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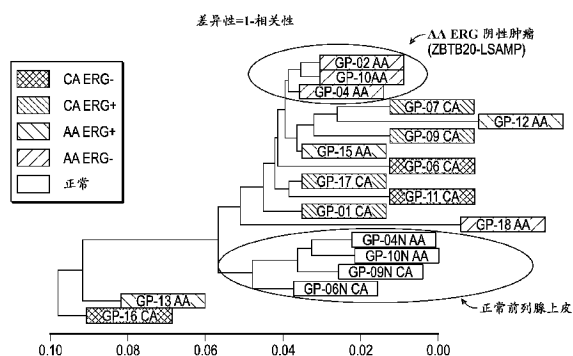
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(54)发明名称

前列腺癌基因谱和使用所述基因谱的方法

(57)摘要

本公开内容提供与前列腺癌有关的基因表达谱,包括区分非洲和高加索血统受试者的某些基因表达谱和对非洲和高加索血统两种受试者是共同的其它基因表达谱。基因表达谱可在核酸或蛋白质水平上进行测量,并可用于根据种族性或前列腺癌的严重程度或侵袭性对前列腺癌进行分层。基因表达谱也可用来鉴定适于前列腺癌治疗的受试者。还提供用于诊断和预测前列腺癌的试剂盒和包含用于检测与非洲或高加索血统受试者的前列腺癌有关的独特基因表达谱的探针的阵列。



1. 一种收集数据用于诊断或预测患者的前列腺癌的方法,所述方法包括:

a) 检测获自患者的生物样品中多个基因的表达,其中所述患者具有非洲血统,且其中因为所述患者具有非洲血统而选择所述多个基因,并且所述多个基因包含下列基因中的至少3个:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1;

b) 检测获自患者的生物样品中多个基因的表达,其中所述患者具有高加索血统,且其中因为所述患者具有高加索血统而选择所述多个基因,并且所述多个基因包含下列基因中的至少4个:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN;或

c) 检测获自患者的生物样品中多个基因的表达,其中所述多个基因包含下列基因中的至少4个:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4。

2. 权利要求1的方法,所述方法进一步包括利用获自步骤a)、步骤b)或步骤c)的表达数据诊断或预测前列腺癌的步骤。

3. 权利要求2的方法,其中与对照样品或阈值相比,1) 下列基因的至少3个:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1;2) 下列基因的至少4个:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3;或3) 下列基因的至少4个的过量表达:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4,表明生物样品中前列腺癌的存在或发生前列腺癌的风险增加。

4. 权利要求1-3中任一项的方法,所述方法进一步包括检测生物样品中ERG基因的表达。

5. 权利要求1-4中任一项的方法,其中所述生物样品是组织样品、细胞样品、血液样品、血清样品或尿液样品。

6. 权利要求1-5中任一项的方法,其中所述生物样品包含前列腺细胞或从前列腺细胞分离的核酸或多肽。

7. 权利要求1-6中任一项的方法,其中在步骤a)、b)或c)中检测核酸表达。

8. 权利要求1-7中任一项的方法,其中在步骤a)、b)或c)中检测多肽表达。

9. 一种用于诊断或预测前列腺癌的试剂盒,所述试剂盒包含多种探针用于检测下列基因的至少3个:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1,其中所述多种探针含有用于检测不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2个不同基因的探针。

10. 一种用于诊断或预测前列腺癌的试剂盒,所述试剂盒包含多种探针用于检测下列基因的至少4个:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3,其中所述多种探针含有用于检测不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2个不同基因的探针。

11. 一种用于诊断或预测前列腺癌的试剂盒,所述试剂盒包含多种探针用于检测下列基因的至少4个:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4,其中所述多种探针含有用于检测不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2个不同基因的探针。

12. 权利要求9-11中任一项的试剂盒,其中所述多种探针选自多种寡核苷酸探针、多种抗体或多种多肽探针。

13. 权利要求9-12中任一项的试剂盒,其中所述多种探针含有用于检测不超过250、

100、50、25、15、10或5个不同基因的探针。

14. 权利要求9-13中任一项的试剂盒,其中所述多种探针与阵列的表面连接。

15. 权利要求14的试剂盒,其中所述阵列包含不超过500、250、100、50、25、15或10个可寻址元件。

16. 权利要求9-15中任一项的试剂盒,其中所述多种探针被标记。

17. 权利要求9-16中任一项的试剂盒,其中所述多种探针另包含用于检测ERG基因的探针。

18. 一种获得生物样品中的基因表达谱的方法,所述方法包括:

a) 使权利要求14或15的阵列与生物样品一起温育,其中所述生物样品获自非洲血统患者;和

b) 测量下列基因的至少3个的表达水平:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1以获得基因表达谱。

19. 一种获得生物样品中的基因表达谱的方法,所述方法包括:

a) 使权利要求14或15的阵列与生物样品一起温育,其中所述生物样品获自高加索血统患者;和

b) 测量下列基因的至少4个的表达水平:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3以获得基因表达谱。

20. 一种获得生物样品中的基因表达谱的方法,所述方法包括:

a) 使权利要求14或15的阵列与生物样品一起温育;和

b) 测量下列基因的至少4个的表达水平:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4以获得基因表达谱。

21. 权利要求18-20中任一项的方法,其中所述生物样品是组织样品、细胞样品、血液样品、血清样品或尿液样品。

22. 权利要求18-21中任一项的方法,其中所述生物样品包含从前列腺细胞分离的核酸或多肽。

23. 权利要求18-22中任一项的方法,其中所述测量步骤包括测量核酸表达水平。

24. 权利要求18-22中任一项的方法,其中所述测量步骤包括测量多肽表达水平。

25. 权利要求18-24中任一项的方法,其中所述测量步骤进一步包括测量ERG基因的表达水平。

26. 一种鉴定需要前列腺癌治疗的患者的方法,其中所述患者具有非洲血统,所述方法包括:

a) 测试患者生物样品的多个基因的过量表达,其中因为所述患者具有非洲血统而选择所述多个基因,并且所述多个基因包含下列基因的至少3个:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1;和

b) 如果与对照样品或阈值相比,生物样品中COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1基因的一个或多个过量表达,则鉴定患者为需要前列腺癌治疗。

27. 权利要求26的方法,如果患者鉴定为需要前列腺癌治疗,则所述方法进一步包括治疗患者的步骤。

28. 一种鉴定需要前列腺癌治疗的患者的方法,其中所述患者具有高加索血统,所述

方法包括：

a) 测试患者生物样品的多个基因的过量表达,其中因为所述患者具有高加索血统而选择所述多个基因,并且所述多个基因包含下列基因的至少4个:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3;和

b) 如果与对照样品或阈值相比,生物样品中PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3基因的一个或多个过量表达,则鉴定患者为需要前列腺癌治疗。

29. 权利要求28的方法,如果患者鉴定为需要前列腺癌治疗,则所述方法进一步包括治疗患者的步骤。

30. 一种治疗患者的前列腺癌的方法,其中所述患者具有非洲血统,所述方法包括:

a) 测试患者生物样品的多个基因的表达,其中因为所述患者具有非洲血统而选择所述多个基因,并且所述多个基因包含下列基因的至少3个:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1;

b) 如果步骤a)中的测试显示与对照样品或阈值相比患者过量表达下列基因的一个或多个,则对患者进行治疗:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1。

31. 一种治疗患者的前列腺癌的方法,其中所述患者具有高加索血统,所述方法包括:

a) 测试患者生物样品的多个基因的表达,其中因为所述患者具有高加索血统而选择所述多个基因,并且所述多个基因包含下列基因的至少4个:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3;

b) 如果步骤a)中的测试显示与对照样品或阈值相比患者过量表达下列基因的一个或多个,则对患者进行治疗:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3。

32. 权利要求28-31中任一项的方法,所述方法进一步包括测试生物样品的ERG基因的表达。

33. 权利要求1-8中任一项的方法,其中所述多个基因由不超过100、90、80、70、60、50、40、30、25、20、15、14、13、12、11、10、9、8、7、6、5、4、3或2个基因组成。

34. 权利要求1-8或18-33中任一项的方法,其中所述方法是计算机执行方法。

前列腺癌基因谱和使用所述基因谱的方法

[0001] 相关申请的交叉引用

本申请要求2013年12月30日提交的美国临时专利申请号61/921,739的权益,并依赖于其提交日期,其整个内容通过引用结合到本申请中。

[0002] 政府利益

本发明部分地在政府支持下完成。政府在本发明中享有一定权益。

[0003] 序列表

本申请含有电子提交的ASCII格式的序列表,并通过引用以其整体结合到本文中。2014年12月29日创建的所述ASCII副本名为HMJ-145-PCT_SL.txt,大小为344,410字节。

[0004] 发明背景

到2013年,估计238,590名男性将被诊断为前列腺癌(CaP),并估计29,720名男性将死于该疾病[1]。这种恶性肿瘤是美国男性癌症相关死亡的第二主要原因。另外,与其它人种相比,非裔美国(AA)男性具有因CaP所致的最高发病率和死亡率[1]。从表现和诊断到治疗、生存和生命质量,都存在人种差异[2]。研究人员提出社会经济地位(SES)对包括CaP特异性死亡率在内的这些差异产生显著影响[3]。同样,有证据显示,获得护理的机会减少与CaP结局差有关,所述结局差在AA男性中比在高加索美国(CA)男性中更普遍[4]。

[0005] 然而,存在其中AA男性具有与CA男性类似的结局的群体。Sridhar和同事[5]发表了元分析,其中他们得出结论,当说明SES时,在AA和CA男性之间在总体生存和CaP特异性生存方面没有差异。类似地,军人和退伍军人群体(同样的访问和筛选系统)在种族间在生存方面未观察到差异[6],且到2000年代早期在退伍军人组群中在诊断时病理期的差异缩小[7]。值得注意的是,这两项研究表明,与CA男性相比,AA男性更可能具有较高的Gleason评分和PSA水平[6,7]。

[0006] 虽然社会经济因素可能对CaP结局产生影响,但是它们似乎无法说明与诊断和疾病风险有关的所有变量。若干研究支持与CA男性相比AA男性具有较高的CaP发病率[1,8,9]。研究还显示AA男性具有诊断时显著较高的PSA、活组织检查中较高等级的疾病、各阶段较大的肿瘤体积和根治性前列腺切除术前较短的PSA倍增时间[10-12]。在有关应激和炎症反应的肿瘤微环境中注意到CA和AA男性的前列腺癌之间的生物学差异[13]。虽然在生物学差异的作用方面仍有争议,但是所表现的发病率和疾病侵袭性中观察到的差异表明AA和CA男性之间前列腺癌病变的不同途径的潜在作用。

[0007] 在过去十年内,大量研究集中在癌基因的改变及其在CaP中的作用[14-16]。在CaP中过量表达并且是CaP中最普遍已知的癌基因的TMPRSS2/ERG基因融合物中注意到种族性和人种间流行率的变化[17,18]。累计数据表明在种族性间ERG致癌变化有差异[17,19-21]。在描述ERG过量表达和ERG剪接变体的最初的论文中注意到与AA男性相比CA男性中显著较大的ERG表达[17,21]。该差异在有高Gleason等级(8-10)肿瘤的患者中在CA和AA之间甚至更明显(50%与16%)。因此,ERG是这些人种群(ethnic group)间的主要体细胞基因改变。但除TMPRSS2/ERG以外,对有关AA和CA男性间的CaP差异的遗传基础知之甚少,甚至未知[24]。

[0008] 因此,需要对不同种族人群有特异性并提供更准确的诊断和/或预后潜力的新的生物标志物和治疗标志物。因此,可利用非洲和高加索血统患者的单独基因表达谱以诊断或预测不同种族人群中的CaP,并根据这些种族特异性基因表达特性提供更有信息的治疗选择。

[0009] 发明概述

本公开内容提供与前列腺癌有关的基因表达谱和使用所述基因表达谱的方法。可利用基因表达谱检测样品中的前列腺癌细胞或预测患者发生前列腺癌的可能性。基因表达谱也可用来评价前列腺癌的严重程度或病期或评估疗法的有效性或在治疗后监测前列腺癌的进程或消退(例如手术后的无病复发)。可测量核酸或蛋白质水平下的基因表达谱。一方面,基因表达谱是非洲血统患者特有的。另一方面,基因表达谱是高加索血统患者特有的。

[0010] 因此,一方面涉及与非洲血统患者中的前列腺癌有关的基因表达谱,其中基因表达谱包含下列基因的组合:COL10A1、H0XC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1。

[0011] 另一方面涉及与高加索血统患者中的前列腺癌有关的基因表达谱,其中基因表达谱包含下列基因的组合:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN。

[0012] 又一方面涉及代表两个人种群中前列腺癌的最大差异表达基因的基因表达谱,并包括下列基因的组合:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4。在某些实施方案中,基因表达谱至少包含DLX1和NKX2-3。在一个实施方案中,该组合至少包括DLX1和NKX2-3。

[0013] 这些基因谱可用于收集用于诊断或预测前列腺癌的数据的方法,所述方法包括测量已公开的基因谱之一中代表性数目的基因的表达,其中在获自患者的样品中测量基因表达。所收集的基因表达数据可用来预测受试者是否患有前列腺癌或将发生前列腺癌或预测前列腺癌的病期或严重程度。所收集的基因表达数据还可用于知会有关治疗或监测患者的决定。鉴于这些独特基因表达谱的鉴定,本领域技术人员可确定哪一个已鉴定的基因包括在基因谱型分析中。基因的代表性数目可包括列于具体谱中的基因的全部或基因的某些较少数目,例如3或4或更多个。在某些实施方案中,该方法进一步包括检测与前列腺癌有关的一个或多个其它基因的表达,包括但不限于ERG、PSA和PCA3。

[0014] 另一方面涉及用于诊断或预测前列腺癌的试剂盒。在一个实施方案中,试剂盒被设计成用于诊断或预测非洲血统患者的前列腺癌,并包含用于检测下列基因(或由所述基因编码的多肽)的至少1个(优选至少3个)的多种探针:COL10A1、H0XC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1。在某些实施方案中,多种探针选自多种寡核苷酸探针、多种抗体或多种多肽探针。在其它实施方案中,多种探针含有用于不超过500、100、50、25、15、10、9、8、7、6、5、4、3或2个基因(或多肽)的探针。在一个实施方案中,试剂盒进一步包含用于检测与前列腺癌有关的一个或多个其它基因的表达的探针,包括但不限于ERG、PSA和PCA3。

[0015] 在另一个实施方案中,试剂盒被设计成用于诊断或预测高加索血统患者的前列腺癌,并包含用于检测下列基因(或由所述基因编码的多肽)的至少1个(优选至少3个)的多种探针:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN。在某些实施方案中,多种探针选自多种寡核苷酸探针、多种抗体或多种多肽探针。在其它实施方案中,多种探针含有用于不超过500、100、50、25、15、10、9、8、7、6、5、4、3或2个基因(或多肽)的探针。在某些实施方案中,该方法进一步包括检测与前列腺癌有关的一个或多个其它基因的表达,包括但不

限于ERG、PSA和PCA3。

[0016] 在另外又一个实施方案中,用于诊断或预测前列腺癌的试剂盒包含用于检测下列基因(或由所述基因编码的多肽)的至少1个(优选至少4个)的多种探针:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4。在一个实施方案中,所述基因包含DLX1和/或NKX2-3。在某些实施方案中,多种探针选自多种寡核苷酸探针、多种抗体或多种多肽探针。在其它实施方案中,多种探针含有用于不超过500、100、50、25、15、10、9、8、7、6、5、4、3或2个基因(或多肽)的探针。在某些实施方案中,该方法进一步包括检测与前列腺癌有关的一个或多个其它基因的表达,包括但不限于ERG、PSA和PCA3。

[0017] 在相关方面,本公开内容提供用于诊断和/或预测前列腺癌的阵列。在一个实施方案中,阵列包含(a)基质和(b)固定在基质上用于检测下列人基因的至少3个的表达的多种探针:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1。在另一个实施方案中,阵列包含(a)基质和(b)固定在基质上用于检测下列人基因的至少3个的表达的多种探针:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN。在另外又一个实施方案中,阵列包含(a)基质和(b)固定在基质上用于检测下列人基因的至少4个的表达的多种探针:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4。在某些实施方案中,阵列进一步包含用于检测与前列腺癌有关的一个或多个其它基因的表达的探针,包括但不限于ERG、PSA和PCA3。

[0018] 探针优选排列在可寻址元件(addressable element)内的基质上以利于检测。优选阵列包含有限数量的可寻址元件使得将阵列与较综合的阵列(例如基因组阵列等)区分开来。因此,在一个实施方案中,阵列包含500个或更少个可寻址元件。在另一个实施方案中,阵列包含不超过250、100、50或25个可寻址元件。在另一个实施方案中,将不超过1000种多核苷酸探针固定在阵列上。另一方面,本公开内容提供使用本文所述阵列检测生物样品中的基因表达的方法。使用检测基因表达的这些阵列也可以是用于检测或预测生物样品中的前列腺癌的方法的一部分。

[0019] 另一方面,本公开内容提供使用基因表达谱以鉴定需要前列腺癌治疗的方法。在一个实施方案中,患者具有非洲血统,并且所述方法包括a)测试患者生物样品的多个基因的过量表达,其中因为患者具有非洲血统而选择所述多个基因,并且所述多个基因包含下列基因的至少3个:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1;和b)如果与对照样品或阈值相比,生物样品中COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1基因的一个或多个过量表达,则鉴定患者为需要前列腺癌治疗。在另一个实施方案中,患者具有高加索血统,且所述方法包括a)测试患者生物样品的多个基因的过量表达,其中因为患者具有高加索血统而选择所述多个基因,并且所述多个基因包含下列基因的至少4个:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3;和b)如果与对照样品或阈值相比,生物样品中PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3基因的一个或多个过量表达,则鉴定患者为需要前列腺癌治疗。在某些实施方案中,该方法进一步包括检测与前列腺癌有关的一个或多个其它基因的表达,包括但不限于ERG、PSA和PCA3。所述方法还进一步包括治疗患者的步骤。

[0020] 附图简述

并入且构成本说明书的一部分的附图阐明某些实施方案,并且与书面描述一起,用来解释本文公开的抗体和方法的某些原理。

[0021] 图1显示采用平均连锁方法 (average-linkage method) 的14个肿瘤和4个正常样品的分层聚类分析 (hierarchicalclustering analysis,HCA)。HCA揭示正常患者的不同聚类 (GP-04、GP-10、GP-09和GP-06) 和AA、ERG融合阴性患者的另一种不同的聚类 (GP-02、GP-10和GP-04)。聚类基于基因的表达水平。所有组都被彩色编码。

[0022] 图2A是具有14个肿瘤和4个正常样品聚类的热图,其中非裔美籍患者在热图的左侧,CA在热图的右侧。热图中存在的基因是AA和CA患者的过量表达和表达不足基因 (肿瘤与正常) 的重叠。

[0023] 图2B提供在来自AA和CA患者的肿瘤和正常样品两者中最前3种过量表达基因的表达值 ($\log_2$)。

[0024] 图3A是显示在AA患者中始终过量表达且在CA患者中同时表达不足或显示无变化的基因的热图。

[0025] 图3B是显示在CA患者中始终过量表达且在AA患者中同时表达不足或显示无变化的基因的热图。

[0026] 图4显示本发明一些实施方案的系统的示意图。具体地说,该图说明按照所公开的系统和方法可用于计算机系统106执行的各种硬件、软件和其它资源。在所示实施方案中,计算机系统106可包括与在操作系统控制下或与操作系统联合操作的随机存储器连接的一个或多个处理器110。实施方案中的处理器110可包括在一个或多个服务器、群集器或其它计算机或硬件资源中,或可采用基于云的资源执行。操作系统可为例如LinuxTM操作系统、UnixTM操作系统或其它开放源码或专有操作系统或平台的分配。处理器110可与数据存储112 (例如保存在硬盘驱动器或驱动器阵列上的数据库) 通信以访问或保存程序指令或其它数据。

[0027] 处理器110可进一步通过网络接口108通信,网络接口108进而可通过一个或多个网络104 (例如互连网或其它公共或专用网络) 通信,使得可从客户机102或其它装置或服务程序中接受查询或其它要求。另外,处理器110可利用网络接口108通过一个或多个网络104向用户发送信息、指令、工作流查询、部分工作流或其它数据。网络接口104可包括一个或多个服务器或与一个或多个服务器通信连接。客户机102可为例如与互连网连接的个人计算机。

[0028] 一般而言,可对处理器110进行编程或配制以执行实施本文公开的方法的控制逻辑和控制操作。处理器110可与协处理器114进一步通信连接 (即通过通信信道连接)。协处理器114可为经配制以实施本文公开的方法的专用硬件和/或固件部件。因此,可通过处理器110和/或协处理器114实施本文公开的方法。

[0029] 计算机系统106的其它配置、相关网络连接和其它硬件、软件和服务程序资源是可能的。

[0030] 发明详述

下面将详细参考不同的示例性实施方案,在附图中说明了其实例。要了解下面的详细描述为了使读者更全面地理解本发明方面的某些实施方案、特征和详细资料而提供,不应解释为限制本发明的范围。

[0031] 定义

为了更容易地理解本发明,首先定义了某些术语。在整个详细描述中给出了其它定义。

[0032] 术语“非洲血统的”是指自认为具有非洲血统的个人,包括自认为是非洲裔美国人的个人和已确定具有与非洲祖先相关的遗传标记(亦称祖先信息标记(AIM))的个人,所述祖先信息标记例如Judith Kidd等, *Analyses of a set of 128 ancestry informative single-nucleotide polymorphisms in a global set of 119 population samples* (整套119群样品中一套128种提供祖先信息的单核苷酸多态性的分析), *Investigative Genetics*, (2):1, 2011 (所述参考资料通过引用以其整体予以结合)中鉴定的AIM。

[0033] 术语“高加索血统的”是指自认为具有高加索血统的个人,包括自认为是高加索美国人的个人和已确定具有与高加索(例如欧洲、北非或亚洲(西亚、中亚或南亚)祖先相关的遗传标记(亦称祖先信息标记(AIM))的个人,祖先信息标记例如Judith Kidd等, *Analyses of a set of 128 ancestry informative single-nucleotide polymorphisms in a global set of 119 population samples* (整套119群样品中一套128种提供祖先信息的单核苷酸多态性的分析), *Investigative Genetics*, (2):1, 2011 (所述参考资料通过引用以其整体予以结合)中鉴定的AIM。

[0034] 术语“抗体”是指免疫球蛋白或其抗原结合片段,并包括包含抗原结合片段或抗原结合结构域的任何多肽。该术语包括但不限于多克隆、单克隆、单特异性、多特异性、人源化、人、单链、嵌合、合成、重组、杂合、突变、移植和体外产生的抗体。除非之前有措词“完整”,否则术语“抗体”包括抗体片段例如Fab、F(ab')₂、Fv、scFv、Fd、dAb和保留抗原结合功能的其它抗体片段。除非另有说明,否则抗体不必来自任何特殊来源,也不通过任何特殊方法产生。

[0035] 术语“检测”意指本领域已知的用于测定核酸或蛋白质的存在或量的各种方法的任一种。如本说明书中所用,术语“检测”包括定性或定量检测。

[0036] 术语“基因表达谱”是指样品中多个基因的表达水平。如本领域所理解的一样,可通过测量核酸(例如基因组DNA或mRNA)或由核酸编码的多肽的表达,分析基因的表达水平。

[0037] 术语“分离的”当在多肽或核酸的情况下使用时是指其天然环境基本上没有,因此可与可能天然存在的多肽或核酸区分开来的多肽或核酸。例如,分离的多肽或核酸基本上不含细胞物质或其来源于其中的细胞或组织源的其它多肽或核酸。

[0038] 术语“多肽”、“肽”和“蛋白质”在本文可互换使用,是指氨基酸的聚合物。

[0039] 本文所用术语“多肽探针”是指可用于蛋白质检测测定法(例如质谱法)以定量测定生物样品中的目标多肽的标记的(例如同位素标记的)多肽。

[0040] 术语“引物”意指能够与靶核酸的区域或其互补序列结合,并促进靶核酸的核酸扩增的多核苷酸。一般来讲,引物可具有可通过核酸聚合酶延伸的游离3'端。引物一般还包括能够通过直接与靶核酸的至少1条链或与该靶序列互补的链进行互补碱基相互使用而杂交的碱基序列。引物可包含靶标特异性序列和任选不与靶序列互补的其它序列。这些非互补序列可包含例如启动子序列或限制性内切核酸酶识别位点。

[0041] “变异”或“变体”是指在小至单一碱基或较长间隔上不同于参比的等位基因序列。

[0042] 术语“ERG”或“ERG基因”是指Ets相关基因(ERG),其被指定唯一的Hugo Gene Nomenclature Committee (HGNC)标识码:HGNC:3446,并包括在前列腺癌中是普遍的ERG基

因融合产物,包括TMPRSS2-ERG融合产物。分析ERG或ERG基因的表达包括分析与前列腺癌有关的ERG基因融合产物的表达,例如TMPRSS2-ERG。

[0043] 前列腺癌中的基因表达谱

采用下一代测序技术以鉴定CaP的新的生物标志物和治疗靶标。对7名高加索血统患者和7名非洲血统患者(包括各患者的匹配对照的共28个样品)的组群间的获自组织学上确定的和精确解剖的原发CaP样本(80-95%肿瘤,主要Gleason模式3)的高质量基因组序列数据和覆盖度进行了比较,以评价所观察到的2个人种群之间CaP发病率和死亡率的差异。这些数据和提供来自针对临床病理特征匹配的非裔和高加索血统的CaP患者的前列腺癌基因组的第一手评价。

