lys Leu Asp Asn Gln Asn Met Lys Ala Ile Lys Gly Leu Glu Asp Arg  
 355 360 365

Leu Tyr Ala Leu Asp Gln Met Ile Ala Ser Cys Gly Arg Leu Val Asn  
 370 375 380

Glu Gln Lys Glu Leu Ala Gln Gly Phe Leu Ala Asn Gln Lys Arg Ala  
 385 390 395 400

Glu Asn Leu Lys Asp Ala Ser Val Leu Pro Asp Leu Cys Leu Ser His  
 405 410 415

Ala Asn Gln Leu Met Ile Met Leu Gln Asn His Arg Lys Leu Leu Asp  
 420 425 430

Ile Lys Gln Lys Cys Thr Thr Ala Lys Gln Glu Leu Ala Asn Asn Leu  
 435 440 445

# ES 2 534 734 A1

His Val Arg Leu Lys Trp Cys Cys Phe Val Met Leu His Ala Asp Gln  
 450 455 460

Asp Gly Glu Lys Leu Gln Ala Leu Leu Arg Leu Val Ile Glu Leu Leu  
 465 470 475 480

Glu Arg Val Lys Ile Val Glu Ala Leu Ser Thr Val Pro Gln Met Tyr  
 485 490 495

Cys Leu Ala Val Val Glu Val Val Arg Arg Lys Met Phe Ile Lys His  
 500 505 510

Tyr Arg Glu Trp Ala Gly Ala Leu Val Lys Asp Gly Lys Arg Leu Tyr  
 515 520 525

Glu Ala Glu Lys Ser Lys Arg Glu Ser Phe Gly Lys Leu Phe Arg Lys  
 530 535 540

Ser Phe Leu Arg Asn Arg Leu Phe Arg Gly Leu Asp Ser Trp Pro Pro  
 545 550 555 560

Ser Phe Cys Thr Gln Lys Pro Arg Lys Phe Asp Cys Glu Leu Pro Asp  
 565 570 575

Ile Ser Leu Lys Asp Leu Gln Phe Leu Gln Ser Phe Cys Pro Ser Glu  
 580 585 590

Val Gln Pro Phe Leu Arg Val Pro Leu Leu Cys Asp Phe Glu Pro Leu  
 595 600 605

His Gln His Val Leu Ala Leu His Asn Leu Val Lys Ala Ala Gln Ser  
 610 615 620

Leu Asp Glu Met Ser Gln Thr Ile Thr Asp Leu Leu Ser Glu Gln Lys  
 625 630 635 640

Ala Ser Val Ser Gln Thr Ser Pro Gln Ser Ala Ser Ser Pro Arg Met  
 645 650 655

Glu Ser Thr Ala Gly Ile Thr Thr Thr Thr Ser Pro Arg Thr Pro Pro  
 660 665 670

Pro Leu Thr Val Gln Asp Pro Leu Cys Pro Ala Val Cys Pro Leu Glu  
 675 680 685

# ES 2 534 734 A1

Glu Leu Ser Pro Asp Ser Ile Asp Ala His Thr Phe Asp Phe Glu Thr  
 690 695 700

Ile Pro His Pro Asn Ile Glu Gln Thr Ile His Gln Val Ser Leu Asp  
 705 710 715 720

Leu Asp Ser Leu Ala Glu Ser Pro Glu Ser Asp Phe Met Ser Ala Val  
 725 730 735

Asn Glu Phe Val Ile Glu Glu Asn Leu Ser Ser Pro Asn Pro Ile Ser  
 740 745 750

Asp Pro Gln Ser Pro Glu Met Met Val Glu Ser Leu Tyr Ser Ser Val  
 755 760 765

Ile Asn Ala Ile Asp Ser Arg Arg Met Gln Asp Thr Asn Val Cys Gly  
 770 775 780

Lys Glu Asp Phe Gly Asp His Thr Ser Leu Asn Val Gln Leu Glu Arg  
 785 790 795 800

Cys Arg Val Val Ala Gln Asp Ser His Phe Ser Ile Gln Thr Ile Lys  
 805 810 815

Glu Asp Leu Cys His Phe Arg Thr Phe Val Gln Lys Glu Gln Cys Asp  
 820 825 830

Phe Ser Asn Ser Leu Lys Cys Thr Ala Val Glu Ile Arg Asn Ile Ile  
 835 840 845

Glu Lys Val Lys Cys Ser Leu Glu Ile Thr Leu Lys Glu Lys His Gln  
 850 855 860

Lys Glu Leu Leu Ser Leu Lys Asn Glu Tyr Glu Gly Lys Leu Asp Gly  
 865 870 875 880

Leu Ile Lys Glu Thr Glu Glu Asn Glu Asn Lys Ile Lys Lys Leu Lys  
 885 890 895

Gly Glu Leu Val Cys Leu Glu Glu Val Leu Gln Asn Lys Asp Asn Glu  
 900 905 910

Phe Ala Leu Val Lys His Glu Lys Glu Ala Val Ile Cys Leu Gln Asn  
 915 920 925

# ES 2 534 734 A1

Glu Lys Asp Gln Lys Leu Leu Glu Met Glu Asn Ile Met His Ser Gln  
 930 935 940

Asn Cys Glu Ile Lys Glu Leu Lys Gln Ser Arg Glu Ile Val Leu Glu  
 945 950 955 960

Asp Leu Lys Lys Leu His Val Glu Asn Asp Glu Lys Leu Gln Leu Leu  
 965 970 975

Arg Ala Glu Leu Gln Ser Leu Glu Gln Ser His Leu Lys Glu Leu Glu  
 980 985 990

Asp Thr Leu Gln Val Arg His Ile Gln Glu Phe Glu Lys Val Met Thr  
 995 1000 1005

Asp His Arg Val Ser Leu Glu Glu Leu Lys Lys Glu Asn Gln Gln  
 1010 1015 1020

Ile Ile Asn Gln Ile Gln Glu Ser His Ala Glu Ile Ile Gln Glu  
 1025 1030 1035

Lys Glu Lys Gln Leu Gln Glu Leu Lys Leu Lys Val Ser Asp Leu  
 1040 1045 1050

Ser Asp Thr Arg Cys Lys Leu Glu Val Glu Leu Ala Leu Lys Glu  
 1055 1060 1065

Ala Glu Thr Asp Glu Ile Lys Ile Leu Leu Glu Glu Ser Arg Ala  
 1070 1075 1080

Gln Gln Lys Glu Thr Leu Lys Ser Leu Leu Glu Gln Glu Thr Glu  
 1085 1090 1095

Asn Leu Arg Thr Glu Ile Ser Lys Leu Asn Gln Lys Ile Gln Asp  
 1100 1105 1110

Asn Asn Glu Asn Tyr Gln Val Gly Leu Ala Glu Leu Arg Thr Leu  
 1115 1120 1125

Met Thr Ile Glu Lys Asp Gln Cys Ile Ser Glu Leu Ile Ser Arg  
 1130 1135 1140

His Glu Glu Glu Ser Asn Ile Leu Lys Ala Glu Leu Asn Lys Val  
 1145 1150 1155

# ES 2 534 734 A1

Thr	Ser	Leu	His	Asn	Gln	Ala	Phe	Glu	Ile	Glu	Lys	Asn	Leu	Lys
	1160					1165					1170			
Glu	Gln	Ile	Ile	Glu	Leu	Gln	Ser	Lys	Leu	Asp	Ser	Glu	Leu	Ser
	1175					1180					1185			
Ala	Leu	Glu	Arg	Gln	Lys	Asp	Glu	Lys	Ile	Thr	Gln	Gln	Glu	Glu
	1190					1195					1200			
Lys	Tyr	Glu	Ala	Ile	Ile	Gln	Asn	Leu	Glu	Lys	Asp	Arg	Gln	Lys
	1205					1210					1215			
Leu	Val	Ser	Ser	Gln	Glu	Gln	Asp	Arg	Glu	Gln	Leu	Ile	Gln	Lys
	1220					1225					1230			
Leu	Asn	Cys	Glu	Lys	Asp	Glu	Ala	Ile	Gln	Thr	Ala	Leu	Lys	Glu
	1235					1240					1245			
Phe	Lys	Leu	Glu	Arg	Glu	Val	Val	Glu	Lys	Glu	Leu	Leu	Glu	Lys
	1250					1255					1260			
Val	Lys	His	Leu	Glu	Asn	Gln	Ile	Ala	Lys	Ser	Pro	Ala	Ile	Asp
	1265					1270					1275			
Ser	Thr	Arg	Gly	Asp	Ser	Ser	Ser	Leu	Val	Ala	Glu	Leu	Gln	Glu
	1280					1285					1290			
Lys	Leu	Gln	Glu	Glu	Lys	Ala	Lys	Phe	Leu	Glu	Gln	Leu	Glu	Glu
	1295					1300					1305			
Gln	Glu	Lys	Arg	Lys	Asn	Glu	Glu	Met	Gln	Asn	Val	Arg	Thr	Ser
	1310					1315					1320			
Leu	Ile	Ala	Glu	Gln	Gln	Thr	Asn	Phe	Asn	Thr	Val	Leu	Thr	Arg
	1325					1330					1335			
Glu	Lys	Met	Arg	Lys	Glu	Asn	Ile	Ile	Asn	Asp	Leu	Ser	Asp	Lys
	1340					1345					1350			
Leu	Lys	Ser	Thr	Met	Gln	Gln	Gln	Glu	Arg	Asp	Lys	Asp	Leu	Ile
	1355					1360					1365			
Glu	Ser	Leu	Ser	Glu	Asp	Arg	Ala	Arg	Leu	Leu	Glu	Glu	Lys	Lys
	1370					1375					1380			