[0044] 两个人种群中CaP的最前面的差异表达基因包括:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4。因此,从生物样品中收集这些基因的至少2、3、4、5、6、7、8、9或10个的表达数据提供唯一的基因表达谱用于诊断或预测受试者的前列腺癌。

[0045] 某些实施方案涉及收集数据用于诊断或预测CaP的方法,所述方法包括检测生物样品中下列基因的至少2、3、4、5、6、7、8、9、10、11、12、13、14或15个的表达:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4。所述方法可任选包括从受试者中获得生物样品的额外步骤。所述方法可任选包括利用所收集的基因表达数据诊断或预测CaP的额外步骤。在一个实施方案中,与对照样品或阈值相比,下列基因的至少2、3、4、5、6、7、8、9、10、11、12、13、14或15个的过量表达:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4,表明生物样品中存在CaP或发生CaP的可能性增加。收集数据或诊断和/或预测CaP的方法可进一步包括检测与前列腺癌有关的其它基因的表达,包括但不限于ERG、PSA和PCA3。在某些实施方案中,所述方法包括检测不超过100、90、80、70、60、50、40、30、25、20、15、14、13、12、11、10、9、8、7、6、5、4、3或2个基因的表达。

[0046] 在一个实施方案中,所述方法包括检测DLX1和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测NKX2-3和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测DLX1和NKX2-3和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测PHGR1和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测THBS4和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测GAP43和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测FFAR2和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测GCNT1和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测SIM2和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测STX19和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测的表达KLB和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测APOF和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测LOC283177和表1所列一个或多个其它基因的表达。在另一个实施方案中,所述方法包括检测TRPM4和表1所列一个或多个其它基因的表达。

[0047] 已知人DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、

STX19、KLB、APOF、LOC283177和TRPM4的核酸和氨基酸序列。表1提供这些基因的由Hugo Gene Nomenclature Committee (HGNC) 和Entrez Gene指定的唯一标识码和代表性序列的登记号,所述序列通过引用以其整体结合到本文中。

[0048] 表1

基因	HGNC ID	Entrez Gene ID	登记号
DLX1	2914	1745	NM_178120.4, GI:84043957
NKX2-3	7836	159296	NM_145285.2 GI:148746210
CRISP3	16904	10321	NM_006061.2 GI:300244559
PHGR1	37226	644844	NM_001145643.1 GI:224548949
THBS4	11788	7060	NM_003248.4 GI:291167798
AMACR	451	23600	NM_014324.5 GI:266456114
GAP43	4140	2596	AK091466.1 GI:21749841
FFAR2	4501	2867	NM_005306.2 GI:227430361
GCNT1	4203	2650	NM_001097634.1 GI:148277030
SIM2	10833	6493	NM_005069.3 GI:194239685
STX19	19300	415117	NM_001001850.2 GI:344313159
KLB	15527	152831	NM_175737.3 GI:198041706
APOF	615	319	BC026257.1 GI:20072209
LOC283177	N/A	283177	AK095081.1 GI:21754271
TRPM4	17993	54795	NM_017636.3 GI:304766649

下列基因被鉴定为与非洲血统患者相比在高加索血统患者的前列腺肿瘤中过量表达: PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3。因此,获得这些基因的至少1、2、3、4、5、6、7或8个的表达数据提供唯一的基因表达谱用于诊断或预测高加索血统患者的前列腺癌。

[0049] 某些实施方案涉及收集数据用于诊断或预测高加索血统患者的CaP的方法,所述方法包括检测生物样品中下列基因的至少1、2、3、4、5、6、7或8个的表达:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3,其中生物样品获自高加索血统患者。所述方法可任选包括获取高加索血统患者的生物样品的额外步骤。所述方法可任选包括利用所收集的基因表达数据诊断或预测CaP的额外步骤。在诊断或预测CaP的方法中,与对照样品或阈值相比,下列基因的至少1、2、3、4、5、6、7或8个的过量表达:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3,表明生物样品中存在CaP或发生CaP的风险增加。收集数据或诊断和/或预测CaP的方法可进一步包括检测与前列腺癌有关的其它基因的表达,包括但不限于ERG、PSA和PCA3。在某些实施方案中,所述方法包括检测的表达不超过100、90、80、70、60、50、40、30、25、20、15、14、13、12、11、10、9、8、7、6、5、4、3或2个基因。

[0050] 在一个实施方案中,所述方法包括检测ALOX15以及PCA3、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3的一个或多个的表达。在另一个实施方案中,所述方法包括检测CDH19以及PCA3、AMACR、ALOX15、OR51E2/PSGR、F5、FZD8和CLDN3的一个或多个的表达。在另一个实施方案中,所述方法包括检测F5以及PCA3、AMACR、ALOX15、OR51E2/PSGR、CDH19、FZD8和CLDN3的一个或多个的表达。在另一个实施方案中,所述方法包括检测FZD8以及PCA3、

AMACR、ALOX15、OR51E2/PSGR、CDH19、F5和CLDN3的一个或多个的表达。在另一个实施方案中,所述方法包括检测CLDN3以及PCA3、AMACR、ALOX15、OR51E2/PSGR、CDH19、F5和FZD8的一个或多个的表达。在另一个实施方案中,所述方法包括检测PCA3以及AMACR和ALOX15、CDH19、F5、FZD8和CLDN3的一个或多个的表达。

[0051] 表2提供在高加索血统患者中更频繁地过量表达的这些基因的HGNC和Entrez Gene指定的唯一标识码和代表性序列的登记号,所述序列通过引用以其整体结合到本文中。

[0052] 表2

基因	HGNC ID	Entrez Gene ID	NCBI参考
PCA3	8637	50652	AF103907.1 GI:6165973
ALOX15	433	246	NM_001140.3 GI:40316936
AMACR	451	23600	NM_014324.5 GI:266456114
CDH19	1758	28513	NM_021153.3 GI:402534572
OR51E2/PSGR	15195	81285	AY033942.1 GI:16943640
F5	3542	2153	NM_000130.4 GI:119395710
FZD8	4046	8325	AB043703.1 GI:13623798
CLDN3	2045	1365	NM_001306.3 GI:171541813

下列基因被鉴定为与高加索血统患者相比在非洲世系患者的前列腺肿瘤中过量表达:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1。因此,获得这些基因的至少1、2、3、4、5、6或7个的表达数据提供唯一的基因表达谱用于诊断或预测非洲血统患者的前列腺癌。

[0053] 某些实施方案涉及收集数据用于诊断或预测非洲血统患者的CaP的方法,所述方法包括检测生物样品中下列基因的至少1、2、3、4、5、6或7个的表达:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1,其中生物样品获自非洲血统患者。所述方法可任选包括获得非洲血统患者的生物样品的额外步骤。所述方法可任选包括利用所收集的基因表达数据诊断或预测CaP的额外步骤。在诊断或预测CaP的方法中,与对样品或阈值相比,下列基因的至少1、2、3、4、5、6或7个的过量表达:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1,表明生物样品中存在CaP或发生CaP的风险增加。收集数据或诊断和/或预测CaP的方法可进一步包括检测与前列腺癌有关的其它基因的表达,包括但不限于ERG、PSA和PCA3。在某些实施方案中,所述方法包括检测的表达不超过100、90、80、70、60、50、40、30、25、20、15、14、13、12、11、10、9、8、7、6、5、4、3或2个基因。

[0054] 在一个实施方案中,所述方法包括检测COL10A1以及HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1的一个或多个的表达。在另一个实施方案中,所述方法包括检测HOXC4以及COL10A1、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1的一个或多个的表达。在另一个实施方案中,所述方法包括检测ESPL1以及COL10A1、HOXC4、MMP9、ABCA13、PCDHGA1和AGSK1的一个或多个的表达。在另一个实施方案中,所述方法包括检测MMP9以及COL10A1、HOXC4、ESPL1、ABCA13、PCDHGA1和AGSK1的一个或多个的表达。在另一个实施方案中,所述方法包括检测ABCA13以及COL10A1、HOXC4、ESPL1、MMP9、PCDHGA1和AGSK1的一个或多个的表达。在另一个实施方案中,所述方法包括检测PCDHGA1以及COL10A1、HOXC4、ESPL1、MMP9、ABCA13和AGSK1的一个或多个的表达。在另一个实施方案中,所述方法包括检测AGSK1以及COL10A1、HOXC4、

ESPL1、MMP9、ABCA13和PCDHGA1的一个或多个的表达。

[0055] 表3提供在非洲血统患者中更频繁地过量表达的这些基因的由HGNC和Entrez Gene指定的唯一标识码和代表性序列的登记号,所述序列通过引用以其整体结合到本文中。

[0056] 表3

基因	HGNC ID	Entrez Gene ID	NCBI参考
COL10A1	2185	1300	NM_000493.3 GI: 98985802
HOXC4	5126	3221	NM_014620.5 GI: 546232084
ESPL1	16856	9700	NM_012291.4 GI: 134276942
MMP9	7176	4318	NM_004994.2 GI: 74272286
ABCA13	14638	154664	AY204751.1 GI: 30089663
PCDHGA1	8696	56114	NM_018912.2 GI: 14196453
AGSK1	N/A	80154	NR_026811 GI: 536293433 NR_033936.3 GI: 536293365 NR_103496.2 GI: 536293435

另外,28个样品的全基因组序列分析鉴定出65个基因突变以较高置信度存在于所分析的14个前列腺肿瘤的至少1个中。在所分析的前列腺肿瘤中具有最高等位基因频率的65个基因突变发生在下列基因中:GLI1、IRX4、PAPPA、SPOP、TEX15、ZNF292、ANKRD11、FAT4、HECW2、KIAA1109、SHROOM3、SPOP、TTC36、ZNR3、C17orf65、DEGS2、NEK3、KIAA0947、LSP1、NOX3、AKR1B1、ARHGAP12、ITGA4、PVRL4、RBM26、UCN3、CATSPERB、FCRL2、CACNA1E、CORO6、DMKN、EXT1、HEATR7B2、NDUFB5、GPR180、LRRC4、TPRA1、ZIM2、C12orf50、ELMO2、RBM26、SEC14L1、TNFSF11、C9orf125、CDC73、ITSN1、KCNK16、LRRC7、METTL6、MOSC1、RP11-50B3.2、STAB2、STARD13、PTPRT、RBPJ、UBA2、DIAPH3、IL18R1、LIPF、SLITRK5、TMEM132E、POT1、RB1CC1、TAOK1和UNC5A。这65个基因中,已知只有SPOP具有与前列腺癌有关的突变。因此,鉴定样品中这些基因突变的一个或多个可提供可用于诊断或预测前列腺癌的基因特征。

[0057] 某些实施方案涉及收集数据用于诊断或预测CaP的方法,所述方法包括检测生物样品中下列基因的至少2、3、4、5、6、7、8、9、10、15、20、25、30、35、40、45或50个的一个或多个突变的表达:GLI1、IRX4、PAPPA、SPOP、TEX15、ZNF292、ANKRD11、FAT4、HECW2、KIAA1109、SHROOM3、SPOP、TTC36、ZNR3、C17orf65、DEGS2、NEK3、KIAA0947、LSP1、NOX3、AKR1B1、ARHGAP12、ITGA4、PVRL4、RBM26、UCN3、CATSPERB、FCRL2、CACNA1E、CORO6、DMKN、EXT1、HEATR7B2、NDUFB5、GPR180、LRRC4、TPRA1、ZIM2、C12orf50、ELMO2、RBM26、SEC14L1、TNFSF11、C9orf125、CDC73、ITSN1、KCNK16、LRRC7、METTL6、MOSC1、RP11-50B3.2、STAB2、STARD13、PTPRT、RBPJ、UBA2、DIAPH3、IL18R1、LIPF、SLITRK5、TMEM132E、POT1、RB1CC1、TAOK1和UNC5A。所述方法可任选包括从受试者中获得生物样品的额外步骤。所述方法可任选包括使用所收集的基因突变数据诊断或预测CaP的额外步骤。在诊断或预测CaP的方法中,检出下列基因的至少2、3、4、5、6、7、8、9、10、15、20、25、30、35、40、45或50个的一个或多个突变:GLI1、IRX4、PAPPA、SPOP、TEX15、ZNF292、ANKRD11、FAT4、HECW2、KIAA1109、SHROOM3、SPOP、TTC36、

ZNRF3、C17orf65、DEGS2、NEK3、KIAA0947、LSP1、NOX3、AKR1B1、ARHGAP12、ITGA4、PVRL4、RBM26、UCN3、CATSPERB、FCRL2、CACNA1E、CORO6、DMKN、EXT1、HEATR7B2、NDUFB5、GPR180、LRRC4、TPRA1、ZIM2、C12orf50、ELMO2、RBM26、SEC14L1、TNFSF11、C9orf125、CDC73、ITSN1、KCNK16、LRRC7、METTL6、MOSC1、RP11-50B3.2、STAB2、STARD13、PTPRT、RBPJ、UBA2、DIAPH3、IL18R1、LIPF、SLITRK5、TMEM132E、POT1、RB1CC1、TAOK1和UNC5A,表明生物样品中存在CaP或发生CaP的风险增加。在某些实施方案中,所述方法包括检测不超过100、90、80、70、60、50、40、30、25、20、15、14、13、12、11、10、9、8、7、6、5、4、3或2个突变基因的表达。

[0058] 表4提供这些基因的HGNC指定的唯一标识码及其Entrez Gene ID,所述序列通过引用以其整体结合到本文中。另外,表4提供在前列腺肿瘤和匹配的正常样品中鉴定的各个突变的频率。

[0059] 表4

基因	肿瘤频率	正常频率	HGNC ID	Entrez Gene ID
GLI1	G:21/T:23 (52%)	G:37/T:0 (0%)	20500	79820
IRX4	G:18/A:19 (51%)	G:42/A:0 (0%)	14875	79368
PAPPA	C:21/T:20 (48%)	C:40/T:0 (0%)	1392	777
SPOP	A:18/C:15 (45%)	A:39/C:0 (0%)	21356	84940
TEX15	C:25/T:21 (45%)	C:32/T:0 (0%)	25063	93099
ZNF292	T:14/A:11 (44%)	T:40/A:0 (0%)	3512	2131
ANKRD11	C:19/A:14 (42%)	C:41/A:0 (0%)	26857	133558
FAT4	C:26/T:19 (42%)	C:30/T:0 (0%)	7700	4711
HECW2	C:22/T:16 (42%)	C:42/T:0 (0%)	28899	160897
KIAA1109	A:19/G:14 (42%)	A:47/G:0 (0%)	15586	64101
SHROOM3	G:23/A:16 (41%)	G:39/A:0 (0%)	30413	131601
SPOP	G:20/C:14 (41%)	G:37/C:0 (0%)	12875	23619
TTC36	G:21/A:15 (41%)	G:30/A:0 (0%)	26665	160419
ZNRF3	C:15/T:10 (40%)	C:31/T:0 (0%)	17233	63916
C17orf65	T:19/C:12 (38%)	T:41/C:0 (0%)	20327	64062
DEGS2	C:19/G:12 (38%)	C:41/G:0 (0%)	10698	6397
NEK3	G:24/C:15 (38%)	G:32/C:0 (0%)	11926	8600
KIAA0947	G:28/A:17 (37%)	G:35/A:0 (0%)	28180	84302
LSP1	G:18/T:11 (37%)	G:38/T:0 (0%)	16783	79577
NOX3	C:22/T:13 (37%)	C:38/T:0 (0%)	6183	6453
AKR1B1	T:19/A:11 (36%)	T:47/A:0 (0%)	14464	83795
ARHGAP12	G:24/A:14 (36%)	G:40/A:0 (0%)	18531	57554
ITGA4	A:30/G:17 (36%)	A:35/G:0 (0%)	28343	131965
PVRL4	C:26/T:15 (36%)	C:21/T:0 (0%)	26189	64757
RBM26	C:30/G:17 (36%)	C:61/G:0 (0%)	15446	26121
UCN3	T:24/G:14 (36%)	T:41/G:0 (0%)	18629	55576
CATSPERB	T:36/G:20 (35%)	T:46/G:0 (0%)	19164	90627

FCRL2	G:26/A:14 (35%)	G:32/A:0 (0%)	9682	11122
CACNA1E	C:25/T:13 (34%)	C:40/T:0 (0%)	5724	3516
CORO6	T:30/A:16 (34%)	T:24/A:0 (0%)	30661	10054
DMKN	A:23/C:12 (34%)	A:37/C:0 (0%)	15480	81624
EXT1	G:23/A:12 (34%)	G:31/A:0 (0%)	5988	8809
HEATR7B2	C:23/T:12 (34%)	C:41/T:0 (0%)	6622	8513
NDUFB5	A:32/C:17 (34%)	A:55/C:0 (0%)	20295	26050
GPR180	A:32/G:16 (33%)	A:41/G:0 (0%)	26991	124842
LRRC4	T:14/G:7 (33%)	T:40/G:0 (0%)	17284	25913
TPRA1	A:18/C:9 (33%)	A:33/C:0 (0%)	15574	9821
ZIM2	C:28/T:14 (33%)	C:30/T:0 (0%)	29259	57551
C12orf50	C:35/A:17 (32%)	C:38/A:0 (0%)	12567	90249
ELMO2	T:35/C:17 (32%)	T:45/C:0 (0%)	20500	79820
RBM26	C:34/T:16 (32%)	C:58/T:0 (0%)	14875	79368
SEC14L1	T:31/G:15 (32%)	T:35/G:0 (0%)	1392	777
TNFSF11	A:33/C:16 (32%)	A:44/C:0 (0%)	21356	84940
C9orf125	T:26/G:12 (31%)	T:27/G:0 (0%)	25063	93099
CDC73	G:31/T:14 (31%)	G:44/T:0 (0%)	3512	2131
ITSN1	T:31/C:14 (31%)	T:40/C:0 (0%)	26857	133558
KCNK16	C:24/A:11 (31%)	C:39/A:0 (0%)	7700	4711
LRRC7	C:39/T:18 (31%)	C:32/T:0 (0%)	28899	160897
METTL6	A:28/G:13 (31%)	A:35/G:0 (0%)	15586	64101
MOSC1	A:20/G:9 (31%)	A:35/G:0 (0%)	30413	131601
RP11-50B3.2	G:26/A:12 (31%)	G:44/A:0 (0%)	12875	23619
STAB2	G:20/A:9 (31%)	G:38/A:0 (0%)	26665	160419
STARD13	C:24/T:11 (31%)	C:35/T:0 (0%)	17233	63916
PTPRT	C:30/T:13 (30%)	C:40/T:0 (0%)	20327	64062
RBPJ	C:23/T:9/G:1 (30%)	C:30/T:0 (0%)	10698	6397
UBA2	T:25/A:11 (30%)	T:46/A:0 (0%)	11926	8600
DIAPH3	C:39/A:16 (29%)	C:32/A:0 (0%)	28180	84302
IL18R1	G:34/T:14 (29%)	G:42/T:0 (0%)	16783	79577
LIPF	G:29/T:12 (29%)	G:43/T:0 (0%)	6183	6453
SLITRK5	G:22/A:9 (29%)	G:45/A:0 (0%)	14464	83795
TMEM132E	C:34/T:14 (29%)	C:32/T:0 (0%)	18531	57554
POT1	T:30/C:12 (28%)	T:46/C:0 (0%)	28343	131965
RB1CC1	A:27/C:11 (28%)	A:42/C:0 (0%)	26189	64757
TAOK1	A:25/C:10 (28%)	A:44/C:0 (0%)	15446	26121
UNC5A	G:27/A:11 (28%)	G:38/A:0 (0%)	18629	55576

GLI1突变在所分析的肿瘤中显示最高的等位基因频率,并且还与SPOP (一种已知具有

与前列腺癌有关的突变的基因)具有共同途径。因此,在一个实施方案中,本文所述方法包括单独或与表4所列基因突变的一个或多个组合检测GLI1突变。

[0060] 收集数据或诊断和/或预测CaP的方法可进一步包括检测与前列腺癌有关的其它基因的表达,包括但不限于ERG、PSA和PCA3。

[0061] 检测基因表达

如本文所用,测量或检测前述基因或核酸任一个的表达包括测量或检测相当于目标基因的任何核酸转录物(例如mRNA、cDNA或基因组DNA)或由其编码的蛋白质。如果基因与一个以上的mRNA转录物或同种型有关,则可通过测量或检测基因的mRNA转录物的一个或多个或与基因有关的mRNA转录物的全部,来测量或检测基因的表达。

[0062] 通常,可根据mRNA或cDNA水平检测或测量基因表达,尽管适当时也可使用蛋白质水平。可采用用于测量mRNA水平、cDNA或蛋白质水平的任何定量或定性方法。检测或测量mRNA或cDNA水平的合适方法包括例如RNA印迹法、微阵列分析或核酸扩增程序,例如反转录PCR(RT-PCR)或实时RT-PCR,亦称定量RT-PCR(qRT-PCR)。所述方法是本领域众所周知的。参见例如Sambrook等, *Molecular Cloning: A Laboratory Manual*, 第4版, Cold Spring Harbor Press, Cold Spring Harbor, N.Y., 2012。其它技术包括基因表达的数字化多路复用分析,例如nCounter[®] (NanoString Technologies, Seattle, WA) 基因表达测定法,其进一步描述于[22]、[23]、US20100112710和US20100047924,以上所有通过引用以其整体结合到本文中。

[0063] 检测目标核酸通常包括靶标(例如mRNA、cDNA或基因组DNA)和探针之间的杂交。用于前列腺癌基因表达谱的基因的序列是已知的(见上文)。因此,本领域技术人员可容易地设计用于检测这些基因的杂交探针。参见例如Sambrook等, *Molecular Cloning: A Laboratory Manual*, 第4版, Cold Spring Harbor Press, Cold Spring Harbor, N.Y., 2012。各个探针基本上对其靶标应有特异性,以避免任何交叉杂交和假阳性。在从转录物中衍生物质时,使用特异性探针的一个替代是使用特异性试剂(例如在cDNA产生期间,或在扩增期间使用靶标特异性引物)。在两种情况下,可通过与在所分析的基因组内基本上是唯一的靶标的部分杂交,实现特异性,例如与聚A尾杂交不会提供特异性。如果靶标具有多个剪接变体,则有可能设计识别对各变体是共同的区域的杂交试剂和/或使用一种以上试剂,所述试剂的每一种可识别一个或多个变体。

[0064] 优选采用微阵列分析或基于PCR的方法。在这方面,测量前列腺癌组织中的前述核酸的表达可包括例如使含有或疑似含有前列腺癌细胞的样品与对目标基因有特异性的多核苷酸探针或与经设计以扩增目标基因的一部分的引物接触,并分别检测探针与核酸靶标的结合或核酸的扩增。设计PCR引物的详细方案是本领域已知的。参见例如Sambrook等, *Molecular Cloning: A Laboratory Manual*, 第4版, Cold Spring Harbor Press, Cold Spring Harbor, N.Y., 2012。类似地,制备和使用微阵列分析基因表达的详细方案是本领域已知和本文描述的。

[0065] 备选或此外,基因的表达水平可在蛋白质水平上测定,意味着测量由上述基因编码的蛋白质的水平。用于测定蛋白质的水平的若干方法和装置是众所周知的,包括例如描述于例如美国专利号6,143,576、6,113,855、6,019,944、5,985,579、5,947,124、5,939,272、5,922,615、5,885,527、5,851,776、5,824,799、5,679,526、5,525,524、5,458,852和5,

480,792的免疫测定法,其每一个通过引用以其整体结合到本文中。这些测定法包括各种夹心、竞争性或非竞争性测定方式,以产生与目标蛋白质的存在或量有关的信号。可采用任何合适的免疫测定法,例如,侧向流动、酶联免疫测定法(ELISA)、放射免疫测定法(RIA)、竞争结合测定法等。描述了用于抗体阵列的多种形式。所述阵列通常包括对待检测的不同蛋白质有特异性的不同抗体。例如,可使用至少100种不同的抗体来检测100种不同的蛋白质靶标,每种抗体对每个靶标有特异性。还可使用对特定蛋白质靶标有特异性的其它配体,例如公开于W0/2008/048970的合成抗体,其通过引用以其整体结合到本文中。可从肽或小分子的随机文库中选择具有所需结合特异性的其它化合物。美国专利号5,922,615(其通过引用以其整体结合到本文中)描述了使用膜上的固定化抗体的多个分立区带以检测阵列中的多种靶抗原的装置。可使用微量滴定板或自动化以利于大量不同蛋白质的检测。

[0066] 免疫测定法的一个类型,称为核酸检测免疫测定法(NADIA),将免疫测定法的蛋白质抗原检测的特异性与聚合酶链式反应(PCR)的灵敏度和精确度结合。这种增强的DNA-免疫测定方法与酶免疫测定法的类似,包括抗体结合反应和中间洗涤步骤,只是酶标记被DNA链置换,且采用扩增技术(例如PCR)通过扩增反应检验。示例性NADIA技术描述于美国专利号5,665,539和公开的美国申请2008/0131883,其两个通过引用以其整体结合到本文中。简单地说,NADIA使用对目标蛋白质有特异性和用试验特异性核酸标记的第一(报道)抗体。核酸的存在不干扰抗体的结合,抗体也不干扰核酸扩增和检测。通常,把对目标蛋白质上的不同表位有特异性的第二(俘获)抗体包被在固相(例如顺磁粒子)上。使报道抗体/核酸缀合物在微量滴定板中与样品反应,以与靶抗原形成第一免疫复合物。然后将免疫复合物俘获在用俘获抗体包被的固相粒子上,形成不溶性夹心免疫复合物。洗涤微粒子以除去过量的未结合的报道抗体/核酸缀合物。然后通过使悬浮粒子进行扩增反应(例如PCR)并监测扩增的核酸产物,来检测结合的核酸标记。