## ES 2 534 734 A1

Lys Leu Glu Glu Glu Val Ser Lys Leu Arg Ser Ser Ser Phe Val  
 1385 1390 1395

Pro Ser Pro Tyr Val Ala Thr Ala Pro Glu Leu Tyr Gly Ala Cys  
 1400 1405 1410

Ala Pro Glu Leu Pro Gly Glu Ser Asp Arg Ser Ala Val Glu Thr  
 1415 1420 1425

Ala Asp Glu Gly Arg Val Asp Ser Ala Met Glu Thr Ser Met Met  
 1430 1435 1440

Ser Val Gln Glu Asn Ile His Met Leu Ser Glu Glu Lys Gln Arg  
 1445 1450 1455

Ile Met Leu Leu Glu Arg Thr Leu Gln Leu Lys Glu Glu Glu Asn  
 1460 1465 1470

Lys Arg Leu Asn Gln Arg Leu Met Ser Gln Ser Met Ser Ser Val  
 1475 1480 1485

Ser Ser Arg His Ser Glu Lys Ile Ala Ile Arg Asp Phe Gln Val  
 1490 1495 1500

Gly Asp Leu Val Leu Ile Ile Leu Asp Glu Arg His Asp Asn Tyr  
 1505 1510 1515

Val Leu Phe Thr Val Ser Pro Thr Leu Tyr Phe Leu His Ser Glu  
 1520 1525 1530

Ser Leu Pro Ala Leu Asp Leu Lys Pro Ala Ser Gly Ala Ser Arg  
 1535 1540 1545

Arg Pro Trp Val Leu Gly Lys Val Met Glu Lys Glu Tyr Cys Gln  
 1550 1555 1560

Ala Lys Lys Ala Gln Asn Arg Phe Lys Val Pro Leu Gly Thr Lys  
 1565 1570 1575

Phe Tyr Arg Val Lys Ala Val Ser Trp Asn Lys Lys Val  
 1580 1585 1590

<210> 164  
 <211> 1594



ES 2 534 734 A1

<212> PRT

<213> Homo sapiens

<400> 164

Met Lys Leu Tyr Val Phe Leu Val Asn Thr Gly Thr Thr Leu Thr Phe  
1 5 10 15

Asp Thr Glu Leu Thr Val Gln Thr Val Ala Asp Leu Lys His Ala Ile  
20 25 30

Gln Ser Lys Tyr Lys Ile Ala Ile Gln His Gln Val Leu Val Val Asn  
35 40 45

Gly Gly Glu Cys Met Ala Ala Asp Arg Arg Val Cys Thr Tyr Ser Ala  
50 55 60

Gly Thr Asp Thr Asn Pro Ile Phe Leu Phe Asn Lys Glu Met Ile Leu  
65 70 75 80

Cys Asp Arg Pro Pro Ala Ile Pro Lys Thr Thr Phe Ser Thr Glu Asn  
85 90 95

Asp Met Glu Ile Lys Val Glu Glu Ser Leu Met Met Pro Ala Val Phe  
100 105 110

His Thr Val Ala Ser Arg Thr Gln Leu Ala Leu Glu Met Tyr Glu Val  
115 120 125

Ala Lys Lys Leu Cys Ser Phe Cys Glu Gly Leu Val His Asp Glu His  
130 135 140

Leu Gln His Gln Gly Trp Ala Ala Ile Met Ala Asn Leu Glu Asp Cys  
145 150 155 160