[0067] 虽然免疫测定法通常已被用于蛋白质的鉴定和量化,但是质谱学(MS)技术的最新发展导致灵敏的高通量MS蛋白质分析的研发。MS方法可用来检测复杂生物样品中的少量蛋白质。例如,可在MS分析之前使生物样品分级来进行定向MS。用于进行MS分析前的这类分级的常见技术包括二维电泳、液相色谱法和毛细管电泳[25],所述参考文献通过引用以其整体结合到本文中。还出现选择反应监测(SRM),亦称多反应监测(MRM),作为有用的高通量基于MS的技术用于定量测定复杂生物样品中的靶定蛋白质,包括由基因融合(例如TMPRSS2/ERG)编码的前列腺癌生物标志物[26,27],所述参考文献通过引用以其整体结合到本文中。

[0068] 样品

本申请所述方法包括前列腺细胞中基因表达谱的分析。这些前列腺细胞存在于生物样品中,例如前列腺组织、血液、血清、血浆、尿液、唾液或前列腺液。可在检测基因表达前从细胞中分离核酸或多肽。

[0069] 在一个实施方案中,生物样品包含前列腺组织并通过活组织检查(例如直肠或经会阴活检)获得。在另一个实施方案中,生物样品是尿液。尿液样品可在直肠指检(DRE)或前列腺活检后收集。在另一个实施方案中,样品是血液、血清或血浆,并含有从原发性肿瘤剥离的循环肿瘤细胞。样品还可含有肿瘤来源的外来体。外来体是小的(通常30-100 nm)膜结合颗粒,它从正常细胞、患病细胞和肿瘤细胞中释放,并存在于血液和其它体液中。本申请公开的方法可与从多种哺乳动物收集的样品,但优选与从人类受试者获得的样品一起使

用。

[0070] 对照

对照可以是任何合适的参比,其允许评价与在包含非癌前列腺细胞(例如匹配受试者的正常前列腺上皮细胞)的样品或所述样品库中相同基因的表达相比的前列腺癌细胞中的基因表达水平。因此,例如,对照可以是与试验样品一起同时或相继分析的来自同一受试者的样品,或对照可以是已知是非癌的前列腺样品库中的上述目标基因的平均表达水平。或者,对照可通过样品中其它基因的mRNA拷贝数界定,其它基因例如可用来使基因表达水平归一化的持家基因(例如PBGD或GAPDH)。因此,对照可包括在例如用作标准物或参比的预制备微阵列中或在反映样品或非癌样品库中相关基因的表达谱的数据中,例如可以是电子数据库或计算机程序的一部分。

[0071] 基因过量表达和表达降低可通过任何合适的方法测定,例如通过将试验样品中基因的表达与对照(例如阳性或阴性对照)进行比较,或通过使用绝对表达的预定“截止值”或阈值。可如前所述提供对照。不论所用方法,过量表达和表达降低可定义为大于或小于非癌前列腺细胞或组织中相同基因或其它基因(例如持家基因)的表达水平的任何表达水平。进一步举例说明,过量表达可定义为是与非癌前列腺细胞或组织相比的至少约1.2倍、1.5倍、2倍、2.5倍、5倍、10倍、20倍、50倍、100倍或甚至更大表达的表达式,表达降低可类似地定义为是与非癌前列腺细胞或组织相比的至少约1/1.2、1/1.5、1/2、1/2.5、1/5、1/10、1/20、1/50、1/100或甚至更低表达的表达式。在一个实施方案中,本文所用的过量表达或表达降低被定义为分别是与对照样品或阈值相比的至少约2倍或1/2的表达式。

[0072] 前列腺癌

本公开内容提供与前列腺癌有关的基因表达谱。可利用基因表达谱检测样品中的前列腺癌细胞或测量前列腺癌的严重程度或侵袭性,例如区分高度分化的前列腺(WD)癌和分化差的(PD)前列腺癌。

[0073] 当在活检中发现前列腺癌时,通常进行分级以估计它将如何快地生长和扩散。最常用的前列腺癌分级系统,称为Gleason分级,根据其在显微镜下观察到的形式,以1-5的标度评价前列腺癌细胞。

[0074] 仍像健康前列腺细胞的癌细胞具有边界清晰可辨的均一形式,并被视为高度分化的(Gleason 1和2级)。癌细胞越接近地类似于前列腺组织,细胞将越像正常前列腺组织运行,且癌越少侵袭性。Gleason 3级,最常见的等级,显示中等分化的细胞,也就是说仍有些高度分化,但是边界非清晰可辨。分化差的癌细胞具有边界分辨不清的随机形式,并且不再像前列腺组织(Gleason 4和5级),表明更大侵袭性的癌。

[0075] 前列腺癌常常具有不同等级的区域。通过将肿瘤内的2种最常见的癌细胞形式的等级相加求出综合Gleason评分。例如,如果最常见的形式是4级,次最常见的形式是3级,则综合Gleason评分为4+3=7。如果肿瘤内只有一种形式,则综合Gleason评分可低至1+1=2或高达5+5=10。2-4的综合评分被视为高度分化的,5-6的评分被视为中等分化的,7-10的评分被视为分化差。有高Gleason评分的癌症更可能在发现时早已扩散到前列腺以外。

[0076] 一般而言,Gleason评分越低,癌症侵袭性越小且预后越好(展望治愈或长期生存)。Gleason评分越高,癌症侵袭性越大且长期无转移生存的预后越差。

[0077] 阵列

平行测量多个基因的RNA转录物水平的一种便利方法是使用阵列(在本领域亦称为微阵列)。使用阵列评价和比较基因表达水平的技术是本领域众所周知的,包括合适的杂交、检测和数据处理方案。有用的阵列包括固定在单独位置(例如可寻址元件)处的固体基质(例如玻璃支持物例如显微镜载玻片或膜)上的多种多核苷酸探针(通常为DNA),使得可检测杂交可发生在探针和转录物之间以表明存在的各种转录物的量。本申请公开的阵列可用于检测所需基因组合的表达的方法中,在整个本申请中论述了所述组合。

[0078] 在一个实施方案中,阵列包含(a)基质和(b) 2、3、4、5、6、7、8、9或10个或更多个不同的可寻址元件,所述各可寻址元件包含至少1种多核苷酸探针用于检测下列人基因之一的mRNA转录物的表达(或从mRNA转录物合成的cDNA):DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4。

[0079] 在另一个实施方案中,阵列包含(a)基质和(b) 2、3、4、5、6、7或8个或更多个不同的可寻址元件,所述各可寻址元件包含至少1种多核苷酸探针用于检测下列人基因之一的mRNA转录物的表达(或从mRNA转录物合成的cDNA):PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3。

[0080] 在另外又一个实施方案中,阵列包含(a)基质和(b) 2、3、4、5、6或7个或更多个不同的可寻址元件,所述各可寻址元件包含至少1种多核苷酸探针用于检测下列人基因之一的mRNA转录物的表达(或从mRNA转录物合成的cDNA):COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1。

[0081] 本文所用术语“可寻址元件”意指这样的元件,即在预定位置与基质连接并特异性结合已知靶分子,使得当检测出靶标结合时(例如通过荧光标记),根据基质上元件的位置,提供有关所结合的分子的特性的信息。如果可寻址元件不与相同的靶标基因结合,则对于本公开内容的目的是“不同的”。可寻址元件包含对指定基因的mRNA转录物有特异性一种或多种多核苷酸探针或从mRNA转录物合成的cDNA。可寻址元件可包含1拷贝以上的多核苷酸,可包含一种以上不同的多核苷酸,条件是所有的多核苷酸结合相同的靶分子。在已知基因表达一种以上的mRNA转录物时,基因的可寻址元件可包含针对不同转录物的不同探针,或被设计成检出对转录物的两种或更多种(或全部)是共同的核酸序列的探针。或者,阵列可包含不同转录物的可寻址元件。可寻址元件还可包含可检测标记,其合适的实例是本领域众所周知的。

[0082] 阵列可包含与除以下以外的mRNA或cDNA结合的可寻址元件:1) DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4;2) PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3;或3) COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1。然而,能够检测多种靶标(例如mRNA或多肽靶标)的阵列,例如设计成用于细胞系、染色体、基因组等的全面表达概况的阵列,对于收集数据以用于诊断和/或预测前列腺癌是不经济和不方便的。因此,为了促进作为例如与本文所述方法联合的诊断工具或筛查的阵列的便利使用,阵列优选包含少数可寻址元件。在这一方面,在一个实施方案中,阵列包含不超过约1000个不同的可寻址元件,更优选不超过约500个不同的可寻址元件,不超过约250个不同的可寻址元件,或甚至不超过约100个不同的可寻址元件,例如约75个或更少个不同的可寻址元件,或甚至约50个或更少个不同的可寻址元件。当然,甚至较小的阵列可包含约25个或更少个不同的可寻址元件,例如约15个或更

少个不同的可寻址元件或约12个或更少个不同的可寻址元件。甚至可将阵列限于约7个不同的可寻址元件而不干扰其功能性。

[0083] 还可通过限制阵列上多核苷酸探针的数目,将这些诊断阵列与更全面的基因组阵列等区分开来。因此,在一个实施方案中,阵列具有固定在基质上的针对不超过1000个基因的多核苷酸探针。在其它实施方案中,阵列具有固定在基质上的针对不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2个基因的寡核苷酸探针。

[0084] 基质可以是多核苷酸可与之共价或非共价连接的任何刚性或半刚性支持物。合适的基质包括膜、滤器、芯片、载玻片、圆片(wafer)、纤维、珠粒、凝胶、毛细管、板、聚合物、微粒子等。对基质是合适的材料包括例如尼龙、玻璃、陶瓷、塑料、二氧化硅、铝硅酸盐、硼硅酸盐、金属氧化物例如氧化铝和氧化镍、各种粘土、硝化纤维等。

[0085] 可寻址元件的多核苷酸(亦称为“探针”)可在预定的一维或二维排列上与基质连接,使得与探针杂交或结合的形式易与特定基因的表达相关联。因为探针位于基质的指定位置上(即元件是“可寻址的”),杂交或结合形式和强度产生特有的表达谱,这可根据特定基因的表达水平来解释,并且可按照本文所述方法与前列腺癌相关联。

[0086] 多核苷酸和多肽探针可通过本领域已知的任何合适方法产生(参见例如Sambrook等, *Molecular Cloning: A Laboratory Manual*, 第4版, Cold Spring Harbor Press, Cold Spring Harbor, N.Y., 2012)。例如,可通过常规技术(例如PCR或合成),使用mRNA或cDNA靶标本身的核酸序列(例如表1-4中公开的核酸序列),产生与本文所述基因的mRNA转录物(或从其合成的cDNA)特异性结合的多核苷酸探针。本文所用术语“片段”意指包含约10个或更多个核苷酸、约15个或更多个核苷酸、约20个或更多个核苷酸、约30或更多个或甚至约50个或更多个核苷酸的多核苷酸序列的连续部分或一部分。进一步举例说明,可通过包含与mRNA转录物(例如SEQ ID NO: 2)或其片段互补或与SEQ ID NO: 2充分互补或其选择性与SEQ ID NO: 2结合的片段的核酸序列的多核苷酸,提供与DLX1的mRNA转录物(或其相应的cDNA)结合的多核苷酸探针。对于本文所述其它基因也同样如此。多核苷酸探针的确切性质对本发明不是关键的;可使用可选择性结合mRNA或cDNA靶标的任何探针。通常,多核苷酸探针可包含10个或更多个核苷酸、20个或更多个、50个或更多个或100个或更多个核苷酸。为了赋予足够的特异性,探针可与靶序列(例如表1-4中公开的核酸序列)的互补序列有约90%或更高、优选约95%或更高(例如约98%或更高或约99%或更高)的序列同一性,如通过例如应用众所周知的基础局部比对搜索工具(Basic Local Alignment Search Tool, BLAST)算法(可通过National Center for Biotechnology Information (NCBI), Bethesda, Md.获得)测定。

[0087] 杂交反应的严格性可容易地通过本领域普通技术人员确定,一般根据探针长度、洗涤温度和盐浓度任经验计算。一般而言,对于适当退火,较长的探针需要较高的温度,而较短的探针需要较低的温度。当互补链存在于低于其解链温度的环境下时,杂交一般取决于变性核酸序列再退火的能力。探针和可杂交序列之间所需同源性的程度越高,可使用的相对温度越高。因此,因此得出结论,较高的相对温度往往可使反应条件较严格,而较低的相对温度则较不严格。有关杂交反应严格性的其它详情和解释参见Ausubel等, *Current Protocols in Molecular Biology*, Wiley Interscience Publishers, (1995)。

[0088] 本文所用“严格条件”或“高严格性条件”根据以下识别,但不限于此:(1) 对于洗涤

使用低的离子强度和高的温度,例如0.015 M氯化钠/0.0015 M柠檬酸钠/0.1%十二烷基硫酸钠,在50℃下;(2)在杂交期间使用变性剂,例如甲酰胺,例如50% (v/v) 甲酰胺与0.1%牛血清白蛋白/0.1%聚蔗糖 (Ficoll)/0.1%聚乙烯吡咯烷酮/50 mM磷酸钠缓冲液 (pH 6.5) 与750 mM氯化钠、75 mM柠檬酸钠,在42℃下;或(3)使用50%甲酰胺、5XSSC (0.75 M NaCl、0.075 M柠檬酸钠)、50 mM磷酸钠 (pH 6.8)、0.1%焦磷酸钠、5X Denhardt溶液、声波处理的鲑精DNA (50μg/ml)、0.1% SDS和10%硫酸葡聚糖,在42℃下,其中在42℃下在0.2XSSC (氯化钠/柠檬酸钠) 中并在50%甲酰胺中在55℃下洗涤,接着包括含有0.1XSSC的EDTA、在55℃下的高严格性洗涤。Sambrook等, *Molecular Cloning: A Laboratory Manual*, New York: Cold Spring Harbor Press, 1989描述了“中等严格条件”,但不限于此,包括使用不比上述那些严格的洗涤溶液和杂交条件(例如温度、离子强度和% SDS)。中等严格条件的实例是在包含以下的溶液在37℃下温育过夜:20%甲酰胺、5XSSC (150 mM NaCl、15 mM柠檬酸三钠)、50 mM磷酸钠 (pH 7.6)、5X Denhardt溶液、10%硫酸葡聚糖和20 mg/mL变性已剪切鲑精DNA,接着在1XSSC中在约37-50℃下洗涤过滤器。技术人员应了解需要时如何调节温度、离子强度等以适应例如探针长度等因素。

[0089] 阵列可包含为多核苷酸阵列所共有的其它元件。例如,阵列还可包括用作对照、标准物或参比分子(例如持家基因或其部分(例如PBGD或GAPDH))的一个或多个元件,以助于表达水平的归一化或核酸品质和结合特征、试剂品质和有效性、杂交成功、分析阈值和成功等的测定。阵列或可寻址元件的这些其它共同方面,以及符合本发明的用于构建和使用阵列的方法,包括产生、标记和使合适探针与基质连接是本领域众所周知的。就本发明的方法而论,阵列的其它方面如本文之前描述的一样。

[0090] 在一个实施方案中,阵列包含(a)基质和(b)两个或更多个不同的可寻址元件,所述各可寻址元件包含至少1种多核苷酸探针用于检测下列人基因之一的mRNA转录物的表达:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4,其中阵列包含不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2个可寻址元件。在某些实施方案中,阵列包含至少3、4、5、6、7、10、12或15个不同的可寻址元件。

[0091] 在另一个实施方案中,阵列包含两个或更多个不同的可寻址元件,其每一个包含至少1种多核苷酸探针用于检测下列人基因之一的mRNA转录物的表达:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3,其中阵列包含不超过500、不超过250、不超过100、不超过50、不超过25或不超过15个可寻址元件。在一个实施方案中,阵列包含至少3、4、5、6、7、10、12或15个不同的可寻址元件。

[0092] 在另一个实施方案中,阵列包含两个或更多个不同的可寻址元件,其每一个包含至少1种多核苷酸探针用于检测下列人基因之一的mRNA转录物的表达:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1,其中阵列包含不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2个可寻址元件。在一个实施方案中,阵列包含至少3、4、5、6、7、10、12或15个不同的可寻址元件。

[0093] 阵列也可用来平行测量多种蛋白质的蛋白质水平。所述阵列包含携带与多种蛋白质特异性结合的多种配体的一个或多个支持物,其中多种蛋白质包含不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2种不同的蛋白质。配体任选与平面支持物或珠粒连接。在

一个实施方案中,配体是抗体。待使用阵列检测的蛋白质相当于由本文所述目标核酸编码的蛋白质,包括公开的特定基因表达谱。因此,各配体(例如抗体)被设计成与靶标蛋白质之一(例如表1-4公开的多肽序列)结合。如同核酸阵列一样,各配体优选与不同的可寻址元件缔合以利于检测样品中不同的蛋白质。

[0094] 患者治疗

本申请描述了诊断和预测获自受试者的样品中的前列腺癌的方法,其中分析了前列腺细胞和/或组织中的基因表达。如果样品显示过量表达某些基因或表达某些基因突变,则受试者患有前列腺癌或不同程度的晚期(例如WD或PD前列腺癌)前列腺癌的可能性加大。如果是这样的结果的话,检测或预测前列腺癌的方法可包括下列步骤的一个或多个:知会患者他们可能患有前列腺癌、WD前列腺癌或PD前列腺癌;前列腺组织的证实性组织学检查;和/或通过前列腺癌疗法治疗患者。

[0095] 因此,在某些方面,如果检测步骤表明受试者患有前列腺癌,则该方法进一步包括从受试者中采取前列腺活检和检查活检(例如组织学检查)中的前列腺组织的步骤以证实患者是否患有前列腺癌。或者,检测或预测前列腺癌的方法可用来评价对治疗的需要或监测对治疗的反应(例如手术或其它疗法后的无病复发),并因此可包括治疗患有前列腺癌的受试者的额外步骤。

[0096] 前列腺癌治疗选择包括手术、放射疗法、激素疗法、化学疗法、生物疗法或高强度聚焦超声。获准用于前列腺癌的药物包括:Enzalutamide (XTANDI)、醋酸阿比特龙、卡巴他赛(Cabazitaxel)、地加瑞克、Jevtana (卡巴他赛)、泼尼松、Provenge (西普鲁塞T)、西普鲁塞T或多西他赛。因此在阳性结果之后,本申请所述方法可包括手术、放射疗法、激素疗法、化学疗法、生物疗法或高强度聚焦超声的进一步步骤。

[0097] 药物筛选

由本申请所述方法提供的与前列腺癌有关的基因表达谱或其缺乏也可用于在临床试验中或在前列腺癌动物模型中筛选药物。可按与监测各个患者类似的方式对药物进行临床试验,只是将平行给予前列腺癌患者人群,通常与给予安慰剂的对照人群进行比较。

[0098] 可分析各个患者及治疗人群或对照人群间基因表达水平的变化。在各个患者水平上的分析提供试验结束时患者总体状况的指示(即基因表达谱是否表明前列腺癌的存在或严重程度(例如WD或PD))和/或该表达谱在试验过程中是接近还是远离这类指示变化的指示。可汇集人群中各个患者的结果,以允许在治疗人群和对照人群之间进行比较。

[0099] 可在非人动物前列腺癌模型中进行类似试验。既然这样,在正对其进行试验的非人动物的任何物种中,所检测的基因的表达水平是上文引用的人基因的物种变体或同源物。虽然在人前列腺癌患者中测定的人基因的平均表达水平不必直接与动物模型中同源基因的表达水平相比较,但是人类值仍然可用来提供非人同源物表达水平的改变是处于朝向还是远离前列腺癌的诊断或WD或PD前列腺癌的预测的指示。试验中各动物的表达谱可提供试验结束时动物状况的指示(即,基因表达谱是否表明前列腺癌的存在或严重程度(例如WD或PD))和/或试验期间所述状况的变化。可在群体和所比较的治疗人群和对照人群间汇集各动物的结果。然后可比较2个群体间的基因表达水平的平均变化。

[0100] 计算机执行模型

按照本发明的所有方面和实施方案,所提供的方法可为计算机执行的。

[0101] 可在数字计算机中,分析基因表达水平并与受试者的状况(例如前列腺癌的存在或疾病的严重程度(例如WD或PD前列腺癌))相关联。任选所述计算机与接收与基因表达水平相关的实验测定信号的扫描仪等直接连接。或者,可通过其它方法输入表达水平。可对计算机编程以将原始信号转化成表达水平(绝对或相对),将测量表达水平与一个或多个参比表达水平或这类值的标度进行比较。还可根据与一个或多个参比表达水平的比较对计算机编程以对表达水平赋值或指定其它标识,并汇集表达谱中多个基因的所述值或标识。还可对计算机编程以输出提供表示前列腺癌的存在或严重程度的值或其它标识以及用于确定所述值或标识的任何原始或中间数据。

[0102] 一台典型的计算机(参见美国专利号6,785,613;图4和5)包括使以下主要子系统互连的总线:例如中央处理器、系统存储器、输入/输出控制器、外部设备例如经由并行端口打印机、经由显示适配器的显示屏、串行端口、键盘、固定磁盘驱动器和有效接收外部存储设备的端口(例如USB端口)。可连接许多其它设置,例如经由I/O控制器的扫描仪、与串行端口或网络接口连接的鼠标。计算机含有保存允许计算机执行多种功能的代码的计算机可读介质。这些功能包括上述接收输入和发送输出的控制自动化设备。自动化设备可包括用于递送测定表达水平的试剂的机器臂以及小容器,例如用于进行表达分析的微量滴定板孔。

[0103] 一台典型的计算机系统106还可包括与在操作系统控制下或与操作系统联合操作的随机存储器连接的如图4给出和上文所述的一个或多个处理器110。

[0104] 在一个实施方案中,本发明的计算机执行方法的任一种可包括通过至少1个处理器获得反映生物样品中的下列人基因的至少2、3、4、5、6、7、8、9、10、11、12、13、14或15个的表达水平的信息的步骤:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4。

[0105] 在一个实施方案中,所述计算机执行方法包括至少1个处理器获得反映DLX1和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映NKX2-3和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映DLX1和NKX2-3和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映PHGR1和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映THBS4和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映GAP43和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映FFAR2和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映GCNT1和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映SIM2和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映STX19和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映KLB和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映APOF和表1所列一个或多个其它基因的表达水

平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映LOC283177和表1所列一个或多个其它基因的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映TRPM4和表1所列一个或多个其它基因的表达水平的信息。

[0106] 在另一个实施方案中,本发明的计算机执行方法的任一种可包括获得至少1个处理器反映获自高加索血统患者的生物样品中下列人基因的至少2、3、4、5、6、7或8个的表达水平的信息的步骤:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3。

[0107] 在一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映ALOX15以及PCA3、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映CDH19以及PCA3、AMACR、ALOX15、OR51E2/PSGR、F5、FZD8和CLDN3的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映F5以及PCA3、AMACR、ALOX15、OR51E2/PSGR、CDH19、FZD8和CLDN3的一个或多个的表达水平的通信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映FZD8以及PCA3、AMACR、ALOX15、OR51E2/PSGR、CDH19、F5和CLDN3的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映CLDN3以及PCA3、AMACR、ALOX15、OR51E2/PSGR、CDH19、F5和FZD8的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映PCA3以及AMACR和ALOX15、CDH19、F5、FZD8和CLDN3的一个或多个的表达水平的信息。

[0108] 在另一个实施方案中,本发明的计算机执行方法的任一种可包括通过至少1个处理器获得反映获自非洲血统患者的生物样品中的下列人基因的至少2、3、4、5、6或7个的表达水平的信息的步骤:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1。

[0109] 在一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映COL10A1以及HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映HOXC4以及COL10A1、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映ESPL1以及COL10A1、HOXC4、MMP9、ABCA13、PCDHGA1和AGSK1的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映MMP9以及COL10A1、HOXC4、ESPL1、ABCA13、PCDHGA1和AGSK1的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映ABCA13以及COL10A1、HOXC4、ESPL1、MMP9、PCDHGA1和AGSK1的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映PCDHGA1以及COL10A1、HOXC4、ESPL1、MMP9、ABCA13和AGSK1的一个或多个的表达水平的信息。在另一个实施方案中,所述计算机执行方法包括通过至少1个处理器获得反映AGSK1以及COL10A1、HOXC4、ESPL1、MMP9、ABCA13和PCDHGA1的一个或多个的表达水平的信息。

[0110] 在本发明的计算机执行方法的另一个实施方案中,所述方法可另外包括以下步骤:i)通过至少1个处理器测定一个或多个对照基因的表达水平和以下的表达水平之间的差异:1)生物样品中下列人基因的至少2、3、4、5、6、7、8、9、10、11、12、13、14或15个:DLX1、

NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4; 2) 获自高加索血统患者的生物样品中下列人基因的至少2、3、4、5、6、7或8个: PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3; 或3) 获自非洲血统患者的生物样品中下列人基因的至少2、3、4、5、6或7个: COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1; 和(ii) 以用户可读格式输出测定步骤中得到的差异。