Ser Asn Ser Tyr Gln Lys Leu Leu Phe Lys Phe Glu Ser Ile Tyr Ser  
165 170 175

Asn Tyr Leu Gln Ser Ile Glu Asp Ile Lys Leu Lys Leu Thr His Leu  
180 185 190

Gly Thr Ala Val Ser Val Met Ala Lys Ile Pro Leu Leu Glu Cys Leu  
195 200 205

ES 2 534 734 A1

Thr Arg His Ser Tyr Arg Glu Cys Leu Gly Arg Leu Asp Ser Leu Pro  
 210 215 220

Glu His Glu Asp Ser Glu Lys Ala Glu Met Lys Arg Ser Thr Glu Leu  
 225 230 235 240

Val Leu Ser Pro Asp Met Pro Arg Thr Thr Asn Glu Ser Leu Leu Thr  
 245 250 255

Ser Phe Pro Lys Ser Val Glu His Val Ser Pro Asp Thr Ala Asp Ala  
 260 265 270

Glu Ser Gly Lys Glu Ile Arg Glu Ser Cys Gln Ser Thr Val His Gln  
 275 280 285

Gln Asp Glu Thr Thr Ile Asp Thr Lys Asp Gly Asp Leu Pro Phe Phe  
 290 295 300

Asn Val Ser Leu Leu Asp Trp Ile Asn Val Gln Asp Arg Pro Asn Asp  
 305 310 315 320

Val Glu Ser Leu Val Arg Lys Cys Phe Asp Ser Met Ser Arg Leu Asp  
 325 330 335

Pro Arg Ile Ile Arg Pro Phe Ile Ala Glu Cys Arg Gln Thr Ile Ala  
 340 345 350

Lys Leu Asp Asn Gln Asn Met Lys Ala Ile Lys Gly Leu Glu Asp Arg  
 355 360 365

Leu Tyr Ala Leu Asp Gln Met Ile Ala Ser Cys Gly Arg Leu Val Asn  
 370 375 380

Glu Gln Lys Glu Leu Ala Gln Gly Phe Leu Ala Asn Gln Lys Arg Ala  
 385 390 395 400

Glu Asn Leu Lys Asp Ala Ser Val Leu Pro Asp Leu Cys Leu Ser His  
 405 410 415

Ala Asn Gln Leu Met Ile Met Leu Gln Asn His Arg Lys Leu Leu Asp  
 420 425 430

Ile Lys Gln Lys Cys Thr Thr Ala Lys Gln Glu Leu Ala Asn Asn Leu  
 435 440 445

# ES 2 534 734 A1

His Val Arg Leu Lys Trp Cys Cys Phe Val Met Leu His Ala Asp Gln  
 450 455 460

Asp Gly Glu Lys Leu Gln Ala Leu Leu Arg Leu Val Ile Glu Leu Leu  
 465 470 475 480

Glu Arg Val Lys Ile Val Glu Ala Leu Ser Thr Val Pro Gln Met Tyr  
 485 490 495

Cys Leu Ala Val Val Glu Val Val Arg Arg Lys Met Phe Ile Lys His  
 500 505 510

Tyr Arg Glu Trp Ala Gly Ala Leu Val Lys Asp Gly Lys Arg Leu Tyr  
 515 520 525

Glu Ala Glu Lys Ser Lys Arg Glu Ser Phe Gly Lys Leu Phe Arg Lys  
 530 535 540

Ser Phe Leu Arg Asn Arg Leu Phe Arg Gly Leu Asp Ser Trp Pro Pro  
 545 550 555 560

Ser Phe Cys Thr Gln Lys Pro Arg Lys Phe Asp Cys Glu Leu Pro Asp  
 565 570 575

Ile Ser Leu Lys Asp Leu Gln Phe Leu Gln Ser Phe Cys Pro Ser Glu  
 580 585 590

Val Gln Pro Phe Leu Arg Val Pro Leu Leu Cys Asp Phe Glu Pro Leu  
 595 600 605

His Gln His Val Leu Ala Leu His Asn Leu Val Lys Ala Ala Gln Ser  
 610 615 620

Leu Asp Glu Met Ser Gln Thr Ile Thr Asp Leu Leu Ser Glu Gln Lys  
 625 630 635 640