[0111] 在本发明的计算机执行方法的另一个实施方案中, 所述方法可进一步包括根据输出步骤中得到的差异, 以用户可读格式输出受试者患有前列腺癌、高度分化的前列腺癌或分化差的前列腺癌的测定结果。

[0112] 试剂盒

可在试剂盒中安排用于本申请所述方法的多核苷酸探针和/或引物或抗体或多肽探针。因此, 一个实施方案涉及用于诊断或预测前列腺癌的试剂盒, 其包含用于检测下列人基因的至少2、3、4、5、6、7、8、8、9、10、11、12、13、14或15个的多种多核苷酸探针: DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4, 其中多种多核苷酸探针含有针对不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2个基因的多核苷酸探针。在一个实施方案中, 多种多核苷酸探针包含用于检测上述基因的至少4或5个的多核苷酸探针, 其中多种多核苷酸探针含有用于不超过10个基因的多核苷酸探针。多核苷酸探针可以是任选标记的。试剂盒可任选包括用于扩增下列人基因的至少2、3、4、5、6、7、8、8、9、10、11、12、13、14或15个的mRNA转录物的一部分的多核苷酸引物: DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM4。

[0113] 另一个实施方案涉及用于诊断或预测高加索血统患者的前列腺癌的试剂盒, 试剂盒包含用于检测下列人基因的至少3、4、5、6、7或8个的多种多核苷酸探针: PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3, 其中多种多核苷酸探针含有用于不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2个基因的多核苷酸探针。在一个实施方案中, 多种多核苷酸探针包含用于检测上述基因的至少4或5个的多核苷酸探针, 其中多种多核苷酸探针含有用于不超过10个基因的多核苷酸探针。多核苷酸探针可以是任选标记的。试剂盒可任选包括用于扩增下列人基因的至少3、4、5、6、7或8个的mRNA转录物的多核苷酸引物: PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3。

[0114] 又一个实施方案涉及用于诊断或预测非洲血统患者的前列腺癌的试剂盒, 试剂盒包含用于检测下列人基因的至少3、4、5、6或7个的多种多核苷酸探针: COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1, 其中多种多核苷酸探针含有用于不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2个基因的多核苷酸探针。在一个实施方案中, 多种多核苷酸探针包含用于检测上述基因的至少4或5个的多核苷酸探针, 其中多种多核苷酸探针含有用于不超过10个基因的多核苷酸探针。多核苷酸探针可以是任选标记的。试剂盒可任选包括用于扩增下列人基因的至少3、4、5、6或7个的mRNA转录物的多核苷酸引物: COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1。

[0115] 用于诊断或预测前列腺癌的试剂盒还可包含抗体。因此, 在一个实施方案中, 用于诊断或预测前列腺癌的试剂盒包含用于检测由下列人基因编码的多肽的至少3、4、5、6、7、8、9、10、11、12、13、14或15种的多种抗体: DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、

GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM,其中多种抗体含有不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2种多肽的抗体。在一个实施方案中,多种抗体包含用于检测由上述基因编码的多肽的至少4或5种的抗体且其中多种抗体含有不超过10种多肽的抗体。抗体可以是任选标记的。

[0116] 在另一个实施方案中,用于诊断或预测高加索血统患者的前列腺癌的试剂盒包含用于检测由下列人基因编码的多肽的至少3、4、5、6或7种的多种抗体:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3,其中多种抗体含有不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2种多肽的抗体。在一个实施方案中,多种抗体包含用于检测由上述基因编码的多肽的至少4或5种的抗体且其中多种抗体含有不超过10种多肽的抗体。抗体可以是任选标记的。

[0117] 在另外又一个实施方案中,用于诊断或预测非洲血统患者的前列腺癌的试剂盒,其包含用于检测由下列人基因编码的多肽的至少3、4、5、6或7种的多种抗体:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1,其中多种抗体含有不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2种多肽的抗体。在一个实施方案中,多种抗体包含用于检测由上述基因编码的多肽的至少4或5种的抗体且其中多种抗体含有不超过10种多肽的抗体。抗体可以是任选标记的。

[0118] 另一方面,用于诊断或预测前列腺癌的试剂盒可包含可用于例如光谱测定方法(例如质谱法)的多肽探针。因此,在一个实施方案中,用于诊断或预测前列腺癌的试剂盒包含用于检测由下列人基因编码的多肽的至少3、4、5、6、7、8、9、10、11、12、13、14或15种的多种多肽探针:DLX1、NKX2-3、CRISP3、PHGR1、THBS4、AMACR、GAP43、FFAR2、GCNT1、SIM2、STX19、KLB、APOF、LOC283177和TRPM,其中多种多肽探针含有不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2种多肽的多肽探针。在一个实施方案中,多种多肽探针包含用于检测由上述基因编码的多肽的至少4或5种的多肽探针,且其中多种多肽探针含有不超过10种多肽的多肽探针。多肽探针可以是任选标记的。

[0119] 在另一个实施方案中,用于诊断或预测高加索血统患者的前列腺癌的试剂盒包含用于检测由下列人基因编码的多肽的至少3、4、5、6、7或8种的多种多肽探针:PCA3、ALOX15、AMACR、CDH19、OR51E2/PSGR、F5、FZD8和CLDN3,其中多种多肽探针含有不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2种多肽的多肽探针。在一个实施方案中,多种多肽探针包含用于检测由上述基因编码的多肽的至少4或5种的多肽探针,且其中多种多肽探针含有不超过10种多肽的多肽探针。多肽探针可以是任选标记的。

[0120] 在另外又一个实施方案中,用于诊断或预测非洲血统患者的前列腺癌的试剂盒包含用于检测由下列人基因编码的多肽的至少3、4、5、6或7种的多种多肽探针:COL10A1、HOXC4、ESPL1、MMP9、ABCA13、PCDHGA1和AGSK1,其中多种多肽探针含有不超过500、250、100、50、25、15、10、9、8、7、6、5、4、3或2种多肽的多肽探针。在一个实施方案中,多种多肽探针包含用于检测由上述基因编码的多肽的至少4或5种的多肽探针,且其中多种多肽探针含有不超过10种多肽的多肽探针。多肽探针可以是任选标记的。

[0121] 在一个实施方案中,试剂盒包括公开了在所公开的方法中使用试剂盒内容物的方法的说明资料。说明资料可以许多形式提供,包括但不限于书面形式(例如硬拷贝纸等)、以电子形式(例如计算机磁盘或光盘)提供或可以是可视的(例如可视文件)。试剂盒还可包括

有利于试剂盒针对其而设计的特殊应用的部件。因此,例如,试剂盒可另外包括常规用于实施特定方法的其它试剂,包括但不限于缓冲液、酶、标记化合物等。所述试剂盒和合适的内容物为本领域技术人员所熟知。试剂盒还可包括参比或对照样品。参比或对照样品可以是生物样品或数据库。

[0122] 如上所述,本申请中描述的多核苷酸或多肽探针和抗体任选用可检测标记进行标记。可以使用与本领域普通技术人员已知的探针或抗体技术联用的任何可检测标记。在一个具体的实施方案中,探针用选自以下的可检测标记进行标记:荧光标记、化学发光标记、猝灭剂、放射性标记、生物素、质量标签和/或金。

[0123] 除非另有定义,否则本文所用的全部技术和科学术语都具有本领域普通技术人员通常理解的相同含义。虽然类似或等同于本文所述的方法和材料可用于实施或测试本发明,但下面描述了合适的方法和材料。本文提及的所有出版物、专利申请、专利和其它参考文献通过引用以其整体结合到本文中。万一有抵触,则以本说明书(包括定义)为准。另外,材料、方法和实施例只是说明性的,并无意是限制性的。

实施例

[0124] 实施例1. 比较基因组DNA分析

在7名AA和7名CA CaP患者(28个样本)的组群中,使用原发性前列腺肿瘤和相应的正常组织(血液)进行了比较全基因组分析。根据以下标准选择组群:基本治疗根治性前列腺切除术、无新辅助治疗、Gleason 3+3和3+4级(代表在诊断/基本治疗时PSA筛查的CaP的大部分)、具有80%或更高肿瘤细胞内容物的冷冻肿瘤组织、得到超过2 μ g高分子量基因组DNA的解剖肿瘤组织、相应血液基因组DNA的可得性和患者临床病理数据。

[0125] 将28个样品送往Illumina Inc. (UK)以测序。应用Illumina的ELAND比对算法,对来自肿瘤样品的序列与参比基因组作图。测序报告良好的覆盖度(平均37)。应用Strelka算法,同时进行调用单核苷酸多态性(SNP)、小插入与小缺失(InDel)、拷贝数变异(CNV)和结构变异(SV)的变体。在该组群中,以预期频率鉴定出所有已建立的CaP突变(TMPRSS2/ERG、SPOP、CHD1和PTEN)。

[0126] 在14名患者的至少2名中鉴定出具有SNV、CNV或InDel体细胞突变的31个基因(包括已知突变):AC091435.2、APC、ASMTL、ASMTL-AS1、CDC73、CHD1、CSF2RA、EYS、FRG1、FRG1B、HK2、IL3RA、KLLN、LIPF、LOC100293744、MT-ATP6、MT-BD4、MT-CO1、MT-CYB、MT-ND2、MT-ND3、MUC16、MUC6、NOX3、PDHA2、PTEN、SLC25A6、SLC9B1、SPOP、TRAV20和USH2A。

[0127] 突变似乎不显示与任何特定组(AA-、AA+、CA-、CA+)有关。然而,未料到AA患者中不存在PTEN缺失。在2个CA病例中检测到明确的PTEN缺失,在另外3个CA病例中PTEN缺失不太明显,表明在CA病例中PTEN缺失的潜在排外性。

[0128] 实施例2. 比较RNA分析

为了补充基因组DNA分析,在相同的前列腺肿瘤样品组群中进行了RNA-Seq分析。RNA-Seq技术具有询问包括基因融合、基因和转录物表达在内的转录物组的多个方面的能力。从14名患者的4位中收集周围的正常组织。正常组织样品中的2个来自AA男性,2个来自CA男性。

[0129] 将RNA样品运送到Expression Analysis (Durham,NC)用于转录物组测序。测序统

计学的详细资料如下:测序类型:配对末端,各样品的平均读取长度:50nt,平均读取质量:37,读取数目:每个样品约3100万。

[0130] 以fastq格式获取各样品的表达分析的原始读取。这些文件含有通过Illumina的纯度滤器的所有序列和由Illumina phred度量限定的全碱基(per-base)质量分数。在实际分析之前,针对低质量读取(质量分数<20)、伪像/复制序列和衔接序列,将这些原始读取过滤。

[0131] 在该分析中,从UCSC网站下载用于制图的人参比基因组(hg19)。应用TopHat软件2.0.8版(一种可用于制图的免费开放源码工具),使Clean Paired末端读取与hg19参比基因组进行比对,并且在比对中对于各读取允许不超过2个错配。采用Bowtie(一种超高通量短读取比对器(aligner)),将TopHat图读取至参比基因组。软件输出多份文件用于进一步分析:制图读取(mapped read)、融合连接处、剪接点、插入和缺失文件。

[0132] 应用Cufflinks,一种装配转录物、估计其丰度和测试RNA-Seq样品中的差异表达和调节的开放源码工具,将比对的读取装配成转录物。Cufflinks根据该基因的所有已知的剪接变体/同种型,计算出基因的表达水平。

[0133] Cufflinks测量每百万制图读取每千碱基转录物的片段(Fragments per Kilobase of transcript per Million mapped reads,FPKM)中的转录物和基因丰度水平。FPKM方程式如下定义:

$$FPKM = \frac{C}{LN}$$

C为特征(转录物、外显子)中可制图读取的数目,L为特征中的长度(单位:kb),N为特征中可制图读取的总数(单位:百万)。FPKM归一化方法消除用于比较样品间基因表达的差异的基因长度和测序偏差。

[0134] Cufflinks包中包括的Cuffdiff程序计算出CaP肿瘤和正常样品间的差异表达,并包括样品间表达的各实测变化的p值。根据实验条件,Cuffdiff允许输入多个样品文件。基因和转录物表达水平以表格格式报告,并且这些文件含有基因信息、各基因的log2标度倍数变化、P值和错误发现率(FDR)。用Genomatix Pathway分析软件进行有关统计显著性基因的途径分析和基因本体论生物进程(Gene Ontology Biological Processes)。

[0135] 根据其表达水平,应用分层聚类(应用R包进行)将样品分类。图1. 所有18个样品(14个肿瘤和4个正常)的聚类表明肿瘤和正常样品之间的清晰分界。然而,未按照AA和CA组使大多数肿瘤样品聚类。引人关注的是,4个融合阴性AA样品中的3个聚类在1组中,并且根据患者随访研究,3名患者中的2名发生转移(在该组群中仅2名转移),第3人有生化复发。

[0136] 从14个肿瘤(7个AA和7个CA)和4个正常(2个AA和2个CA)样品获得基因表达谱。肿瘤和正常样品之间的比较分析的限制是所有肿瘤样品的正常样品的可得性。因此,在当前的分析中,将各组内的2个正常样品合并在一起,将平均值与其相应组进行比较。

[0137] 在初步分析中,通过将各组内的肿瘤与正常样品进行比较产生各个患者的基因表达谱。使用在肿瘤中过量表达/表达不足至少2倍的倍数变化(肿瘤/正常比)和P值<0.05提取统计显著性基因。在非裔美国人和高加索美国人组中,101个基因和180个基因分别为统计显著性的(2倍且P值<0.05)。非裔美国人列表中几个前列腺癌文献相关基因包括CRISP3、SIM2、THBS4和MMP9;高加索美国人列表包括AMACR、APOF、CRISP3、OR51E2(PSGR)、SIM2和

THBS4。

[0138] AA基因列表与CA基因列表的比较显示在两个人种群中84个基因是共同的。共同基因列表包括前列腺癌中少数充分研究的基因像AMACR、CRISP3和SIM2。DLX1、NKX3-2和CRISP3在该列表中是最前的过量表达的基因。图2. 在两个人种群中最始终过量表达的基因是DLX1和NKX2-3。表5列出在AA和CA前列腺肿瘤两者中前15个过量表达的基因(通过倍数变化排序)。

[0139] 表5

基因符号	AA	CA
DLX1	168.76	94.24
NKX2-3	128.58	49.14
CRISP3*	128.08	711.14
PHGR1	44.04	100.24
THBS4	17.37	18.87
AMACR*	11.89	25
GAP43	7.19	7.99
FFAR2	7.03	8.54
GCNT1	6.62	15.23
SIM2*	6.41	9.68
STX19	5.98	7.67
KLB	5.07	5.91
APOF	5.04	19.42
LOC283177	4.86	7
TRPM4	4.35	6.48
* 前列腺癌中已知的基因交替(gene alternation)		

类似地,将CA组(180个基因)的肿瘤/正常比与AA组的肿瘤/正常比进行比较。该基因列表显示一些充分研究的前列腺癌基因,例如与AA组相比,PCA3 (10倍)、PSGR (5倍)和AMACR (2倍)在CA组中过量表达(图3B)。另外,将TMPRSS2/ERG融合阳性样品的基因表达水平与融合阴性样品进行比较。CRISP3、GLDC和TDRD1是TMPRSS2/ERG融合阳性样品中的最前面的差异表达基因,而COL2A1和PLA2G7是TMPRSS2/ERG融合阴性样品中的最前面的差异表达基因。表6给出与AA组相比CA组前列腺肿瘤中最前面的差异表达基因。

[0140] 表6

基因符号	CA	AA
PCA3*	94.76	6.09
ALOX15	79.68	9.66
AMACR*	25	11.89
CDH19	13.73	1.43
OR51E2/PSGR	10.79	2.8
F5	8.89	4.16
FZD8	7.72	3.08
CLDN3	5.28	2.58
* 现有的前列腺癌诊断标志物		

将AA组(101个基因)中差异表达基因列表的肿瘤/正常比与CA组中的肿瘤/正常比进行比较以评价AA人种特异性基因表达趋势。图3A的热图显示在AA组中始终上调且在CA组中同时下调(或表达无变化)的基因。在该列表中,MMP9是被发现在AA组中极强上调但在CA组中下调的首位基因。表7给出与CA组相比AA组前列腺肿瘤中最前面的差异表达基因。

[0141] 表7

基因符号	AA	CA
COL10A1	539.86	16.81
HOXC4	72.06	13.13
ESPL1	35.49	1.92
MMP9	32.23	0.27
ABCA13	22.65	2.02
PCDHGA1	15.15	1.82
AGSK1	6.09	0.98

本文引用的所有专利、专利申请和发表的参考文献均通过引用以其整体结合到本文中。虽然参照其优选的实施方案特别显示和描述了本发明,但本领域技术人员应了解,可在不偏离随附权利要求书所包括的本发明的范围的情况下在其中进行形式和详细资料的各种改变。

[0142] 参考文献

下列参考文献被引用于本申请中,并且提供有关本发明领域的总体信息以及提供本申请中论述的测定法和其它详细资料。下列参考文献通过引用以其整体结合到本文中。

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序列表

<110> THE HENRY M. JACKSON FOUNDATION FOR THE ADVANCEMENT OF
MILITARY MEDICINE, INC.
GENOMATIX

<120> 前列腺癌基因谱和使用所述基因谱的方法

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Gly His Gly Asp Ser Gly Leu Cys Pro Gln Gly Tyr Val His Thr Val
85 90 95

Leu Arg Asp Ser Cys Ser Glu Pro Lys Glu His Glu Glu Glu Pro Glu
100 105 110

[0005]

Val Val Arg Asp Arg Ser Gln Lys Ser Cys Gln Leu Lys Lys Ser Leu
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Glu Thr Ala Gly Asp Cys Lys Ala Ala Glu Glu Ser Glu Arg Pro Lys
130 135 140

Pro Arg Ser Arg Arg Lys Pro Arg Val Leu Phe Ser Gln Ala Gln Val
145 150 155 160

Phe Glu Leu Glu Arg Arg Phe Lys Gln Gln Arg Tyr Leu Ser Ala Pro
165 170 175

Glu Arg Glu His Leu Ala Ser Ser Leu Lys Leu Thr Ser Thr Gln Val
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Lys Ile Trp Phe Gln Asn Arg Arg Tyr Lys Cys Lys Arg Gln Arg Gln
195 200 205

Asp Lys Ser Leu Glu Leu Gly Ala His Ala Pro Pro Pro Pro Arg
210 215 220

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

Pro Ser Ala Gln Ala Tyr Gly Ala Pro Tyr Ser Val Gly Ala Ser Ala
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Tyr Ser Tyr Asn Ser Phe Pro Ala Tyr Gly Tyr Gly Asn Ser Ala Ala
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Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Tyr Ser
275 280 285

Ser Ser Tyr Gly Cys Ala Tyr Pro Ala Gly Gly Gly Gly Gly Gly Gly
290 295 300

[0006]

Gly Thr Ser Ala Ala Thr Thr Ala Met Gln Pro Ala Cys Ser Ala Ala
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Gly Gly Gly Pro Phe Val Asn Val Ser Asn Leu Gly Gly Phe Gly Ser
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Gly Gly Ser Ala Gln Pro Leu His Gln Gly Thr Ala Ala Gly Ala Ala
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Cys Ala Gln Gly Thr Leu Gln Gly Ile Arg Ala Trp
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<213> 智人

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[0008]

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<213> 智人

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Ala Asn Glu Asp Lys Asp Pro Ala Phe Thr Ala Leu Leu Thr Thr Gln

35 40 45

Thr Gln Val Gln Arg Glu Ile Val Asn Lys His Asn Glu Leu Arg Arg

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Ala Val Ser Pro Pro Ala Arg Asn Met Leu Lys Met Glu Trp Asn Lys
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Glu Ala Ala Ala Asn Ala Gln Lys Trp Ala Asn Gln Cys Asn Tyr Arg
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His Ser Asn Pro Lys Asp Arg Met Thr Ser Leu Lys Cys Gly Glu Asn
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Leu Tyr Met Ser Ser Ala Ser Ser Ser Trp Ser Gln Ala Ile Gln Ser
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Trp Phe Asp Glu Tyr Asn Asp Phe Asp Phe Gly Val Gly Pro Lys Thr
130 135 140

Pro Asn Ala Val Val Gly His Tyr Thr Gln Val Val Trp Tyr Ser Ser
145 150 155 160

[0009]

Tyr Leu Val Gly Cys Gly Asn Ala Tyr Cys Pro Asn Gln Lys Val Leu
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Lys Tyr Tyr Tyr Val Cys Gln Tyr Cys Pro Ala Gly Asn Trp Ala Asn
180 185 190

Arg Leu Tyr Val Pro Tyr Glu Gln Gly Ala Pro Cys Ala Ser Cys Pro
195 200 205

Asp Asn Cys Asp Asp Gly Leu Cys Thr Asn Gly Cys Lys Tyr Glu Asp
210 215 220

Leu Tyr Ser Asn Cys Lys Ser Leu Lys Leu Thr Leu Thr Cys Lys His
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Gln Leu Val Arg Asp Ser Cys Lys Ala Ser Cys Asn Cys Ser Asn Ser

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Pro Pro Gly His Cys Gly Pro Pro Pro Gly His Gly Pro Gly Pro Cys
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Gly Pro Pro Pro His His Gly Pro Gly Pro Cys Gly Pro Pro Pro Gly
35 40 45

His Gly Pro Gly Pro Cys Gly Pro Pro Pro His His Gly Pro Gly Pro
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Cys Gly Pro Pro Pro Gly His Gly Pro Gly His Pro Pro Pro Gly Pro
65 70 75 80

His His

[0012]

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<212> DNA

<213> 智人

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Val Leu Thr Asp Pro Ala Leu Asn Asp Leu Tyr Val Ile Ser Thr Phe
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Lys Leu Gln Thr Lys Ser Ser Ala Thr Ile Phe Gly Leu Tyr Ser Ser
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Lys Ala Ile Leu Arg Tyr Leu Lys Asn Asp Gly Lys Val His Leu Val
100 105 110
Val Phe Asn Asn Leu Gln Leu Ala Asp Gly Arg Arg His Arg Ile Leu
115 120 125
Leu Arg Leu Ser Asn Leu Gln Arg Gly Ala Gly Ser Leu Glu Leu Tyr
130 135 140
Leu Asp Cys Ile Gln Val Asp Ser Val His Asn Leu Pro Arg Ala Phe
145 150 155 160
Ala Gly Pro Ser Gln Lys Pro Glu Thr Ile Glu Leu Arg Thr Phe Gln

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Arg Lys Pro Gln Asp Phe Leu Glu Glu Leu Lys Leu Val Val Arg Gly			
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Ser Leu Phe Gln Val Ala Ser Leu Gln Asp Cys Phe Leu Gln Gln Ser			
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Glu Pro Leu Ala Ala Thr Gly Thr Gly Asp Phe Asn Arg Gln Phe Leu			
210	215	220	
Gly Gln Met Thr Gln Leu Asn Gln Leu Leu Gly Glu Val Lys Asp Leu			
225	230	235	240
Leu Arg Gln Gln Val Lys Glu Thr Ser Phe Leu Arg Asn Thr Ile Ala			
245	250	255	
[0014]			
Glu Cys Gln Ala Cys Gly Pro Leu Lys Phe Gln Ser Pro Thr Pro Ser			
260	265	270	
Thr Val Val Pro Pro Ala Pro Pro Ala Pro Pro Thr Arg Pro Pro Arg			
275	280	285	
Arg Cys Asp Ser Asn Pro Cys Phe Arg Gly Val Gln Cys Thr Asp Ser			
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Arg Asp Gly Phe Gln Cys Gly Pro Cys Pro Glu Gly Tyr Thr Gly Asn			
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Gly Ile Thr Cys Ile Asp Val Asp Glu Cys Lys Tyr His Pro Cys Tyr			
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Pro Gly Val His Cys Ile Asn Leu Ser Pro Gly Phe Arg Cys Asp Ala			
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Cys Pro Val Gly Phe Thr Gly Pro Met Val Gln Gly Val Gly Ile Ser
355 360 365

Phe Ala Lys Ser Asn Lys Gln Val Cys Thr Asp Ile Asp Glu Cys Arg
370 375 380

Asn Gly Ala Cys Val Pro Asn Ser Ile Cys Val Asn Thr Leu Gly Ser
385 390 395 400

Tyr Arg Cys Gly Pro Cys Lys Pro Gly Tyr Thr Gly Asp Gln Ile Arg
405 410 415

Gly Cys Lys Ala Glu Arg Asn Cys Arg Asn Pro Glu Leu Asn Pro Cys
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Ser Val Asn Ala Gln Cys Ile Glu Glu Arg Gln Gly Asp Val Thr Cys
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[0015]

Val Cys Gly Val Gly Trp Ala Gly Asp Gly Tyr Ile Cys Gly Lys Asp
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Val Asp Ile Asp Ser Tyr Pro Asp Glu Glu Leu Pro Cys Ser Ala Arg
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Asn Cys Lys Lys Asp Asn Cys Lys Tyr Val Pro Asn Ser Gly Gln Glu
485 490 495

Asp Ala Asp Arg Asp Gly Ile Gly Asp Ala Cys Asp Glu Asp Ala Asp
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Gly Asp Gly Ile Leu Asn Glu Gln Asp Asn Cys Val Leu Ile His Asn
515 520 525

Val Asp Gln Arg Asn Ser Asp Lys Asp Ile Phe Gly Asp Ala Cys Asp
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Asn Cys Leu Ser Val Leu Asn Asn Asp Gln Lys Asp Thr Asp Gly Asp
545 550 555 560

Gly Arg Gly Asp Ala Cys Asp Asp Asp Met Asp Gly Asp Gly Ile Lys
565 570 575

Asn Ile Leu Asp Asn Cys Pro Lys Phe Pro Asn Arg Asp Gln Arg Asp
580 585 590

Lys Asp Gly Asp Gly Val Gly Asp Ala Cys Asp Ser Cys Pro Asp Val
595 600 605

Ser Asn Pro Asn Gln Ser Asp Val Asp Asn Asp Leu Val Gly Asp Ser
610 615 620

Cys Asp Thr Asn Gln Asp Ser Asp Gly Asp Gly His Gln Asp Ser Thr
625 630 635 640

[0016]

Asp Asn Cys Pro Thr Val Ile Asn Ser Ala Gln Leu Asp Thr Asp Lys
645 650 655

Asp Gly Ile Gly Asp Glu Cys Asp Asp Asp Asp Asn Asp Gly Ile
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Pro Asp Leu Val Pro Pro Gly Pro Asp Asn Cys Arg Leu Val Pro Asn
675 680 685

Pro Ala Gln Glu Asp Ser Asn Ser Asp Gly Val Gly Asp Ile Cys Glu
690 695 700

Ser Asp Phe Asp Gln Asp Gln Val Ile Asp Arg Ile Asp Val Cys Pro
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Glu Asn Ala Glu Val Thr Leu Thr Asp Phe Arg Ala Tyr Gln Thr Val
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Val Leu Asp Pro Glu Gly Asp Ala Gln Ile Asp Pro Asn Trp Val Val
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Leu Asn Gln Gly Met Glu Ile Val Gln Thr Met Asn Ser Asp Pro Gly
755 760 765

Leu Ala Val Gly Tyr Thr Ala Phe Asn Gly Val Asp Phe Glu Gly Thr
770 775 780

Phe His Val Asn Thr Gln Thr Asp Asp Asp Tyr Ala Gly Phe Ile Phe
785 790 795 800

Gly Tyr Gln Asp Ser Ser Ser Phe Tyr Val Val Met Trp Lys Gln Thr
805 810 815

Glu Gln Thr Tyr Trp Gln Ala Thr Pro Phe Arg Ala Val Ala Glu Pro
820 825 830

[0017]

Gly Ile Gln Leu Lys Ala Val Lys Ser Lys Thr Gly Pro Gly Glu His
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Leu Arg Asn Ser Leu Trp His Thr Gly Asp Thr Ser Asp Gln Val Arg
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Leu Leu Trp Lys Asp Ser Arg Asn Val Gly Trp Lys Asp Lys Val Ser
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Tyr Arg Trp Phe Leu Gln His Arg Pro Gln Val Gly Tyr Ile Arg Val
885 890 895

Arg Phe Tyr Glu Gly Ser Glu Leu Val Ala Asp Ser Gly Val Thr Ile
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Asp Thr Thr Met Arg Gly Gly Arg Leu Gly Val Phe Cys Phe Ser Gln

915

920

925

Glu Asn Ile Ile Trp Ser Asn Leu Lys Tyr Arg Cys Asn Asp Thr Ile
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<211> 3233

<212> DNA

<213> 智人

<400> 10

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<211> 382

<212> PRT

<213> 智人

<400> 11

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Gly Lys Arg Ser Leu Val Leu Asp Leu Lys Gln Pro Arg Gly Ala Ala			
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Val Leu Arg Arg Leu Cys Lys Arg Ser Asp Val Leu Leu Glu Pro Phe			
65	70	75	80
Arg Arg Gly Val Met Glu Lys Leu Gln Leu Gly Pro Glu Ile Leu Gln			
85	90	95	
Arg Glu Asn Pro Arg Leu Ile Tyr Ala Arg Leu Ser Gly Phe Gly Gln			
100	105	110	
[0021]			
Ser Gly Ser Phe Cys Arg Leu Ala Gly His Asp Ile Asn Tyr Leu Ala			
115	120	125	
Leu Ser Gly Val Leu Ser Lys Ile Gly Arg Ser Gly Glu Asn Pro Tyr			
130	135	140	
Ala Pro Leu Asn Leu Leu Ala Asp Phe Ala Gly Gly Gly Leu Met Cys			
145	150	155	160
Ala Leu Gly Ile Ile Met Ala Leu Phe Asp Arg Thr Arg Thr Gly Lys			
165	170	175	
Gly Gln Val Ile Asp Ala Asn Met Val Glu Gly Thr Ala Tyr Leu Ser			
180	185	190	
Ser Phe Leu Trp Lys Thr Gln Lys Leu Ser Leu Trp Glu Ala Pro Arg			
195	200	205	

Gly Gln Asn Met Leu Asp Gly Gly Ala Pro Phe Tyr Thr Thr Tyr Arg
 210 215 220

Thr Ala Asp Gly Glu Phe Met Ala Val Gly Ala Ile Glu Pro Gln Phe
 225 230 235 240

Tyr Glu Leu Leu Ile Lys Gly Leu Gly Leu Lys Ser Asp Glu Leu Pro
 245 250 255

Asn Gln Met Ser Met Asp Asp Trp Pro Glu Met Lys Lys Lys Phe Ala
 260 265 270

Asp Val Phe Ala Glu Lys Thr Lys Ala Glu Trp Cys Gln Ile Phe Asp
 275 280 285

Gly Thr Asp Ala Cys Val Thr Pro Val Leu Thr Phe Glu Glu Val Val
 290 295 300

[0022]

His His Asp His Asn Lys Glu Arg Gly Ser Phe Ile Thr Ser Glu Glu
 305 310 315 320

Gln Asp Val Ser Pro Arg Pro Ala Pro Leu Leu Leu Asn Thr Pro Ala
 325 330 335

Ile Pro Ser Phe Lys Arg Asp Pro Phe Ile Gly Glu His Thr Glu Glu
 340 345 350

Ile Leu Glu Glu Phe Gly Phe Ser Arg Glu Glu Ile Tyr Gln Leu Asn
 355 360 365

Ser Asp Lys Ile Ile Glu Ser Asn Lys Val Lys Ala Ser Leu
 370 375 380

<210> 12

<211> 3352

<212> DNA

<213> 智人

<400> 12

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[0023]

[0024]

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[0025]

<210> 13

<211> 238

<212> PRT

<213> 智人

<400> 13

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Asp Gln Lys Ile Glu Gln Asp Gly Ile Lys Pro Glu Asp Lys Ala His

20 25 30

Lys Ala Ala Thr Lys Ile Gln Ala Ser Phe Arg Gly His Ile Thr Arg

35 40 45

Lys Lys Leu Lys Gly Glu Lys Lys Asp Asp Val Gln Ala Ala Glu Ala

50 55 60

Glu Ala Asn Lys Lys Asp Glu Ala Pro Val Ala Asp Gly Val Glu Lys

65 70 75 80

Lys Gly Glu Gly Thr Thr Thr Ala Glu Ala Ala Pro Ala Thr Gly Ser
85 90 95

Lys Pro Asp Glu Pro Gly Lys Ala Gly Glu Thr Pro Ser Glu Glu Lys
100 105 110

Lys Gly Glu Gly Asp Ala Ala Thr Glu Gln Ala Ala Pro Gln Ala Pro
115 120 125

Ala Ser Ser Glu Glu Lys Ala Gly Ser Ala Glu Thr Glu Ser Ala Thr
130 135 140

Lys Ala Ser Thr Asp Asn Ser Pro Ser Ser Lys Ala Glu Asp Ala Pro
145 150 155 160

Ala Lys Glu Glu Pro Lys Gln Ala Asp Val Pro Ala Ala Val Thr Ala
165 170 175

[0026]

Ala Ala Ala Thr Thr Pro Ala Ala Glu Asp Ala Ala Ala Lys Ala Thr
180 185 190

Ala Gln Pro Pro Thr Glu Thr Gly Glu Ser Ser Gln Ala Glu Glu Asn
195 200 205

Ile Glu Ala Val Asp Glu Thr Lys Pro Lys Glu Ser Ala Arg Gln Asp
210 215 220

Glu Gly Lys Glu Glu Glu Pro Glu Ala Asp Gln Glu His Ala
225 230 235

<210> 14
<211> 3710
<212> DNA
<213> 智人

<400> 14

[0027]

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[0029]

<210> 15

<211> 330

<212> PRT

<213> 智人

<400> 15

Met Leu Pro Asp Trp Lys Ser Ser Leu Ile Leu Met Ala Tyr Ile Ile

1 5 10 15

Ile Phe Leu Thr Gly Leu Pro Ala Asn Leu Leu Ala Leu Arg Ala Phe

20 25 30

Val Gly Arg Ile Arg Gln Pro Gln Pro Ala Pro Val His Ile Leu Leu

35 40 45

Leu Ser Leu Thr Leu Ala Asp Leu Leu Leu Leu Leu Leu Pro Phe
50 55 60

Lys Ile Ile Glu Ala Ala Ser Asn Phe Arg Trp Tyr Leu Pro Lys Val
65 70 75 80

Val Cys Ala Leu Thr Ser Phe Gly Phe Tyr Ser Ser Ile Tyr Cys Ser
85 90 95

Thr Trp Leu Leu Ala Gly Ile Ser Ile Glu Arg Tyr Leu Gly Val Ala
100 105 110

Phe Pro Val Gln Tyr Lys Leu Ser Arg Arg Pro Leu Tyr Gly Val Ile
115 120 125

Ala Ala Leu Val Ala Trp Val Met Ser Phe Gly His Cys Thr Ile Val
130 135 140

[0030]

Ile Ile Val Gln Tyr Leu Asn Thr Thr Glu Gln Val Arg Ser Gly Asn
145 150 155 160

Glu Ile Thr Cys Tyr Glu Asn Phe Thr Asp Asn Gln Leu Asp Val Val
165 170 175

Leu Pro Val Arg Leu Glu Leu Cys Leu Val Leu Phe Phe Ile Pro Met
180 185 190

Ala Val Thr Ile Phe Cys Tyr Trp Arg Phe Val Trp Ile Met Leu Ser
195 200 205

Gln Pro Leu Val Gly Ala Gln Arg Arg Arg Arg Ala Val Gly Leu Ala
210 215 220

Val Val Thr Leu Leu Asn Phe Leu Val Cys Phe Gly Pro Tyr Asn Val

225	230	235	240
Ser His Leu Val Gly Tyr His Gln Arg Lys Ser Pro Trp Trp Arg Ser			
245	250	255	
Ile Ala Val Val Phe Ser Ser Leu Asn Ala Ser Leu Asp Pro Leu Leu			
260	265	270	
Phe Tyr Phe Ser Ser Ser Val Val Arg Arg Ala Phe Gly Arg Gly Leu			
275	280	285	
Gln Val Leu Arg Asn Gln Gly Ser Ser Leu Leu Gly Arg Arg Gly Lys			
290	295	300	
Asp Thr Ala Glu Gly Thr Asn Glu Asp Arg Gly Val Gly Gln Gly Glu			
305	310	315	320

[0031]

Gly Met Pro Ser Ser Asp Phe Thr Thr Glu
325 330

<210> 16

<211> 2069

<212> DNA

<213> 智人

<400> 16

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[0032]

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<210> 17

<211> 428

<212> PRT

<213> 智人

<400> 17

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Met Leu Arg Thr Leu Leu Arg Arg Arg Leu Phe Ser Tyr Pro Thr Lys
1           5           10           15

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Tyr Tyr Phe Met Val Leu Val Leu Ser Leu Ile Thr Phe Ser Val Leu
          20           25           30

```

[0033]

```

Arg Ile His Gln Lys Pro Glu Phe Val Ser Val Arg His Leu Glu Leu
          35           40           45

```

```

Ala Gly Glu Asn Pro Ser Ser Asp Ile Asn Cys Thr Lys Val Leu Gln
          50           55           60

```

```

Gly Asp Val Asn Glu Ile Gln Lys Val Lys Leu Glu Ile Leu Thr Val
65           70           75           80

```

```

Lys Phe Lys Lys Arg Pro Arg Trp Thr Pro Asp Asp Tyr Ile Asn Met
          85           90           95

```

```

Thr Ser Asp Cys Ser Ser Phe Ile Lys Arg Arg Lys Tyr Ile Val Glu
          100          105          110

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Pro Leu Ser Lys Glu Glu Ala Glu Phe Pro Ile Ala Tyr Ser Ile Val
          115          120          125

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Val His His Lys Ile Glu Met Leu Asp Arg Leu Leu Arg Ala Ile Tyr
130 135 140

Met Pro Gln Asn Phe Tyr Cys Ile His Val Asp Thr Lys Ser Glu Asp
145 150 155 160

Ser Tyr Leu Ala Ala Val Met Gly Ile Ala Ser Cys Phe Ser Asn Val
165 170 175

Phe Val Ala Ser Arg Leu Glu Ser Val Val Tyr Ala Ser Trp Ser Arg
180 185 190

Val Gln Ala Asp Leu Asn Cys Met Lys Asp Leu Tyr Ala Met Ser Ala
195 200 205

Asn Trp Lys Tyr Leu Ile Asn Leu Cys Gly Met Asp Phe Pro Ile Lys
210 215 220

[0034]

Thr Asn Leu Glu Ile Val Arg Lys Leu Lys Leu Leu Met Gly Glu Asn
225 230 235 240

Asn Leu Glu Thr Glu Arg Met Pro Ser His Lys Glu Glu Arg Trp Lys
245 250 255

Lys Arg Tyr Glu Val Val Asn Gly Lys Leu Thr Asn Thr Gly Thr Val
260 265 270

Lys Met Leu Pro Pro Leu Glu Thr Pro Leu Phe Ser Gly Ser Ala Tyr
275 280 285

Phe Val Val Ser Arg Glu Tyr Val Gly Tyr Val Leu Gln Asn Glu Lys
290 295 300

Ile Gln Lys Leu Met Glu Trp Ala Gln Asp Thr Tyr Ser Pro Asp Glu
305 310 315 320

Tyr Leu Trp Ala Thr Ile Gln Arg Ile Pro Glu Val Pro Gly Ser Leu
325 330 335

Pro Ala Ser His Lys Tyr Asp Leu Ser Asp Met Gln Ala Val Ala Arg
340 345 350

Phe Val Lys Trp Gln Tyr Phe Glu Gly Asp Val Ser Lys Gly Ala Pro
355 360 365

Tyr Pro Pro Cys Asp Gly Val His Val Arg Ser Val Cys Ile Phe Gly
370 375 380

Ala Gly Asp Leu Asn Trp Met Leu Arg Lys His His Leu Phe Ala Asn
385 390 395 400

Lys Phe Asp Val Asp Val Asp Leu Phe Ala Ile Gln Cys Leu Asp Glu
405 410 415

[0035]

His Leu Arg His Lys Ala Leu Glu Thr Leu Lys His
420 425

<210> 18

<211> 5984

<212> DNA

<213> 智人

<400> 18

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 <213> 智人

<400> 19
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Asn Gly Glu Phe Tyr Glu Leu Ala Lys Leu Leu Pro Leu Pro Ser Ala
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Ile Thr Ser Gln Leu Asp Lys Ala Ser Ile Ile Arg Leu Thr Thr Ser
 35 40 45

Tyr Leu Lys Met Arg Ala Val Phe Pro Glu Gly Leu Gly Asp Ala Trp
 50 55 60

[0040]

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

Gly Ser His Leu Leu Gln Thr Leu Asp Gly Phe Val Phe Val Val Ala
 85 90 95

Ser Asp Gly Lys Ile Met Tyr Ile Ser Glu Thr Ala Ser Val His Leu
 100 105 110

Gly Leu Ser Gln Val Glu Leu Thr Gly Asn Ser Ile Tyr Glu Tyr Ile
 115 120 125

His Pro Ser Asp His Asp Glu Met Thr Ala Val Leu Thr Ala His Gln
 130 135 140

Pro Leu His His His Leu Leu Gln Glu Tyr Glu Ile Glu Arg Ser Phe
 145 150 155 160

Phe Leu Arg Met Lys Cys Val Leu Ala Lys Arg Asn Ala Gly Leu Thr
165 170 175

Cys Ser Gly Tyr Lys Val Ile His Cys Ser Gly Tyr Leu Lys Ile Arg
180 185 190

Gln Tyr Met Leu Asp Met Ser Leu Tyr Asp Ser Cys Tyr Gln Ile Val
195 200 205

Gly Leu Val Ala Val Gly Gln Ser Leu Pro Pro Ser Ala Ile Thr Glu
210 215 220

Ile Lys Leu Tyr Ser Asn Met Phe Met Phe Arg Ala Ser Leu Asp Leu
225 230 235 240

Lys Leu Ile Phe Leu Asp Ser Arg Val Thr Glu Val Thr Gly Tyr Glu
245 250 255

[0041]

Pro Gln Asp Leu Ile Glu Lys Thr Leu Tyr His His Val His Gly Cys
260 265 270

Asp Val Phe His Leu Arg Tyr Ala His His Leu Leu Leu Val Lys Gly
275 280 285

Gln Val Thr Thr Lys Tyr Tyr Arg Leu Leu Ser Lys Arg Gly Gly Trp
290 295 300

Val Trp Val Gln Ser Tyr Ala Thr Val Val His Asn Ser Arg Ser Ser
305 310 315 320

Arg Pro His Cys Ile Val Ser Val Asn Tyr Val Leu Thr Glu Ile Glu
325 330 335

Tyr Lys Glu Leu Gln Leu Ser Leu Glu Gln Val Ser Thr Ala Lys Ser
340 345 350

Gln Asp Ser Trp Arg Thr Ala Leu Ser Thr Ser Gln Glu Thr Arg Lys
355 360 365

Leu Val Lys Pro Lys Asn Thr Lys Met Lys Thr Lys Leu Arg Thr Asn
370 375 380

Pro Tyr Pro Pro Gln Gln Tyr Ser Ser Phe Gln Met Asp Lys Leu Glu
385 390 395 400

Cys Gly Gln Leu Gly Asn Trp Arg Ala Ser Pro Pro Ala Ser Ala Ala
405 410 415

Ala Pro Pro Glu Leu Gln Pro His Ser Glu Ser Ser Asp Leu Leu Tyr
420 425 430

Thr Pro Ser Tyr Ser Leu Pro Phe Ser Tyr His Tyr Gly His Phe Pro
435 440 445

[0042]

Leu Asp Ser His Val Phe Ser Ser Lys Lys Pro Met Leu Pro Ala Lys
450 455 460

Phe Gly Gln Pro Gln Gly Ser Pro Cys Glu Val Ala Arg Phe Phe Leu
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Ser Thr Leu Pro Ala Ser Gly Glu Cys Gln Trp His Tyr Ala Asn Pro
485 490 495

Leu Val Pro Ser Ser Ser Ser Pro Ala Lys Asn Pro Pro Glu Pro Pro
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Ala Asn Thr Ala Arg His Ser Leu Val Pro Ser Tyr Glu Ala Pro Ala
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Ala Ala Val Arg Arg Phe Gly Glu Asp Thr Ala Pro Pro Ser Phe Pro

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Ala Pro Glu Cys Cys Ala Pro Pro Thr Pro Glu Ala Pro Gly Ala Pro			
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Ala Gln Leu Pro Phe Val Leu Leu Asn Tyr His Arg Val Leu Ala Arg			
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Arg Gly Pro Leu Gly Gly Ala Ala Pro Ala Ala Ser Gly Leu Ala Cys			
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[0043]			
Ala Pro Gly Gly Pro Glu Ala Ala Thr Gly Ala Leu Arg Leu Arg His			
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Leu Gly Ala Ser Val Ile Ile Thr Asn Gly Arg			
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[0044]

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<211> 294

<212> PRT

<213> 智人

<400> 21

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Val Phe Leu Gln Gln Ala Val Ile Tyr Glu Arg Glu Pro Val Ala Glu
35 40 45

Arg His Leu His Glu Ile Gln Lys Leu Gln Glu Ser Ile Asn Asn Leu
50 55 60

Ala Asp Asn Val Gln Lys Phe Gly Gln Gln Gln Lys Ser Leu Val Ala
65 70 75 80

Ser Met Arg Arg Phe Ser Leu Leu Lys Arg Glu Ser Thr Ile Thr Lys
85 90 95

[0047]

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

Val Thr Arg Ile Leu Lys Ser Gln His Ala Ala Met Phe Arg His Phe
130 135 140

Gln Gln Ile Met Phe Ile Tyr Asn Asp Thr Ile Ala Ala Lys Gln Glu
145 150 155 160

Lys Cys Lys Thr Phe Ile Leu Arg Gln Leu Glu Val Ala Gly Lys Glu
165 170 175

Met Ser Glu Glu Asp Val Asn Asp Met Leu His Gln Gly Lys Trp Glu
180 185 190

Val Phe Asn Glu Ser Leu Leu Thr Glu Ile Asn Ile Thr Lys Ala Gln
195 200 205

Leu Ser Glu Ile Glu Gln Arg His Lys Glu Leu Val Asn Leu Glu Asn
210 215 220

Gln Ile Lys Asp Leu Arg Asp Leu Phe Ile Gln Ile Ser Leu Leu Val
225 230 235 240

Glu Glu Gln Gly Glu Ser Ile Asn Asn Ile Glu Met Thr Val Asn Ser
245 250 255

Thr Lys Glu Tyr Val Asn Asn Thr Lys Glu Lys Phe Gly Leu Ala Val
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[0048]

Pro Cys Cys Ser Ser Lys
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<211> 1198

<212> DNA

<213> 智人

<400> 22

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Gly Gly Leu Gln Arg Ser Val Ile Leu Ser Ala Leu Ile Leu Leu Arg

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Glu Gly Ser Trp Lys Lys Asp Gly Lys Gly Pro Ser Ile Trp Asp His
100 105 110

Phe Ile His Thr His Leu Lys Asn Val Ser Ser Thr Asn Gly Ser Ser
115 120 125

Asp Ser Tyr Ile Phe Leu Glu Lys Asp Leu Ser Ala Leu Asp Phe Ile
130 135 140

[0050]

Gly Val Ser Phe Tyr Gln Phe Ser Ile Ser Trp Pro Arg Leu Phe Pro
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Asp Gly Ile Val Thr Val Ala Asn Ala Lys Gly Leu Gln Tyr Tyr Ser
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Thr Leu Leu Asp Ala Leu Val Leu Arg Asn Ile Glu Pro Ile Val Thr
180 185 190

Leu Tyr His Trp Asp Leu Pro Leu Ala Leu Gln Glu Lys Tyr Gly Gly
195 200 205

Trp Lys Asn Asp Thr Ile Ile Asp Ile Phe Asn Asp Tyr Ala Thr Tyr
210 215 220

Cys Phe Gln Met Phe Gly Asp Arg Val Lys Tyr Trp Ile Thr Ile His
225 230 235 240

Asn Pro Tyr Leu Val Ala Trp His Gly Tyr Gly Thr Gly Met His Ala
245 250 255

Pro Gly Glu Lys Gly Asn Leu Ala Ala Val Tyr Thr Val Gly His Asn
260 265 270

Leu Ile Lys Ala His Ser Lys Val Trp His Asn Tyr Asn Thr His Phe
275 280 285

Arg Pro His Gln Lys Gly Trp Leu Ser Ile Thr Leu Gly Ser His Trp
290 295 300

Ile Glu Pro Asn Arg Ser Glu Asn Thr Met Asp Ile Phe Lys Cys Gln
305 310 315 320

Gln Ser Met Val Ser Val Leu Gly Trp Phe Ala Asn Pro Ile His Gly
325 330 335

[0051]

Asp Gly Asp Tyr Pro Glu Gly Met Arg Lys Lys Leu Phe Ser Val Leu
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Phe Phe Ala Phe Ser Phe Gly Pro Asn Asn Phe Lys Pro Leu Asn Thr
370 375 380

Met Ala Lys Met Gly Gln Asn Val Ser Leu Asn Leu Arg Glu Ala Leu
385 390 395 400

Asn Trp Ile Lys Leu Glu Tyr Asn Asn Pro Arg Ile Leu Ile Ala Glu
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Asn Gly Trp Phe Thr Asp Ser Arg Val Lys Thr Glu Asp Thr Thr Ala
420 425 430

Ile Tyr Met Met Lys Asn Phe Leu Ser Gln Val Leu Gln Ala Ile Arg
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Leu Asp Glu Ile Arg Val Phe Gly Tyr Thr Ala Trp Ser Leu Leu Asp
450 455 460

Gly Phe Glu Trp Gln Asp Ala Tyr Thr Ile Arg Arg Gly Leu Phe Tyr
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Val Asp Phe Asn Ser Lys Gln Lys Glu Arg Lys Pro Lys Ser Ser Ala
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[0052]

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Phe Ser Asp Pro His Leu Tyr Val Trp Asn Ala Thr Gly Asn Arg Leu
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Leu His Arg Val Glu Gly Val Arg Leu Lys Thr Arg Pro Ala Gln Cys
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Thr Asp Phe Val Asn Ile Lys Lys Gln Leu Glu Met Leu Ala Arg Met
580 585 590