Ala Ser Val Ser Gln Thr Ser Pro Gln Ser Ala Ser Ser Pro Arg Met  
 645 650 655

Glu Ser Thr Ala Gly Ile Thr Thr Thr Thr Ser Pro Arg Thr Pro Pro  
 660 665 670

Pro Leu Thr Val Gln Asp Pro Leu Cys Pro Ala Val Cys Pro Leu Glu  
 675 680 685

# ES 2 534 734 A1

Glu Leu Ser Pro Asp Ser Ile Asp Ala His Thr Phe Asp Phe Glu Thr  
 690 695 700

Ile Pro His Pro Asn Ile Glu Gln Thr Ile His Gln Val Ser Leu Asp  
 705 710 715 720

Leu Asp Ser Leu Ala Glu Ser Pro Glu Ser Asp Phe Met Ser Ala Val  
 725 730 735

Asn Glu Phe Val Ile Glu Glu Asn Leu Ser Ser Pro Asn Pro Ile Ser  
 740 745 750

Asp Pro Gln Ser Pro Glu Met Met Val Glu Ser Leu Tyr Ser Ser Val  
 755 760 765

Ile Asn Ala Ile Asp Ser Arg Arg Met Gln Asp Thr Asn Val Cys Gly  
 770 775 780

Lys Glu Asp Phe Gly Asp His Thr Ser Leu Asn Val Gln Leu Glu Arg  
 785 790 795 800

Cys Arg Val Val Ala Gln Asp Ser His Phe Ser Ile Gln Thr Ile Lys  
 805 810 815

Glu Asp Leu Cys His Phe Arg Thr Phe Val Gln Lys Glu Gln Cys Asp  
 820 825 830

Phe Ser Asn Ser Leu Lys Cys Thr Ala Val Glu Ile Arg Asn Ile Ile  
 835 840 845

Glu Lys Val Lys Cys Ser Leu Glu Ile Thr Leu Lys Glu Lys His Gln  
 850 855 860

Lys Glu Leu Leu Ser Leu Lys Asn Glu Tyr Glu Gly Lys Leu Asp Gly  
 865 870 875 880

Leu Ile Lys Glu Thr Glu Glu Asn Glu Asn Lys Ile Lys Lys Leu Lys  
 885 890 895

Gly Glu Leu Val Cys Leu Glu Glu Val Leu Gln Asn Lys Asp Asn Glu  
 900 905 910

Phe Ala Leu Val Lys His Glu Lys Glu Ala Val Ile Cys Leu Gln Asn  
 915 920 925

# ES 2 534 734 A1

Glu Lys Asp Gln Lys Leu Leu Glu Met Glu Asn Ile Met His Ser Gln  
 930 935 940

Asn Cys Glu Ile Lys Glu Leu Lys Gln Ser Arg Glu Ile Val Leu Glu  
 945 950 955 960