Lys Val Thr His Tyr Arg Phe Ala Leu Asp Trp Ala Ser Val Leu Pro
595 600 605

Thr Gly Asn Leu Ser Ala Val Asn Arg Gln Ala Leu Arg Tyr Tyr Arg

610

615

620

Cys Val Val Ser Glu Gly Leu Lys Leu Gly Ile Ser Ala Met Val Thr
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Tyr Ala Gly Leu Cys Phe Gln Glu Leu Gly Asp Leu Val Lys Leu Trp
675 680 685

Ile Thr Ile Asn Glu Pro Asn Arg Leu Ser Asp Ile Tyr Asn Arg Ser
690 695 700

[0053]

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Tyr Ala Asp Ser His Trp Arg Ala Ala Glu Arg Phe Leu Gln Phe Glu
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Ile Ala Trp Phe Ala Glu Pro Leu Phe Lys Thr Gly Asp Tyr Pro Ala
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Thr Val Asp Phe Cys Ala Leu Asn His Phe Thr Thr Arg Phe Val Met
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His Glu Gln Leu Ala Gly Ser Arg Tyr Asp Ser Asp Arg Asp Ile Gln
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Phe Leu Gln Asp Ile Thr Arg Leu Ser Ser Pro Thr Arg Leu Ala Val
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Ile Pro Trp Gly Val Arg Lys Leu Leu Arg Trp Val Arg Arg Asn Tyr
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Gly Asp Met Asp Ile Tyr Ile Thr Ala Ser Gly Ile Asp Asp Gln Ala
885 890 895

[0054]

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Phe Thr Ser Asp Phe Lys Ala Lys Ser Ser Ile Gln Phe Tyr Asn Lys
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Gln Lys Lys Pro Leu Ile Phe Leu Gly Cys Cys Phe Phe Ser Thr Leu
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Val Leu Leu Leu Ser Ile Ala Ile Phe Gln Arg Gln Lys Arg Arg
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Gly Lys Arg Val Val Ser
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Cys Gln Phe Leu His Pro Lys Ser Leu Pro Gly Phe Ser His Met Ala			
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Gly Leu Gln Lys Gly Arg Ser Thr Glu Arg Asn Val Ser Val Glu Ala			
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Arg Val Gly Arg Ser Leu Pro Thr Glu Asp Cys Glu Asn Glu Lys Glu			
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Gln Ala Val His Asn Val Val Gln Leu Leu Pro Gly Val Gly Thr Phe			
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Lys Ala Arg Glu Arg Gly Arg Asp Gly Ala Ile Asp Leu Gly Tyr Asp
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Leu Leu Met Thr Met Ala Gly Met Ser Gly Gly Pro Met Gly Leu Ala
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[0061]

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<211> 1722

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<213> 智人

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Met Glu Asp Ala Phe Gly Ala Ala Val Val Thr Val Trp Asp Ser Asp

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Ala His Thr Thr Glu Lys Pro Thr Asp Ala Tyr Gly Glu Leu Asp Phe

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Thr Gly Ala Gly Arg Lys His Ser Asn Phe Leu Arg Leu Ser Asp Arg

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[0066]

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130 135 140

Ala Ala Gln Ser Thr Gly Ala Trp Ile Val Thr Gly Gly Leu His Thr

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Gly Ile Gly Arg His Val Gly Val Ala Val Arg Asp His Gln Met Ala

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Gly Cys Leu Gly Gly Glu Asn Arg Phe Arg Leu Arg Leu Glu Ser Tyr
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[0067]

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Gly Ser Glu Glu Phe Glu Thr Ile Val Leu Lys Ala Leu Val Lys Ala

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Cys Gly Ser Ser Glu Ala Ser Ala Tyr Leu Asp Glu Leu Arg Leu Ala
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Asp Ile Gln Trp Arg Ser Phe His Leu Glu Ala Ser Leu Met Asp Ala
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Leu Leu Asn Asp Arg Pro Glu Phe Val Arg Leu Leu Ile Ser His Gly
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Leu Ser Leu Gly His Phe Leu Thr Pro Met Arg Leu Ala Gln Leu Tyr
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[0068]

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Lys Met Cys Ala Pro Arg Tyr Pro Ser Gly Gly Ala Trp Asp Pro His
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Pro Gly Gln Gly Phe Gly Glu Ser Met Tyr Leu Leu Ser Asp Lys Ala
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Asp Leu Leu Leu Trp Ala Leu Leu Leu Asn Arg Ala Gln Met Ala Met
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Tyr Phe Trp Glu Met Gly Ser Asn Ala Val Ser Ser Ala Leu Gly Ala
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Cys Leu Leu Leu Arg Val Met Ala Arg Leu Glu Pro Asp Ala Glu Glu
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Ala Ala Arg Arg Lys Asp Leu Ala Phe Lys Phe Glu Gly Met Gly Val
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Asp Leu Phe Gly Glu Cys Tyr Arg Ser Ser Glu Val Arg Ala Ala Arg
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Leu Leu Leu Arg Arg Cys Pro Leu Trp Gly Asp Ala Thr Cys Leu Gln
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[0069]

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Leu Tyr Phe Trp Ala Phe Thr Leu Leu Cys Glu Glu Leu Arg Gln Gly
820 825 830

Leu Ser Gly Gly Gly Gly Ser Leu Ala Ser Gly Gly Pro Gly Pro Gly
835 840 845

[0070]

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Cys Arg Leu Thr Pro Gly Leu Tyr His Leu Gly Arg Thr Val Leu Cys
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Ile Asp Phe Met Val Phe Thr Val Arg Leu Leu His Ile Phe Thr Val
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Asn Lys Gln Leu Gly Pro Lys Ile Val Ile Val Ser Lys Met Met Lys
915 920 925

Asp Val Phe Phe Phe Leu Phe Phe Leu Gly Val Trp Leu Val Ala Tyr
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Gly Val Ala Thr Glu Gly Leu Leu Arg Pro Arg Asp Ser Asp Phe Pro
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Gln Ile Pro Gln Glu Asp Met Asp Val Ala Leu Met Glu His Ser Asn
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Cys Ser Ser Glu Pro Gly Phe Trp Ala His Pro Pro Gly Ala Gln Ala
995 1000 1005

Gly Thr Cys Val Ser Gln Tyr Ala Asn Trp Leu Val Val Leu Leu
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[0071]

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[0072]

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<211> 662

<212> PRT

<213> 智人

<400> 31

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Gly Ser Asn Asn Gln Val Gln Leu Trp Leu Val Gly Gln His Gly Glu

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25

30

Ala Ala Leu Gly Lys Arg Leu Trp Pro Ala Arg Gly Lys Glu Thr Glu

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40

45

Leu Lys Val Glu Val Pro Glu Tyr Leu Gly Pro Leu Leu Phe Val Lys
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Leu Arg Lys Arg His Leu Leu Lys Asp Asp Ala Trp Phe Cys Asn Trp
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Ile Ser Val Gln Gly Pro Gly Ala Gly Asp Glu Val Arg Phe Pro Cys
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Tyr Arg Trp Val Glu Gly Asn Gly Val Leu Ser Leu Pro Glu Gly Thr
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Gly Arg Thr Val Gly Glu Asp Pro Gln Gly Leu Phe Gln Lys His Arg
115 120 125

Glu Glu Glu Leu Glu Glu Arg Arg Lys Leu Tyr Arg Trp Gly Asn Trp
130 135 140

[0079]

Lys Asp Gly Leu Ile Leu Asn Met Ala Gly Ala Lys Leu Tyr Asp Leu
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Pro Val Asp Glu Arg Phe Leu Glu Asp Lys Arg Val Asp Phe Glu Val
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Ser Leu Ala Lys Gly Leu Ala Asp Leu Ala Ile Lys Asp Ser Leu Asn
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Val Leu Thr Cys Trp Lys Asp Leu Asp Asp Phe Asn Arg Ile Phe Trp
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Cys Gly Gln Ser Lys Leu Ala Glu Arg Val Arg Asp Ser Trp Lys Glu
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Asp Ala Leu Phe Gly Tyr Gln Phe Leu Asn Gly Ala Asn Pro Val Val
225 230 235 240

Leu Arg Arg Ser Ala His Leu Pro Ala Arg Leu Val Phe Pro Pro Gly
245 250 255

Met Glu Glu Leu Gln Ala Gln Leu Glu Lys Glu Leu Glu Gly Gly Thr
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Leu Phe Glu Ala Asp Phe Ser Leu Leu Asp Gly Ile Lys Ala Asn Val
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Ile Leu Cys Ser Gln Gln His Leu Ala Ala Pro Leu Val Met Leu Lys
290 295 300

Leu Gln Pro Asp Gly Lys Leu Leu Pro Met Val Ile Gln Leu Gln Leu
305 310 315 320

Pro Arg Thr Gly Ser Pro Pro Pro Pro Leu Phe Leu Pro Thr Asp Pro
325 330 335

[0080]

Pro Met Ala Trp Leu Leu Ala Lys Cys Trp Val Arg Ser Ser Asp Phe
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Gln Leu His Glu Leu Gln Ser His Leu Leu Arg Gly His Leu Met Ala
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Glu Val Ile Val Val Ala Thr Met Arg Cys Leu Pro Ser Ile His Pro
370 375 380

Ile Phe Lys Leu Ile Ile Pro His Leu Arg Tyr Thr Leu Glu Ile Asn
385 390 395 400

Val Arg Ala Arg Thr Gly Leu Val Ser Asp Met Gly Ile Phe Asp Gln
405 410 415

Ile Met Ser Thr Gly Gly Gly Gly His Val Gln Leu Leu Lys Gln Ala
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Gly Ala Phe Leu Thr Tyr Ser Ser Phe Cys Pro Pro Asp Asp Leu Ala
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Asp Arg Gly Leu Leu Gly Val Lys Ser Ser Phe Tyr Ala Gln Asp Ala
450 455 460

Leu Arg Leu Trp Glu Ile Ile Tyr Arg Tyr Val Glu Gly Ile Val Ser
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Leu His Tyr Lys Thr Asp Val Ala Val Lys Asp Asp Pro Glu Leu Gln
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Thr Trp Cys Arg Glu Ile Thr Glu Ile Gly Leu Gln Gly Ala Gln Asp
500 505 510

Arg Gly Phe Pro Val Ser Leu Gln Ala Arg Asp Gln Val Cys His Phe
515 520 525

[0081]

Val Thr Met Cys Ile Phe Thr Cys Thr Gly Gln His Ala Ser Val His
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Leu Gly Gln Leu Asp Trp Tyr Ser Trp Val Pro Asn Ala Pro Cys Thr
545 550 555 560

Met Arg Leu Pro Pro Pro Thr Thr Lys Asp Ala Thr Leu Glu Thr Val
565 570 575

Met Ala Thr Leu Pro Asn Phe His Gln Ala Ser Leu Gln Met Ser Ile
580 585 590

Thr Trp Gln Leu Gly Arg Arg Gln Pro Val Met Val Ala Val Gly Gln
595 600 605

His Glu Glu Glu Tyr Phe Ser Gly Pro Glu Pro Lys Ala Val Leu Lys

610

615

620

Lys Phe Arg Glu Glu Leu Ala Ala Leu Asp Lys Glu Ile Glu Ile Arg
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Asn Ala Lys Leu Asp Met Pro Tyr Glu Tyr Leu Arg Pro Ser Val Val
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Glu Asn Ser Val Ala Ile
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<210> 32

<211> 2707

<212> DNA

<213> 智人

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<210> 33

<211> 772

<212> PRT

<213> 智人

[0084]

<400> 33

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Trp Pro Cys Leu Gly Ala Thr Glu Asn Ser Gln Thr Lys Lys Val Lys
          20           25           30

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Gln Pro Val Arg Ser His Leu Arg Val Lys Arg Gly Trp Val Trp Asn
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Gln Phe Phe Val Pro Glu Glu Met Asn Thr Thr Ser His His Ile Gly
          50           55           60

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Gln Leu Arg Ser Asp Leu Asp Asn Gly Asn Asn Ser Phe Gln Tyr Lys
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Leu Leu Gly Ala Gly Ala Gly Ser Thr Phe Ile Ile Asp Glu Arg Thr

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	Gly Asp Ile Tyr Ala Ile Gln Lys Leu Asp Arg Glu Glu Arg Ser Leu		
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	Tyr Ile Leu Arg Ala Gln Val Ile Asp Ile Ala Thr Gly Arg Ala Val		
	115	120	125
	Glu Pro Glu Ser Glu Phe Val Ile Lys Val Ser Asp Ile Asn Asp Asn		
	130	135	140
	Glu Pro Lys Phe Leu Asp Glu Pro Tyr Glu Ala Ile Val Pro Glu Met		
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	Ser Pro Glu Gly Thr Leu Val Ile Gln Val Thr Ala Ser Asp Ala Asp		
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	Gly Gln Pro Tyr Phe Ser Val Glu Pro Thr Thr Gly Val Ile Arg Ile		
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	Ser Ser Lys Met Asp Arg Glu Leu Gln Asp Glu Tyr Trp Val Ile Ile		
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	Gln Ala Lys Asp Met Ile Gly Gln Pro Gly Ala Leu Ser Gly Thr Thr		
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	Ser Val Leu Ile Lys Leu Ser Asp Val Asn Asp Asn Lys Pro Ile Phe		
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	Lys Glu Ser Leu Tyr Arg Leu Thr Val Ser Glu Ser Ala Pro Thr Gly		
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Thr Ser Ile Gly Thr Ile Met Ala Tyr Asp Asn Asp Ile Gly Glu Asn
275 280 285

Ala Glu Met Asp Tyr Ser Ile Glu Glu Asp Asp Ser Gln Thr Phe Asp
290 295 300

Ile Ile Thr Asn His Glu Thr Gln Glu Gly Ile Val Ile Leu Lys Lys
305 310 315 320

Lys Val Asp Phe Glu His Gln Asn His Tyr Gly Ile Arg Ala Lys Val
325 330 335

Lys Asn His His Val Pro Glu Gln Leu Met Lys Tyr His Thr Glu Ala
340 345 350

Ser Thr Thr Phe Ile Lys Ile Gln Val Glu Asp Val Asp Glu Pro Pro
355 360 365

[0086]

Leu Phe Leu Leu Pro Tyr Tyr Val Phe Glu Val Phe Glu Glu Thr Pro
370 375 380

Gln Gly Ser Phe Val Gly Val Val Ser Ala Thr Asp Pro Asp Asn Arg
385 390 395 400

Lys Ser Pro Ile Arg Tyr Ser Ile Thr Arg Ser Lys Val Phe Asn Ile
405 410 415

Asn Asp Asn Gly Thr Ile Thr Thr Ser Asn Ser Leu Asp Arg Glu Ile
420 425 430

Ser Ala Trp Tyr Asn Leu Ser Ile Thr Ala Thr Glu Lys Tyr Asn Ile
435 440 445

Glu Gln Ile Ser Ser Ile Pro Leu Tyr Val Gln Val Leu Asn Ile Asn
450 455 460

Asp His Ala Pro Glu Phe Ser Gln Tyr Tyr Glu Thr Tyr Val Cys Glu
465 470 475 480

Asn Ala Gly Ser Gly Gln Val Ile Gln Thr Ile Ser Ala Val Asp Arg
485 490 495

Asp Glu Ser Ile Glu Glu His His Phe Tyr Phe Asn Leu Ser Val Glu
500 505 510

Asp Thr Asn Asn Ser Ser Phe Thr Ile Ile Asp Asn Gln Asp Asn Thr
515 520 525

Ala Val Ile Leu Thr Asn Arg Thr Gly Phe Asn Leu Gln Glu Glu Pro
530 535 540

Val Phe Tyr Ile Ser Ile Leu Ile Ala Asp Asn Gly Ile Pro Ser Leu
545 550 555 560

[0087]

Thr Ser Thr Asn Thr Leu Thr Ile His Val Cys Asp Cys Gly Asp Ser
565 570 575

Gly Ser Thr Gln Thr Cys Gln Tyr Gln Glu Leu Val Leu Ser Met Gly
580 585 590

Phe Lys Thr Glu Val Ile Ile Ala Ile Leu Ile Cys Ile Met Ile Ile
595 600 605

Phe Gly Phe Ile Phe Leu Thr Leu Gly Leu Lys Gln Arg Arg Lys Gln
610 615 620

Ile Leu Phe Pro Glu Lys Ser Glu Asp Phe Arg Glu Asn Ile Phe Gln
625 630 635 640

Tyr Asp Asp Glu Gly Gly Gly Glu Glu Asp Thr Glu Ala Phe Asp Ile
645 650 655

Ala Glu Leu Arg Ser Ser Thr Ile Met Arg Glu Arg Lys Thr Arg Lys
660 665 670

Thr Thr Ser Ala Glu Ile Arg Ser Leu Tyr Arg Gln Ser Leu Gln Val
675 680 685

Gly Pro Asp Ser Ala Ile Phe Arg Lys Phe Ile Leu Glu Lys Leu Glu
690 695 700

Glu Ala Asn Thr Asp Pro Cys Ala Pro Pro Phe Asp Ser Leu Gln Thr
705 710 715 720

Tyr Ala Phe Glu Gly Thr Gly Ser Leu Ala Gly Ser Leu Ser Ser Leu
725 730 735

Glu Ser Ala Val Ser Asp Gln Asp Glu Ser Tyr Asp Tyr Leu Asn Glu
740 745 750

[0088]

Leu Gly Pro Arg Phe Lys Arg Leu Ala Cys Met Phe Gly Ser Ala Val
755 760 765

Gln Ser Asn Asn
770

<210> 34

<211> 6241

<212> DNA

<213> 智人

<400> 34

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<212> PRT

<213> 智人

<400> 35

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Pro Gly Leu Glu Lys Ala His Phe Trp Val Gly Phe Pro Leu Leu Ser

20 25 30

Met Tyr Val Val Ala Met Phe Gly Asn Cys Ile Val Val Phe Ile Val

35 40 45

Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met

50 55 60

Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile

65 70 75 80

Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Phe Glu Ala Cys

85 90 95

Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr

[0093]

100	105	110
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115	120	125
Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly		
130	135	140
Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Phe Pro Leu Pro Leu		
145	150	155 160
Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser		
165	170	175
Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu		
180	185	190
[0094]		
Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val		
195	200	205
Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val		
210	215	220
Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys		
225	230	235 240
Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro Leu Ile Gly		
245	250	255
Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg		
260	265	270
Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro		
275	280	285

Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala
 290 295 300

Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys
 305 310 315 320

<210> 36

<211> 2799

<212> DNA

<213> 智人

<400> 36

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<210> 37

<211> 2224

<212> PRT

<213> 智人

<400> 37

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Met Phe Pro Gly Cys Pro Arg Leu Trp Val Leu Val Val Leu Gly Thr
1           5           10           15

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[0097]

```

Ser Trp Val Gly Trp Gly Ser Gln Gly Thr Glu Ala Ala Gln Leu Arg
          20           25           30

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Gln Phe Tyr Val Ala Ala Gln Gly Ile Ser Trp Ser Tyr Arg Pro Glu
          35           40           45

```

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Pro Thr Asn Ser Ser Leu Asn Leu Ser Val Thr Ser Phe Lys Lys Ile
          50           55           60

```

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Val Tyr Arg Glu Tyr Glu Pro Tyr Phe Lys Lys Glu Lys Pro Gln Ser
65           70           75           80

```

```

Thr Ile Ser Gly Leu Leu Gly Pro Thr Leu Tyr Ala Glu Val Gly Asp
          85           90           95

```

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Ile Ile Lys Val His Phe Lys Asn Lys Ala Asp Lys Pro Leu Ser Ile
100          105          110

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His Pro Gln Gly Ile Arg Tyr Ser Lys Leu Ser Glu Gly Ala Ser Tyr
115 120 125

Leu Asp His Thr Phe Pro Ala Glu Lys Met Asp Asp Ala Val Ala Pro
130 135 140

Gly Arg Glu Tyr Thr Tyr Glu Trp Ser Ile Ser Glu Asp Ser Gly Pro
145 150 155 160

Thr His Asp Asp Pro Pro Cys Leu Thr His Ile Tyr Tyr Ser His Glu
165 170 175

Asn Leu Ile Glu Asp Phe Asn Ser Gly Leu Ile Gly Pro Leu Leu Ile
180 185 190

Cys Lys Lys Gly Thr Leu Thr Glu Gly Gly Thr Gln Lys Thr Phe Asp
195 200 205

[0098]

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

Ser Gln Ser Ser Ser Leu Met Tyr Thr Val Asn Gly Tyr Val Asn Gly
225 230 235 240

Thr Met Pro Asp Ile Thr Val Cys Ala His Asp His Ile Ser Trp His
245 250 255

Leu Leu Gly Met Ser Ser Gly Pro Glu Leu Phe Ser Ile His Phe Asn
260 265 270

Gly Gln Val Leu Glu Gln Asn His His Lys Val Ser Ala Ile Thr Leu
275 280 285

Val Ser Ala Thr Ser Thr Thr Ala Asn Met Thr Val Gly Pro Glu Gly

290

295

300

Lys Trp Ile Ile Ser Ser Leu Thr Pro Lys His Leu Gln Ala Gly Met
305 310 315 320

Gln Ala Tyr Ile Asp Ile Lys Asn Cys Pro Lys Lys Thr Arg Asn Leu
325 330 335

Lys Lys Ile Thr Arg Glu Gln Arg Arg His Met Lys Arg Trp Glu Tyr
340 345 350

Phe Ile Ala Ala Glu Glu Val Ile Trp Asp Tyr Ala Pro Val Ile Pro
355 360 365

Ala Asn Met Asp Lys Lys Tyr Arg Ser Gln His Leu Asp Asn Phe Ser
370 375 380

[0099]

Asn Gln Ile Gly Lys His Tyr Lys Lys Val Met Tyr Thr Gln Tyr Glu
385 390 395 400

Asp Glu Ser Phe Thr Lys His Thr Val Asn Pro Asn Met Lys Glu Asp
405 410 415

Gly Ile Leu Gly Pro Ile Ile Arg Ala Gln Val Arg Asp Thr Leu Lys
420 425 430

Ile Val Phe Lys Asn Met Ala Ser Arg Pro Tyr Ser Ile Tyr Pro His
435 440 445

Gly Val Thr Phe Ser Pro Tyr Glu Asp Glu Val Asn Ser Ser Phe Thr
450 455 460

Ser Gly Arg Asn Asn Thr Met Ile Arg Ala Val Gln Pro Gly Glu Thr
465 470 475 480

Tyr Thr Tyr Lys Trp Asn Ile Leu Glu Phe Asp Glu Pro Thr Glu Asn
485 490 495

Asp Ala Gln Cys Leu Thr Arg Pro Tyr Tyr Ser Asp Val Asp Ile Met
500 505 510

Arg Asp Ile Ala Ser Gly Leu Ile Gly Leu Leu Leu Ile Cys Lys Ser
515 520 525

Arg Ser Leu Asp Arg Arg Gly Ile Gln Arg Ala Ala Asp Ile Glu Gln
530 535 540

Gln Ala Val Phe Ala Val Phe Asp Glu Asn Lys Ser Trp Tyr Leu Glu
545 550 555 560

Asp Asn Ile Asn Lys Phe Cys Glu Asn Pro Asp Glu Val Lys Arg Asp
565 570 575

[0100]

Asp Pro Lys Phe Tyr Glu Ser Asn Ile Met Ser Thr Ile Asn Gly Tyr
580 585 590

Val Pro Glu Ser Ile Thr Thr Leu Gly Phe Cys Phe Asp Asp Thr Val
595 600 605

Gln Trp His Phe Cys Ser Val Gly Thr Gln Asn Glu Ile Leu Thr Ile
610 615 620

His Phe Thr Gly His Ser Phe Ile Tyr Gly Lys Arg His Glu Asp Thr
625 630 635 640

Leu Thr Leu Phe Pro Met Arg Gly Glu Ser Val Thr Val Thr Met Asp
645 650 655

Asn Val Gly Thr Trp Met Leu Thr Ser Met Asn Ser Ser Pro Arg Ser
660 665 670

Lys Lys Leu Arg Leu Lys Phe Arg Asp Val Lys Cys Ile Pro Asp Asp
675 680 685

Asp Glu Asp Ser Tyr Glu Ile Phe Glu Pro Pro Glu Ser Thr Val Met
690 695 700

Ala Thr Arg Lys Met His Asp Arg Leu Glu Pro Glu Asp Glu Glu Ser
705 710 715 720

Asp Ala Asp Tyr Asp Tyr Gln Asn Arg Leu Ala Ala Ala Leu Gly Ile
725 730 735

Arg Ser Phe Arg Asn Ser Ser Leu Asn Gln Glu Glu Glu Glu Phe Asn
740 745 750

Leu Thr Ala Leu Ala Leu Glu Asn Gly Thr Glu Phe Val Ser Ser Asn
755 760 765

[0101]

Thr Asp Ile Ile Val Gly Ser Asn Tyr Ser Ser Pro Ser Asn Ile Ser
770 775 780

Lys Phe Thr Val Asn Asn Leu Ala Glu Pro Gln Lys Ala Pro Ser His
785 790 795 800

Gln Gln Ala Thr Thr Ala Gly Ser Pro Leu Arg His Leu Ile Gly Lys
805 810 815

Asn Ser Val Leu Asn Ser Ser Thr Ala Glu His Ser Ser Pro Tyr Ser
820 825 830

Glu Asp Pro Ile Glu Asp Pro Leu Gln Pro Asp Val Thr Gly Ile Arg
835 840 845

Leu Leu Ser Leu Gly Ala Gly Glu Phe Lys Ser Gln Glu His Ala Lys
850 855 860

His Lys Gly Pro Lys Val Glu Arg Asp Gln Ala Ala Lys His Arg Phe
865 870 875 880

Ser Trp Met Lys Leu Leu Ala His Lys Val Gly Arg His Leu Ser Gln
885 890 895

Asp Thr Gly Ser Pro Ser Gly Met Arg Pro Trp Glu Asp Leu Pro Ser
900 905 910

Gln Asp Thr Gly Ser Pro Ser Arg Met Arg Pro Trp Lys Asp Pro Pro
915 920 925

Ser Asp Leu Leu Leu Lys Gln Ser Asn Ser Ser Lys Ile Leu Val
930 935 940

Gly Arg Trp His Leu Ala Ser Glu Lys Gly Ser Tyr Glu Ile Ile Gln
945 950 955 960

[0102]

Asp Thr Asp Glu Asp Thr Ala Val Asn Asn Trp Leu Ile Ser Pro Gln
965 970 975

Asn Ala Ser Arg Ala Trp Gly Glu Ser Thr Pro Leu Ala Asn Lys Pro
980 985 990

Gly Lys Gln Ser Gly His Pro Lys Phe Pro Arg Val Arg His Lys Ser
995 1000 1005

Leu Gln Val Arg Gln Asp Gly Gly Lys Ser Arg Leu Lys Lys Ser
1010 1015 1020

Gln Phe Leu Ile Lys Thr Arg Lys Lys Lys Lys Glu Lys His Thr
1025 1030 1035

His His Ala Pro Leu Ser Pro Arg Thr Phe His Pro Leu Arg Ser

1040	1045	1050
Glu Ala Tyr Asn Thr Phe Ser	Glu Arg Arg Leu Lys	His Ser Leu
1055	1060	1065
Val Leu His Lys Ser Asn Glu	Thr Ser Leu Pro Thr	Asp Leu Asn
1070	1075	1080
Gln Thr Leu Pro Ser Met Asp	Phe Gly Trp Ile Ala	Ser Leu Pro
1085	1090	1095
Asp His Asn Gln Asn Ser Ser	Asn Asp Thr Gly Gln	Ala Ser Cys
1100	1105	1110
Pro Pro Gly Leu Tyr Gln Thr	Val Pro Pro Glu Glu	His Tyr Gln
1115	1120	1125
[0103]		
Thr Phe Pro Ile Gln Asp Pro	Asp Gln Met His Ser	Thr Ser Asp
1130	1135	1140
Pro Ser His Arg Ser Ser Ser	Pro Glu Leu Ser Glu	Met Leu Glu
1145	1150	1155
Tyr Asp Arg Ser His Lys Ser	Phe Pro Thr Asp Ile	Ser Gln Met
1160	1165	1170
Ser Pro Ser Ser Glu His Glu	Val Trp Gln Thr Val	Ile Ser Pro
1175	1180	1185
Asp Leu Ser Gln Val Thr Leu	Ser Pro Glu Leu Ser	Gln Thr Asn
1190	1195	1200
Leu Ser Pro Asp Leu Ser His	Thr Thr Leu Ser Pro	Glu Leu Ile
1205	1210	1215

Gln Arg Asn Leu Ser Pro Ala Leu Gly Gln Met Pro Ile Ser Pro
1220 1225 1230

Asp Leu Ser His Thr Thr Leu Ser Pro Asp Leu Ser His Thr Thr
1235 1240 1245

Leu Ser Leu Asp Leu Ser Gln Thr Asn Leu Ser Pro Glu Leu Ser
1250 1255 1260

Gln Thr Asn Leu Ser Pro Ala Leu Gly Gln Met Pro Leu Ser Pro
1265 1270 1275

Asp Leu Ser His Thr Thr Leu Ser Leu Asp Phe Ser Gln Thr Asn
1280 1285 1290

Leu Ser Pro Glu Leu Ser His Met Thr Leu Ser Pro Glu Leu Ser
1295 1300 1305

[0104]

Gln Thr Asn Leu Ser Pro Ala Leu Gly Gln Met Pro Ile Ser Pro
1310 1315 1320

Asp Leu Ser His Thr Thr Leu Ser Leu Asp Phe Ser Gln Thr Asn
1325 1330 1335

Leu Ser Pro Glu Leu Ser Gln Thr Asn Leu Ser Pro Ala Leu Gly
1340 1345 1350

Gln Met Pro Leu Ser Pro Asp Pro Ser His Thr Thr Leu Ser Leu
1355 1360 1365

Asp Leu Ser Gln Thr Asn Leu Ser Pro Glu Leu Ser Gln Thr Asn
1370 1375 1380

Leu Ser Pro Asp Leu Ser Glu Met Pro Leu Phe Ala Asp Leu Ser
1385 1390 1395

Gln Ile Pro Leu Thr Pro Asp Leu Asp Gln Met Thr Leu Ser Pro
1400 1405 1410

Asp Leu Gly Glu Thr Asp Leu Ser Pro Asn Phe Gly Gln Met Ser
1415 1420 1425

Leu Ser Pro Asp Leu Ser Gln Val Thr Leu Ser Pro Asp Ile Ser
1430 1435 1440

Asp Thr Thr Leu Leu Pro Asp Leu Ser Gln Ile Ser Pro Pro Pro
1445 1450 1455

Asp Leu Asp Gln Ile Phe Tyr Pro Ser Glu Ser Ser Gln Ser Leu
1460 1465 1470

Leu Leu Gln Glu Phe Asn Glu Ser Phe Pro Tyr Pro Asp Leu Gly
1475 1480 1485

[0105]

Gln Met Pro Ser Pro Ser Ser Pro Thr Leu Asn Asp Thr Phe Leu
1490 1495 1500

Ser Lys Glu Phe Asn Pro Leu Val Ile Val Gly Leu Ser Lys Asp
1505 1510 1515

Gly Thr Asp Tyr Ile Glu Ile Ile Pro Lys Glu Glu Val Gln Ser
1520 1525 1530

Ser Glu Asp Asp Tyr Ala Glu Ile Asp Tyr Val Pro Tyr Asp Asp
1535 1540 1545

Pro Tyr Lys Thr Asp Val Arg Thr Asn Ile Asn Ser Ser Arg Asp
1550 1555 1560

Pro Asp Asn Ile Ala Ala Trp Tyr Leu Arg Ser Asn Asn Gly Asn
1565 1570 1575

Arg Arg Asn Tyr Tyr Ile Ala Ala Glu Glu Ile Ser Trp Asp Tyr
1580 1585 1590

Ser Glu Phe Val Gln Arg Glu Thr Asp Ile Glu Asp Ser Asp Asp
1595 1600 1605

Ile Pro Glu Asp Thr Thr Tyr Lys Lys Val Val Phe Arg Lys Tyr
1610 1615 1620

Leu Asp Ser Thr Phe Thr Lys Arg Asp Pro Arg Gly Glu Tyr Glu
1625 1630 1635

Glu His Leu Gly Ile Leu Gly Pro Ile Ile Arg Ala Glu Val Asp
1640 1645 1650

Asp Val Ile Gln Val Arg Phe Lys Asn Leu Ala Ser Arg Pro Tyr
1655 1660 1665

[0106]

Ser Leu His Ala His Gly Leu Ser Tyr Glu Lys Ser Ser Glu Gly
1670 1675 1680

Lys Thr Tyr Glu Asp Asp Ser Pro Glu Trp Phe Lys Glu Asp Asn
1685 1690 1695

Ala Val Gln Pro Asn Ser Ser Tyr Thr Tyr Val Trp His Ala Thr
1700 1705 1710

Glu Arg Ser Gly Pro Glu Ser Pro Gly Ser Ala Cys Arg Ala Trp
1715 1720 1725

Ala Tyr Tyr Ser Ala Val Asn Pro Glu Lys Asp Ile His Ser Gly
1730 1735 1740

Leu Ile Gly Pro Leu Leu Ile Cys Gln Lys Gly Ile Leu His Lys

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Asp Ser Asn Met Pro Met Asp Met Arg Glu Phe Val Leu Leu Phe		
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Met Thr Phe Asp Glu Lys Lys Ser Trp Tyr Tyr Glu Lys Lys Ser		
1775	1780	1785
Arg Ser Ser Trp Arg Leu Thr Ser Ser Glu Met Lys Lys Ser His		
1790	1795	1800
Glu Phe His Ala Ile Asn Gly Met Ile Tyr Ser Leu Pro Gly Leu		
1805	1810	1815
Lys Met Tyr Glu Gln Glu Trp Val Arg Leu His Leu Leu Asn Ile		
1820	1825	1830
[0107]		
Gly Gly Ser Gln Asp Ile His Val Val His Phe His Gly Gln Thr		
1835	1840	1845
Leu Leu Glu Asn Gly Asn Lys Gln His Gln Leu Gly Val Trp Pro		
1850	1855	1860
Leu Leu Pro Gly Ser Phe Lys Thr Leu Glu Met Lys Ala Ser Lys		
1865	1870	1875
Pro Gly Trp Trp Leu Leu Asn Thr Glu Val Gly Glu Asn Gln Arg		
1880	1885	1890
Ala Gly Met Gln Thr Pro Phe Leu Ile Met Asp Arg Asp Cys Arg		
1895	1900	1905
Met Pro Met Gly Leu Ser Thr Gly Ile Ile Ser Asp Ser Gln Ile		
1910	1915	1920

Lys Ala Ser Glu Phe Leu Gly Tyr Trp Glu Pro Arg Leu Ala Arg
1925 1930 1935

Leu Asn Asn Gly Gly Ser Tyr Asn Ala Trp Ser Val Glu Lys Leu
1940 1945 1950

Ala Ala Glu Phe Ala Ser Lys Pro Trp Ile Gln Val Asp Met Gln
1955 1960 1965

Lys Glu Val Ile Ile Thr Gly Ile Gln Thr Gln Gly Ala Lys His
1970 1975 1980

Tyr Leu Lys Ser Cys Tyr Thr Thr Glu Phe Tyr Val Ala Tyr Ser
1985 1990 1995

Ser Asn Gln Ile Asn Trp Gln Ile Phe Lys Gly Asn Ser Thr Arg
2000 2005 2010

[0108]

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Gln Gly Cys Glu Val Asn Gly Cys Ser Thr Pro Leu Gly Met Glu
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Asn Gly Lys Ile Glu Asn Lys Gln Ile Thr Ala Ser Ser Phe Lys
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Asn Tyr Thr Tyr Met Pro Asn Gln Phe Asn His Asp Thr Gln Asp Glu

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Ala Gly Leu Glu Val His Gln Phe Trp Pro Leu Val Glu Ile Gln Cys

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Ser Pro Asp Leu Lys Phe Phe Leu Cys Ser Met Tyr Thr Pro Ile Cys
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Leu Glu Asp Tyr Lys Lys Pro Leu Pro Pro Cys Arg Ser Val Cys Glu
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Arg Ala Lys Ala Gly Cys Ala Pro Leu Met Arg Gln Tyr Gly Phe Ala
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Trp Pro Asp Arg Met Arg Cys Asp Arg Leu Pro Glu Gln Gly Asn Pro
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[0117]

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[0118]

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[0119]

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<210> 41

<211> 220

<212> PRT

<213> 智人

<400> 41

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1 5 10 15

Trp Leu Gly Thr Ile Val Cys Cys Ala Leu Pro Met Trp Arg Val Ser

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Ala Phe Ile Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly		
35	40	45
Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys		
50	55	60
Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg		
65	70	75 80
Ala Leu Ile Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val		
85	90	95
Ala Leu Val Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala		
100	105	110
[0123]		
Lys Ala Lys Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala		
115	120	125
Leu Leu Thr Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg		
130	135	140
Asp Phe Tyr Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly		
145	150	155 160
Ala Gly Leu Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly		
165	170	175
Gly Ala Leu Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr		
180	185	190
Ala Thr Lys Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala		
195	200	205

Ser Leu Gly Thr Gly Tyr Asp Arg Lys Asp Tyr Val
 210 215 220

<210> 42

<211> 1318

<212> DNA

<213> 智人

<400> 42

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 acccggagcc acccggtaga gccggccttg ccgcggcagc catgtccatg ggccctggaga 240
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[0124]

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cctttcgttt tgcaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1318

<210> 43
<211> 264
<212> PRT
<213> 智人

<400> 43

Met Ile Met Ser Ser Tyr Leu Met Asp Ser Asn Tyr Ile Asp Pro Lys
1 5 10 15

Phe Pro Pro Cys Glu Glu Tyr Ser Gln Asn Ser Tyr Ile Pro Glu His
20 25 30

Ser Pro Glu Tyr Tyr Gly Arg Thr Arg Glu Ser Gly Phe Gln His His
35 40 45

[0125]

His Gln Glu Leu Tyr Pro Pro Pro Pro Arg Pro Ser Tyr Pro Glu
50 55 60

Arg Gln Tyr Ser Cys Thr Ser Leu Gln Gly Pro Gly Asn Ser Arg Gly
65 70 75 80

His Gly Pro Ala Gln Ala Gly His His His Pro Glu Lys Ser Gln Ser
85 90 95

Leu Cys Glu Pro Ala Pro Leu Ser Gly Ala Ser Ala Ser Pro Ser Pro
100 105 110

Ala Pro Pro Ala Cys Ser Gln Pro Ala Pro Asp His Pro Ser Ser Ala
115 120 125

Ala Ser Lys Gln Pro Ile Val Tyr Pro Trp Met Lys Lys Ile His Val

	130	135	140	
	Ser Thr Val Asn Pro Asn Tyr Asn Gly Gly Glu Pro Lys Arg Ser Arg			
	145	150	155	160
	Thr Ala Tyr Thr Arg Gln Gln Val Leu Glu Leu Glu Lys Glu Phe His			
		165	170	175
	Tyr Asn Arg Tyr Leu Thr Arg Arg Arg Arg Ile Glu Ile Ala His Ser			
	180	185	190	
	Leu Cys Leu Ser Glu Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg			
	195	200	205	
	Met Lys Trp Lys Lys Asp His Arg Leu Pro Asn Thr Lys Val Arg Ser			
	210	215	220	
[0126]	Ala Pro Pro Ala Gly Ala Ala Pro Ser Thr Leu Ser Ala Ala Thr Pro			
	225	230	235	240
	Gly Thr Ser Glu Asp His Ser Gln Ser Ala Thr Pro Pro Glu Gln Gln			
		245	250	255
	Arg Ala Glu Asp Ile Thr Arg Leu			
	260			
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	<211> 2328			
	<212> DNA			
	<213> 智人			
	<400> 41			
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[0127]	tgccgaagct gggggcagct ggggagggtg gggatgggag gggagagaca gaagttgagg	240
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	cagtttgagg agccaaaaga aaatcaaat gaactttcag ttcagagagg cagtctatag	2160
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<210> 45

<211> 264

<212> PRT

<213> 智人

<400> 45

Met Ile Met Ser Ser Tyr Leu Met Asp Ser Asn Tyr Ile Asp Pro Lys

1 5 10 15

Phe Pro Pro Cys Glu Glu Tyr Ser Gln Asn Ser Tyr Ile Pro Glu His

20 25 30

Ser Pro Glu Tyr Tyr Gly Arg Thr Arg Glu Ser Gly Phe Gln His His

35 40 45

His Gln Glu Leu Tyr Pro Pro Pro Pro Arg Pro Ser Tyr Pro Glu

50 55 60

Arg Ala Glu Asp Ile Thr Arg Leu
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<210> 46

<211> 2459

<212> DNA

<213> 智人

<400> 46

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<210> 47

<211> 2120

<212> PRT

<213> 智人

<400> 47

Met Arg Ser Phe Lys Arg Val Asn Phe Gly Thr Leu Leu Ser Ser Gln
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Lys Glu Ala Glu Glu Leu Leu Pro Ala Leu Lys Glu Phe Leu Ser Asn
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Pro Pro Ala Gly Phe Pro Ser Ser Arg Ser Asp Ala Glu Arg Arg Gln
35 40 45

Ala Cys Asp Ala Ile Leu Arg Ala Cys Asn Gln Gln Leu Thr Ala Lys
50 55 60

[0132]

Leu Ala Cys Pro Arg His Leu Gly Ser Leu Leu Glu Leu Ala Glu Leu
65 70 75 80

Ala Cys Asp Gly Tyr Leu Val Ser Thr Pro Gln Arg Pro Pro Leu Tyr
85 90 95

Leu Glu Arg Ile Leu Phe Val Leu Leu Arg Asn Ala Ala Ala Gln Gly
100 105 110

Ser Pro Glu Ala Thr Leu Arg Leu Ala Gln Pro Leu His Ala Cys Leu
115 120 125

Val Gln Cys Ser Arg Glu Ala Ala Pro Gln Asp Tyr Glu Ala Val Ala
130 135 140

Arg Gly Ser Phe Ser Leu Leu Trp Lys Gly Ala Glu Ala Leu Leu Glu
145 150 155 160

Arg Arg Ala Ala Phe Ala Ala Arg Leu Lys Ala Leu Ser Phe Leu Val
165 170 175

Leu Leu Glu Asp Glu Ser Thr Pro Cys Glu Val Pro His Phe Ala Ser
180 185 190

Pro Thr Ala Cys Arg Ala Val Ala Ala His Gln Leu Phe Asp Ala Ser
195 200 205

Gly His Gly Leu Asn Glu Ala Asp Ala Asp Phe Leu Asp Asp Leu Leu
210 215 220

Ser Arg His Val Ile Arg Ala Leu Val Gly Glu Arg Gly Ser Ser Ser
225 230 235 240

Gly Leu Leu Ser Pro Gln Arg Ala Leu Cys Leu Leu Glu Leu Thr Leu
245 250 255

[0133]

Glu His Cys Arg Arg Phe Cys Trp Ser Arg His His Asp Lys Ala Ile
260 265 270

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

Pro Ser Leu Gln Leu Cys Gln Leu Gly Val Lys Leu Leu Gln Val Gly
290 295 300

Glu Glu Gly Pro Gln Ala Val Ala Lys Leu Leu Ile Lys Ala Ser Ala
305 310 315 320

Val Leu Ser Lys Ser Met Glu Ala Pro Ser Pro Pro Leu Arg Ala Leu
325 330 335

Tyr Glu Ser Cys Gln Phe Phe Leu Ser Gly Leu Glu Arg Gly Thr Lys
340 345 350

Arg Arg Tyr Arg Leu Asp Ala Ile Leu Ser Leu Phe Ala Phe Leu Gly
355 360 365

Gly Tyr Cys Ser Leu Leu Gln Gln Leu Arg Asp Asp Gly Val Tyr Gly
370 375 380

Gly Ser Ser Lys Gln Gln Gln Ser Phe Leu Gln Met Tyr Phe Gln Gly
385 390 395 400

Leu His Leu Tyr Thr Val Val Val Tyr Asp Phe Ala Gln Gly Cys Gln
405 410 415

Ile Val Asp Leu Ala Asp Leu Thr Gln Leu Val Asp Ser Cys Lys Ser
420 425 430

Thr Val Val Trp Met Leu Glu Ala Leu Glu Gly Leu Ser Gly Gln Glu
435 440 445

[0134]

Leu Thr Asp His Met Gly Met Thr Ala Ser Tyr Thr Ser Asn Leu Ala
450 455 460

Tyr Ser Phe Tyr Ser His Lys Leu Tyr Ala Glu Ala Cys Ala Ile Ser
465 470 475 480

Glu Pro Leu Cys Gln His Leu Gly Leu Val Lys Pro Gly Thr Tyr Pro
485 490 495

Glu Val Pro Pro Glu Lys Leu His Arg Cys Phe Arg Leu Gln Val Glu
500 505 510

Ser Leu Lys Lys Leu Gly Lys Gln Ala Gln Gly Cys Lys Met Val Ile
515 520 525

Leu Trp Leu Ala Ala Leu Gln Pro Cys Ser Pro Glu His Met Ala Glu
530 535 540

Pro Val Thr Phe Trp Val Arg Val Lys Met Asp Ala Ala Arg Ala Gly
545 550 555 560

Asp Lys Glu Leu Gln Leu Lys Thr Leu Arg Asp Ser Leu Ser Gly Trp
565 570 575

Asp Pro Glu Thr Leu Ala Leu Leu Leu Arg Glu Glu Leu Gln Ala Tyr
580 585 590

Lys Ala Val Arg Ala Asp Thr Gly Gln Glu Arg Phe Asn Ile Ile Cys
595 600 605

Asp Leu Leu Glu Leu Ser Pro Glu Glu Thr Pro Ala Gly Ala Trp Ala
610 615 620

Arg Ala Thr His Leu Val Glu Leu Ala Gln Val Leu Cys Tyr His Asp
625 630 635 640

[0135]

Phe Thr Gln Gln Thr Asn Cys Ser Ala Leu Asp Ala Ile Arg Glu Ala
645 650 655

Leu Gln Leu Leu Asp Ser Val Arg Pro Glu Ala Gln Ala Arg Asp Gln
660 665 670

Leu Leu Asp Asp Lys Ala Gln Ala Leu Leu Trp Leu Tyr Ile Cys Thr
675 680 685

Leu Glu Ala Lys Met Gln Glu Gly Ile Glu Arg Asp Arg Arg Ala Gln
690 695 700

Ala Pro Gly Asn Leu Glu Glu Phe Glu Val Asn Asp Leu Asn Tyr Glu
705 710 715 720

Asp Lys Leu Gln Glu Asp Arg Phe Leu Tyr Ser Asn Ile Ala Phe Asn

	725	730	735
Leu Ala Ala Asp Ala Ala Gln Ser Lys Cys Leu Asp Gln Ala Leu Ala			
740	745	750	
Leu Trp Lys Glu Leu Leu Thr Lys Gly Gln Ala Pro Ala Val Arg Cys			
755	760	765	
Leu Gln Gln Thr Ala Ala Ser Leu Gln Ile Leu Ala Ala Leu Tyr Gln			
770	775	780	
Leu Val Ala Lys Pro Met Gln Ala Leu Glu Val Leu Leu Leu Leu Arg			
785	790	795	800
Ile Val Ser Glu Arg Leu Lys Asp His Ser Lys Ala Ala Gly Ser Ser			
805	810	815	
[0136]			
Cys His Ile Thr Gln Leu Leu Leu Thr Leu Gly Cys Pro Ser Tyr Ala			
820	825	830	
Gln Leu His Leu Glu Glu Ala Ala Ser Ser Leu Lys His Leu Asp Gln			
835	840	845	
Thr Thr Asp Thr Tyr Leu Leu Leu Ser Leu Thr Cys Asp Leu Leu Arg			
850	855	860	
Ser Gln Leu Tyr Trp Thr His Gln Lys Val Thr Lys Gly Val Ser Leu			
865	870	875	880
Leu Leu Ser Val Leu Arg Asp Pro Ala Leu Gln Lys Ser Ser Lys Ala			
885	890	895	
Trp Tyr Leu Leu Arg Val Gln Val Leu Gln Leu Val Ala Ala Tyr Leu			
900	905	910	

Ser Leu Pro Ser Asn Asn Leu Ser His Ser Leu Trp Glu Gln Leu Cys
915 920 925

Ala Gln Gly Trp Gln Thr Pro Glu Ile Ala Leu Ile Asp Ser His Lys
930 935 940

Leu Leu Arg Ser Ile Ile Leu Leu Leu Met Gly Ser Asp Ile Leu Ser
945 950 955 960

Thr Gln Lys Ala Ala Val Glu Thr Ser Phe Leu Asp Tyr Gly Glu Asn
965 970 975

Leu Val Gln Lys Trp Gln Val Leu Ser Glu Val Leu Ser Cys Ser Glu
980 985 990

Lys Leu Val Cys His Leu Gly Arg Leu Gly Ser Val Ser Glu Ala Lys
995 1000 1005

[0137]

Ala Phe Cys Leu Glu Ala Leu Lys Leu Thr Thr Lys Leu Gln Ile
1010 1015 1020

Pro Arg Gln Cys Ala Leu Phe Leu Val Leu Lys Gly Glu Leu Glu
1025 1030 1035

Leu Ala Arg Asn Asp Ile Asp Leu Cys Gln Ser Asp Leu Gln Gln
1040 1045 1050

Val Leu Phe Leu Leu Glu Ser Cys Thr Glu Phe Gly Gly Val Thr
1055 1060 1065

Gln His Leu Asp Ser Val Lys Lys Val His Leu Gln Lys Gly Lys
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Gln Gln Ala Gln Val Pro Cys Pro Pro Gln Leu Pro Glu Glu Glu
1085 1090 1095

Leu Phe	Leu Arg Gly Pro Ala	Leu Glu Leu Val Ala	Thr Val Ala
1100	1105	1110	

Lys Glu	Pro Gly Pro Ile Ala	Pro Ser Thr Asn Ser	Ser Pro Val
1115	1120	1125	

Leu Lys	Thr Lys Pro Gln Pro	Ile Pro Asn Phe Leu	Ser His Ser
1130	1135	1140	

Pro Thr	Cys Asp Cys Ser Leu	Cys Ala Ser Pro Val	Leu Thr Ala
1145	1150	1155	

Val Cys	Leu Arg Trp Val Leu	Val Thr Ala Gly Val	Arg Leu Ala
1160	1165	1170	

Met Gly	His Gln Ala Gln Gly	Leu Asp Leu Leu Gln	Val Val Leu
1175	1180	1185	

[0138]