Asp Leu Lys Lys Leu His Val Glu Asn Asp Glu Lys Leu Gln Leu Leu  
 965 970 975

Arg Ala Glu Leu Gln Ser Leu Glu Gln Ser His Leu Lys Glu Leu Glu  
 980 985 990

Asp Thr Leu Gln Val Arg His Ile Gln Glu Phe Glu Lys Val Met Thr  
 995 1000 1005

Asp His Arg Val Ser Leu Glu Glu Leu Lys Lys Glu Asn Gln Gln  
 1010 1015 1020

Ile Ile Asn Gln Ile Gln Glu Ser His Ala Glu Ile Ile Gln Glu  
 1025 1030 1035

Lys Glu Lys Gln Leu Gln Glu Leu Lys Leu Lys Val Ser Asp Leu  
 1040 1045 1050

Ser Asp Thr Arg Cys Lys Leu Glu Val Glu Leu Ala Leu Lys Glu  
 1055 1060 1065

Ala Glu Thr Asp Glu Ile Lys Ile Leu Leu Glu Glu Ser Arg Ala  
 1070 1075 1080

Gln Gln Lys Glu Thr Leu Lys Ser Leu Leu Glu Gln Glu Thr Glu  
 1085 1090 1095

Asn Leu Arg Thr Glu Ile Ser Lys Leu Asn Gln Lys Ile Gln Asp  
 1100 1105 1110

Asn Asn Glu Asn Tyr Gln Val Gly Leu Ala Glu Leu Arg Thr Leu  
 1115 1120 1125

Met Thr Ile Glu Lys Asp Gln Cys Ile Ser Glu Leu Ile Ser Arg  
 1130 1135 1140

His Glu Glu Glu Ser Asn Ile Leu Lys Ala Glu Leu Asn Lys Val  
 1145 1150 1155

## ES 2 534 734 A1

Thr	Ser	Leu	His	Asn	Gln	Ala	Phe	Glu	Ile	Glu	Lys	Asn	Leu	Lys
	1160					1165					1170			
Glu	Gln	Ile	Ile	Glu	Leu	Gln	Ser	Lys	Leu	Asp	Ser	Glu	Leu	Ser
	1175					1180					1185			
Ala	Leu	Glu	Arg	Gln	Lys	Asp	Glu	Lys	Ile	Thr	Gln	Gln	Glu	Glu
	1190					1195					1200			
Lys	Tyr	Glu	Ala	Ile	Ile	Gln	Asn	Leu	Glu	Lys	Asp	Arg	Gln	Lys
	1205					1210					1215			
Leu	Val	Ser	Ser	Gln	Glu	Gln	Asp	Arg	Glu	Gln	Leu	Ile	Gln	Lys
	1220					1225					1230			
Leu	Asn	Cys	Glu	Lys	Asp	Glu	Ala	Ile	Gln	Thr	Ala	Leu	Lys	Glu
	1235					1240					1245			
Phe	Lys	Leu	Glu	Arg	Glu	Val	Val	Glu	Lys	Glu	Leu	Leu	Glu	Lys
	1250					1255					1260			
Val	Lys	His	Leu	Glu	Asn	Gln	Ile	Ala	Lys	Ser	Pro	Ala	Ile	Asp
	1265					1270					1275			
Ser	Thr	Arg	Gly	Asp	Ser	Ser	Ser	Leu	Val	Ala	Glu	Leu	Gln	Glu
	1280					1285					1290			
Lys	Leu	Gln	Glu	Glu	Lys	Ala	Lys	Phe	Leu	Glu	Gln	Leu	Glu	Glu
	1295					1300					1305			
Gln	Glu	Lys	Arg	Lys	Asn	Glu	Glu	Met	Gln	Asn	Val	Arg	Thr	Ser
	1310					1315					1320			
Leu	Ile	Ala	Glu	Gln	Gln	Thr	Asn	Phe	Asn	Thr	Val	Leu	Thr	Arg
	1325					1330					1335			
Glu	Lys	Met	Arg	Lys	Glu	Asn	Ile	Ile	Asn	Asp	Leu	Ser	Asp	Lys
	1340					1345					1350			
Leu	Lys	Ser	Thr	Met	Gln	Gln	Gln	Glu	Arg	Asp	Lys	Asp	Leu	Ile
	1355					1360					1365			
Glu	Ser	Leu	Ser	Glu	Asp	Arg	Ala	Arg	Leu	Leu	Glu	Glu	Lys	Lys
	1370					1375					1380			

## ES 2 534 734 A1

Lys Leu Glu Glu Glu Val Ser Lys Leu Arg Ser Ser Ser Phe Val  
 1385 1390 1395

Pro Ser Pro Tyr Val Ala Thr Ala Pro Glu Leu Tyr Gly Ala Cys  
 1400 1405 1410

Ala Pro Glu Leu Pro Gly Glu Ser Asp Arg Ser Ala Val Glu Thr  
 1415 1420 1425

Ala Asp Glu Gly Arg Val Asp Ser Ala Met Glu Thr Ser Met Met  
 1430 1435 1440

Ser Val Gln Glu Asn Ile His Met Leu Ser Glu Glu Lys Gln Arg  
 1445 1450 1455

Ile Met Leu Leu Glu Arg Thr Leu Gln Leu Lys Glu Glu Glu Asn  
 1460 1465 1470

Lys Arg Leu Asn Gln Arg Leu Met Ser Gln Ser Met Ser Ser Val  
 1475 1480 1485

Ser Ser Arg His Ser Glu Lys Ile Ala Ile Arg Asp Phe Gln Val  
 1490 1495 1500

Gly Asp Leu Val Leu Ile Ile Leu Asp Glu Arg His Asp Asn Tyr  
 1505 1510 1515

Val Leu Phe Thr Val Ser Pro Thr Leu Tyr Phe Leu His Ser Glu  
 1520 1525 1530

Ser Leu Pro Ala Leu Asp Leu Lys Pro Gly Glu Gly Ala Ser Gly  
 1535 1540 1545

Ala Ser Arg Arg Pro Trp Val Leu Gly Lys Val Met Glu Lys Glu  
 1550 1555 1560

Tyr Cys Gln Ala Lys Lys Ala Gln Asn Arg Phe Lys Val Pro Leu  
 1565 1570 1575

Gly Thr Lys Phe Tyr Arg Val Lys Ala Val Ser Trp Asn Lys Lys  
 1580 1585 1590

Val