Lys Gly	Cys Pro Glu Ala Ala	Glu Arg Leu Thr Gln	Ala Leu Gln
1190	1195	1200	

Ala Ser	Leu Asn His Lys Thr	Pro Pro Ser Leu Val	Pro Ser Leu
1205	1210	1215	

Leu Asp	Glu Ile Leu Ala Gln	Ala Tyr Thr Leu Leu	Ala Leu Glu
1220	1225	1230	

Gly Leu	Asn Gln Pro Ser Asn	Glu Ser Leu Gln Lys	Val Leu Gln
1235	1240	1245	

Ser Gly	Leu Lys Phe Val Ala	Ala Arg Ile Pro His	Leu Glu Pro
1250	1255	1260	

Trp Arg	Ala Ser Leu Leu Leu	Ile Trp Ala Leu Thr	Lys Leu Gly
1265	1270	1275	

Gly Leu Ser Cys Cys Thr Thr	Gln Leu Phe Ala Ser	Ser Trp Gly
1280	1285	1290

Trp Gln Pro Pro Leu Ile Lys	Ser Val Pro Gly Ser	Glu Pro Ser
1295	1300	1305

Lys Thr Gln Gly Gln Lys Arg	Ser Gly Arg Gly Arg	Gln Lys Leu
1310	1315	1320

Ala Ser Ala Pro Leu Arg Leu	Asn Asn Thr Ser Gln	Lys Gly Leu
1325	1330	1335

Glu Gly Arg Gly Leu Pro Cys	Thr Pro Lys Pro Pro	Asp Arg Ile
1340	1345	1350

Arg Gln Ala Gly Pro His Val	Pro Phe Thr Val Phe	Glu Glu Val
1355	1360	1365

[0139]

Cys Pro Thr Glu Ser Lys Pro	Glu Val Pro Gln Ala	Pro Arg Val
1370	1375	1380

Gln Gln Arg Val Gln Thr Arg	Leu Lys Val Asn Phe	Ser Asp Asp
1385	1390	1395

Ser Asp Leu Glu Asp Pro Val	Ser Ala Glu Ala Trp	Leu Ala Glu
1400	1405	1410

Glu Pro Lys Arg Arg Gly Thr	Ala Ser Arg Gly Arg	Gly Arg Ala
1415	1420	1425

Arg Lys Gly Leu Ser Leu Lys	Thr Asp Ala Val Val	Ala Pro Gly
1430	1435	1440

Ser Ala Pro Gly Asn Pro Gly	Leu Asn Gly Arg Ser	Arg Arg Ala
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1445	1450	1455
Lys Lys Val Ala Ser Arg His Cys Glu Glu Arg Arg Pro Gln Arg		
1460	1465	1470
Ala Ser Asp Gln Ala Arg Pro Gly Pro Glu Ile Met Arg Thr Ile		
1475	1480	1485
Pro Glu Glu Glu Leu Thr Asp Asn Trp Arg Lys Met Ser Phe Glu		
1490	1495	1500
Ile Leu Arg Gly Ser Asp Gly Glu Asp Ser Ala Ser Gly Gly Lys		
1505	1510	1515
Thr Pro Ala Pro Gly Pro Glu Ala Ala Ser Gly Glu Trp Glu Leu		
1520	1525	1530
[0140]		
Leu Arg Leu Asp Ser Ser Lys Lys Lys Leu Pro Ser Pro Cys Pro		
1535	1540	1545
Asp Lys Glu Ser Asp Lys Asp Leu Gly Pro Arg Leu Arg Leu Pro		
1550	1555	1560
Ser Ala Pro Val Ala Thr Gly Leu Ser Thr Leu Asp Ser Ile Cys		
1565	1570	1575
Asp Ser Leu Ser Val Ala Phe Arg Gly Ile Ser His Cys Pro Pro		
1580	1585	1590
Ser Gly Leu Tyr Ala His Leu Cys Arg Phe Leu Ala Leu Cys Leu		
1595	1600	1605
Gly His Arg Asp Pro Tyr Ala Thr Ala Phe Leu Val Thr Glu Ser		
1610	1615	1620

Val Ser Ile Thr Cys Arg His Gln Leu Leu Thr His Leu His Arg
1625 1630 1635

Gln Leu Ser Lys Ala Gln Lys His Arg Gly Ser Leu Glu Ile Ala
1640 1645 1650

Asp Gln Leu Gln Gly Leu Ser Leu Gln Glu Met Pro Gly Asp Val
1655 1660 1665

Pro Leu Ala Arg Ile Gln Arg Leu Phe Ser Phe Arg Ala Leu Glu
1670 1675 1680

Ser Gly His Phe Pro Gln Pro Glu Lys Glu Ser Phe Gln Glu Arg
1685 1690 1695

Leu Ala Leu Ile Pro Ser Gly Val Thr Val Cys Val Leu Ala Leu
1700 1705 1710

[0141]

Ala Thr Leu Gln Pro Gly Thr Val Gly Asn Thr Leu Leu Leu Thr
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Arg Leu Glu Lys Asp Ser Pro Pro Val Ser Val Gln Ile Pro Thr
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Gly Gln Asn Lys Leu His Leu Arg Ser Val Leu Asn Glu Phe Asp
1745 1750 1755

Ala Ile Gln Lys Ala Gln Lys Glu Asn Ser Ser Cys Thr Asp Lys
1760 1765 1770

Arg Glu Trp Trp Thr Gly Arg Leu Ala Leu Asp His Arg Met Glu
1775 1780 1785

Val Leu Ile Ala Ser Leu Glu Lys Ser Val Leu Gly Cys Trp Lys
1790 1795 1800

Gly Leu Leu Leu Pro Ser Ser	Glu Glu Pro Gly Pro	Ala Gln Glu
1805	1810	1815

Ala Ser Arg Leu Gln Glu Leu	Leu Gln Asp Cys Gly	Trp Lys Tyr
1820	1825	1830

Pro Asp Arg Thr Leu Leu Lys	Ile Met Leu Ser Gly	Ala Gly Ala
1835	1840	1845

Leu Thr Pro Gln Asp Ile Gln	Ala Leu Ala Tyr Gly	Leu Cys Pro
1850	1855	1860

Thr Gln Pro Glu Arg Ala Gln	Glu Leu Leu Asn Glu	Ala Val Gly
1865	1870	1875

Arg Leu Gln Gly Leu Thr Val	Pro Ser Asn Ser His	Leu Val Leu
1880	1885	1890

[0142]

Val Leu Asp Lys Asp Leu Gln	Lys Leu Pro Trp Glu	Ser Met Pro
1895	1900	1905

Ser Leu Gln Ala Leu Pro Val	Thr Arg Leu Pro Ser	Phe Arg Phe
1910	1915	1920

Leu Leu Ser Tyr Ser Ile Ile	Lys Glu Tyr Gly Ala	Ser Pro Val
1925	1930	1935

Leu Ser Gln Gly Val Asp Pro	Arg Ser Thr Phe Tyr	Val Leu Asn
1940	1945	1950

Pro His Asn Asn Leu Ser Ser	Thr Glu Glu Gln Phe	Arg Ala Asn
1955	1960	1965

Phe Ser Ser Glu Ala Gly Trp	Arg Gly Val Val Gly	Glu Val Pro
1970	1975	1980

Arg Pro	Glu Gln Val Gln Glu	Ala Leu Thr Lys His	Asp Leu Tyr
1985	1990	1995	

Ile Tyr	Ala Gly His Gly Ala	Gly Ala Arg Phe Leu	Asp Gly Gln
2000	2005	2010	

Ala Val	Leu Arg Leu Ser Cys	Arg Ala Val Ala Leu	Leu Phe Gly
2015	2020	2025	

Cys Ser	Ser Ala Ala Leu Ala	Val Arg Gly Asn Leu	Glu Gly Ala
2030	2035	2040	

Gly Ile	Val Leu Lys Tyr Ile	Met Ala Gly Cys Pro	Leu Phe Leu
2045	2050	2055	

Gly Asn	Leu Trp Asp Val Thr	Asp Arg Asp Ile Asp	Arg Tyr Thr
2060	2065	2070	

[0143]

Glu Ala	Leu Leu Gln Gly Trp	Leu Gly Ala Gly Pro	Gly Ala Pro
2075	2080	2085	

Leu Leu	Tyr Tyr Val Asn Gln	Ala Arg Gln Ala Pro	Arg Leu Lys
2090	2095	2100	

Tyr Leu	Ile Gly Ala Ala Pro	Ile Ala Tyr Gly Leu	Pro Val Ser
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Leu Arg
2120

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[0147]

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<213> 智人

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Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser		
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Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu		
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Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr		
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Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly		
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Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr		
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Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe		
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Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu		
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[0150]

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Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
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Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
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[0151]

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Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
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Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
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Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
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[0152]

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	ggcggtgatt gaagacgeet ttgcccgcgc ettcgactg tggagcgcg tgaacccet	480
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	tgccccggc attcaggag acgcccattt cgacgatgac gatttgtgtt ccttgggcaa	660
	ggcgctcgtg gtccaactc ggtttgaaa cgcagatggc gcggcctgcc acttccccit	720
	catcttcgag ggccgctcct actctgcctg caccaccgac ggtcgtccg acggcttgcc	780
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	aaccaccacc acaccgcgc ccacggctcc ccgacggtc tgcctaccg gacccccac	1440
	tgtccacccc teagagcgcc ccacagctgg cccacaggt cccctcag ctggccccac	1500
	aggtccccc actgtggcc ctctacggc cactactgtg cctttgagtc cgttgacga	1560
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	caaggatggg aagtactggc gattctctga gggcaggggg agccggccgc agggccccctt	1680
	ccttategcc gacaagtggc ccgcgctgcc ccgcaagctg gactcggtct ttgaggagcg	1740
	gctctccaag aagcttttct tcttctctgg gcgccaggtg tgggtgtaca caggcgcgtc	1800
	ggtgctgggc ccgaggcgtc tggacaagct gggectggga gccgacgtgg ccnaggtgac	1860
	cggggccctc cggagtggca gggggaagat gctgctgttc agcgggcgcg gcctctggag	1920
	gttcgacgtg aaggcgcaga tggtagatcc ccggagcgcc agcgaggtgg accggatgtt	1980
	ccccgggglg cctttggaca cgcacgacgt ctccaglac cgagagaaag cctatltctg	2040
	ccaggaccgc ttctactggc gctgagttc ccggagtggg ttgaaccagg tggaccaagt	2100
	gggtacglg acctatgaca tcttgcagtg ccttggagac tagggctccc gtcctgtttt	2160
	ggcagtgcca tgtaaattcc cactgggacc aacctgggg aaggagccag ttgcccgat	2220
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[0154]	ctcacctttg tttttgttg gagtgtttct aataaacttg gattctctaa cttttaaaaa	2340
	aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa	2387

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<213> 智人

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<223> 任何氨基酸

<220>

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<222> (2674)..(2674)

<223> 任何氨基酸

<400> 51

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1

5

10

15

Leu Cys Arg Leu Arg Asn Pro Val Leu Phe Leu Ala Glu Phe Phe Trp
20 25 30

Pro Cys Ile Leu Phe Val Ile Leu Thr Val Leu Arg Phe Gln Glu Pro
35 40 45

Pro Arg Tyr Arg Asp Ile Cys Tyr Leu Gln Pro Arg Asp Leu Pro Ser
50 55 60

Cys Gly Val Ile Pro Phe Val Gln Ser Leu Leu Cys Asn Thr Gly Ser
65 70 75 80

Arg Cys Arg Asn Phe Ser Tyr Glu Gly Ser Met Glu His His Phe Arg
85 90 95

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

[0155]

Ala Phe Leu Lys Glu Ile Gln Asp Leu Ala Glu Glu Ile His Gly Met
115 120 125

Met Asp Lys Ala Lys Asn Leu Lys Arg Leu Trp Val Glu Arg Ser Asn
130 135 140

Thr Pro Asp Ser Ser Tyr Gly Ser Ser Phe Phe Thr Met Asp Leu Asn
145 150 155 160

Lys Thr Glu Glu Val Ile Leu Lys Leu Glu Ser Leu His Gln Gln Pro
165 170 175

His Ile Trp Asp Phe Leu Leu Leu Leu Pro Arg Leu His Thr Ser His
180 185 190

Asp His Val Glu Asp Gly Met Asp Val Ala Val Asn Leu Leu Gln Thr
195 200 205

Ile Leu Asn Ser Leu Ile Ser Leu Glu Asp Leu Asp Trp Leu Pro Leu
210 215 220

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

Ser Thr Leu Thr Phe Leu Gln Gln His Gly Val Ala Val Thr Glu Pro
245 250 255

Val Tyr His Leu Ser Met Gln Asn Ile Val Trp Asp Pro Gln Lys Val
260 265 270

Gln Tyr Asp Leu Lys Ser Gln Phe Gly Phe Xaa Asp Leu His Thr Glu
275 280 285

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

[0156]

Ser Leu Glu Lys Met Val Cys Ser Val Leu Ser Ser Thr Ser Glu Asp
305 310 315 320

Glu Ala Glu Lys Trp Gly His Val Gly Gly Cys His Pro Lys Trp Ser
325 330 335

Glu Ala Lys Asn Tyr Leu Val His Ala Val Ser Trp Leu Arg Val Tyr
340 345 350

Gln Gln Val Phe Val Gln Trp Gln Gln Gly Ser Leu Leu Gln Lys Thr
355 360 365

Leu Thr Gly Met Gly His Ser Leu Glu Ala Leu Arg Asn Gln Phe Glu
370 375 380

Glu Glu Ser Lys Pro Trp Lys Val Val Glu Ala Leu His Thr Ala Leu

385	390	395	400
Leu Leu Leu Asn Asp Ser Leu Ser Ala Asp Gly Pro Lys Asp Asn His			
405	410	415	
Thr Phe Pro Lys Ile Leu Gln His Leu Trp Lys Leu Gln Ser Leu Leu			
420	425	430	
Gln Asn Leu Pro Gln Trp Pro Ala Leu Lys Arg Phe Leu Gln Leu Asp			
435	440	445	
Gly Ala Leu Arg Asn Ala Ile Ala Gln Asn Leu His Phe Val Gln Glu			
450	455	460	
Val Leu Ile Cys Leu Glu Thr Ser Ala Asn Asp Phe Lys Trp Phe Glu			
465	470	475	480
[0157]			
Leu Asn Gln Leu Lys Leu Glu Lys Asp Val Phe Phe Trp Glu Leu Lys			
485	490	495	
Gln Met Leu Ala Lys Asn Ala Val Cys Pro Asn Gly Arg Phe Ser Glu			
500	505	510	
Lys Glu Val Phe Leu Pro Pro Gly Asn Ser Ser Ile Trp Gly Gly Leu			
515	520	525	
Gln Gly Leu Leu Cys Tyr Cys Asn Ser Ser Glu Thr Ser Val Leu Asn			
530	535	540	
Lys Leu Leu Gly Ser Val Glu Asp Ala Asp Arg Ile Leu Gln Glu Val			
545	550	555	560
Ile Thr Trp His Lys Asn Met Ser Val Leu Ile Pro Glu Glu Tyr Leu			
565	570	575	

Asp Trp Gln Glu Leu Glu Met Gln Leu Ser Glu Ala Ser Leu Ser Cys
580 585 590

Thr Arg Leu Phe Leu Leu Leu Gly Ala Asp Pro Ser Pro Glu Asn Asp
595 600 605

Val Phe Ser Ser Asp Cys Lys His Gln Leu Val Ser Thr Val Ile Phe
610 615 620

His Thr Leu Glu Lys Thr Gln Phe Phe Leu Glu Gln Ala Tyr Tyr Trp
625 630 635 640

Lys Ala Phe Lys Lys Phe Ile Arg Lys Thr Cys Glu Val Ala Gln Tyr
645 650 655

Val Asn Met Gln Glu Ser Phe Gln Asn Arg Leu Leu Ala Phe Pro Glu
660 665 670

[0158]

Glu Ser Pro Cys Phe Glu Glu Asn Met Asp Trp Lys Met Ile Ser Asp
675 680 685

Asn Tyr Phe Gln Phe Leu Asn Asn Leu Leu Lys Ser Pro Thr Ala Ser
690 695 700

Ile Ser Arg Ala Leu Asn Phe Thr Lys His Leu Leu Met Met Glu Lys
705 710 715 720

Lys Leu His Thr Leu Glu Asp Glu Gln Met Asn Phe Leu Leu Ser Phe
725 730 735

Val Glu Phe Phe Glu Lys Leu Leu Leu Pro Asn Leu Phe Asp Ser Ser
740 745 750

Ile Val Pro Ser Phe His Ser Leu Pro Ser Leu Thr Glu Asp Ile Leu
755 760 765

Asn Ile Ser Ser Leu Trp Thr Asn His Leu Lys Ser Leu Lys Arg Asp
770 775 780

Pro Ser Ala Thr Asp Ala Gln Lys Leu Leu Glu Phe Gly Asn Glu Val
785 790 795 800

Ile Trp Lys Met Gln Thr Leu Gly Ser His Trp Ile Arg Lys Glu Pro
805 810 815

Lys Asn Leu Leu Arg Phe Ile Glu Leu Ile Leu Phe Glu Ile Asn Pro
820 825 830

Lys Leu Leu Glu Leu Trp Ala Tyr Gly Ile Ser Lys Gly Lys Arg Ala
835 840 845

Lys Leu Glu Asn Phe Phe Thr Leu Leu Asn Phe Ser Val Pro Glu Asn
850 855 860

[0159]

Glu Ile Leu Ser Thr Ser Phe Asn Phe Ser Gln Leu Phe His Ser Asp
865 870 875 880

Trp Pro Lys Ser Pro Ala Met Asn Ile Asp Phe Val Arg Leu Ser Glu
885 890 895

Ala Ile Ile Thr Ser Leu His Glu Phe Gly Phe Leu Glu Gln Glu Gln
900 905 910

Ile Ser Glu Ala Leu Asn Thr Val Tyr Ala Ile Arg Asn Ala Ser Asp
915 920 925

Leu Phe Ser Ala Leu Ser Glu Pro Gln Lys Gln Glu Val Asp Lys Ile
930 935 940

Leu Thr His Ile His Leu Asn Val Phe Gln Asp Lys Asp Ser Ala Leu
945 950 955 960

Leu Leu Gln Ile Tyr Ser Ser Phe Tyr Arg Tyr Ile Tyr Glu Leu Leu
965 970 975

Asn Ile Gln Ser Arg Gly Ser Ser Leu Thr Phe Leu Thr Gln Ile Ser
980 985 990

Lys His Ile Leu Asp Ile Ile Lys Gln Phe Asn Phe Gln Asn Ile Ser
995 1000 1005

Lys Ala Phe Ala Phe Leu Phe Lys Thr Ala Glu Val Leu Gly Gly
1010 1015 1020

Ile Ser Asn Val Ser Tyr Cys Gln Gln Leu Leu Ser Ile Phe Asn
1025 1030 1035

Phe Leu Glu Leu Gln Ala Gln Ser Phe Met Ser Thr Glu Gly Gln
1040 1045 1050

[0160]

Glu Leu Glu Val Ile His Thr Thr Leu Thr Gly Leu Lys Gln Leu
1055 1060 1065

Leu Ile Ile Asp Glu Asp Phe Arg Ile Ser Leu Phe Gln Tyr Met
1070 1075 1080

Ser Gln Phe Phe Asn Ser Ser Val Glu Asp Leu Leu Asp Asn Lys
1085 1090 1095

Cys Leu Ile Ser Asp Asn Lys His Ile Ser Ser Val Asn Tyr Ser
1100 1105 1110

Thr Ser Glu Glu Ser Ser Phe Val Phe Pro Leu Ala Gln Ile Phe
1115 1120 1125

Ser Asn Leu Ser Ala Asn Val Ser Val Phe Asn Lys Phe Met Ser

1130	1135	1140
Ile His Cys Thr Val Ser Trp	Leu Gln Met Trp Thr	Glu Ile Trp
1145	1150	1155
Glu Thr Ile Ser Gln Leu Phe	Lys Phe Asp Met Asn	Val Phe Thr
1160	1165	1170
Ser Leu His His Gly Phe Thr	Gln Leu Leu Asp Glu	Leu Glu Asp
1175	1180	1185
Asp Val Lys Val Ser Lys Ser	Cys Gln Gly Ile Leu	Pro Thr His
1190	1195	1200
Asn Val Ala Arg Leu Ile Leu	Asn Leu Phe Lys Asn	Val Thr Gln
1205	1210	1215
[0161]		
Ala Asn Asp Phe His Asn Trp	Glu Asp Phe Leu Asp	Leu Arg Asp
1220	1225	1230
Phe Leu Val Ala Leu Gly Asn	Ala Leu Val Ser Val	Lys Lys Leu
1235	1240	1245
Asn Leu Glu Gln Val Glu Lys	Ser Leu Phe Thr Met	Glu Ala Ala
1250	1255	1260
Leu His Gln Leu Lys Thr Phe	Pro Phe Asn Glu Ser	Thr Ser Arg
1265	1270	1275
Glu Phe Leu Asn Ser Leu Leu	Glu Val Phe Ile Glu	Phe Ser Ser
1280	1285	1290
Thr Ser Glu Tyr Ile Val Arg	Asn Leu Asp Ser Ile	Asn Asp Phe
1295	1300	1305

Leu Ser Asn Asn Leu Thr Asn Tyr Gly Glu Lys Phe Glu Asn Ile
1310 1315 1320

Ile Thr Glu Leu Arg Glu Ala Ile Val Phe Leu Arg Asn Val Ser
1325 1330 1335

His Asp Arg Asp Leu Phe Ser Cys Ala Asp Ile Phe Gln Asn Val
1340 1345 1350

Thr Glu Cys Ile Leu Glu Asp Gly Phe Leu Tyr Val Asn Thr Ser
1355 1360 1365

Gln Arg Met Leu Arg Ile Leu Asp Thr Leu Asn Ser Thr Phe Ser
1370 1375 1380

Ser Glu Asn Thr Ile Ser Ser Leu Lys Gly Cys Ile Val Trp Leu
1385 1390 1395

[0162]

Asp Val Ile Asn His Leu Tyr Leu Leu Ser Asn Ser Ser Phe Ser
1400 1405 1410

Gln Gly Arg Leu Gln Asn Ile Leu Gly Asn Phe Arg Asp Ile Glu
1415 1420 1425

Asn Lys Met Asn Ser Ile Leu Lys Ile Val Thr Trp Val Leu Asn
1430 1435 1440

Ile Lys Lys Pro Leu Cys Ser Ser Asn Gly Ser His Ile Asn Cys
1445 1450 1455

Val Asn Ile Tyr Leu Lys Asp Val Thr Asp Phe Leu Asn Ile Val
1460 1465 1470

Leu Thr Thr Val Phe Glu Lys Glu Lys Lys Pro Lys Phe Glu Ile
1475 1480 1485

Leu Leu Ala Leu Leu Asn Asp Ser Thr Lys Gln Val Arg Met Ser
1490 1495 1500

Ile Asn Asn Leu Thr Thr Asp Phe Asp Phe Ala Ser Gln Ser Asn
1505 1510 1515

Trp Arg Tyr Phe Thr Glu Leu Ile Leu Arg Pro Ile Glu Met Ser
1520 1525 1530

Asp Glu Ile Pro Asn Gln Phe Gln Asn Ile Trp Leu His Leu Ile
1535 1540 1545

Thr Leu Gly Lys Glu Phe Gln Lys Leu Val Lys Gly Ile Tyr Phe
1550 1555 1560

Asn Ile Leu Glu Asn Asn Ser Ser Ser Lys Thr Glu Asn Leu Leu
1565 1570 1575

[0163]

Asn Ile Phe Ala Thr Ser Pro Lys Glu Lys Asp Val Asn Ser Val
1580 1585 1590

Gly Asn Ser Ile Tyr His Leu Ala Ser Tyr Leu Ala Phe Ser Leu
1595 1600 1605

Ser His Asp Leu Gln Asn Ser Pro Lys Ile Ile Ile Ser Pro Glu
1610 1615 1620

Ile Met Lys Ala Thr Gly Leu Gly Ile Gln Leu Ile Arg Asp Val
1625 1630 1635

Phe Asn Ser Leu Met Pro Val Val His His Thr Ser Pro Gln Asn
1640 1645 1650

Ala Gly Tyr Met Gln Ala Leu Lys Lys Val Thr Ser Val Met Arg
1655 1660 1665

Thr Leu Lys Lys Ala Asp Ile Asp Leu Leu Val Asp Gln Leu Glu
1670 1675 1680

Gln Val Ser Val Asn Leu Met Asp Phe Phe Lys Asn Ile Ser Ser
1685 1690 1695

Val Gly Thr Gly Asn Leu Val Val Asn Leu Leu Val Gly Leu Met
1700 1705 1710

Glu Lys Phe Ala Asp Ser Ser His Ser Trp Asn Val Asn His Leu
1715 1720 1725

Leu Gln Leu Ser Arg Leu Phe Pro Lys Asp Val Val Asp Ala Val
1730 1735 1740

Ile Asp Val Tyr Tyr Val Leu Pro His Ala Val Arg Leu Leu Gln
1745 1750 1755

[0164]

Gly Val Pro Gly Lys Asn Ile Thr Glu Gly Leu Lys Asp Val Tyr
1760 1765 1770

Ser Phe Thr Leu Leu His Gly Ile Thr Ile Ser Asn Ile Thr Lys
1775 1780 1785

Glu Asp Phe Ala Ile Val Ile Lys Ile Leu Leu Asp Thr Ile Glu
1790 1795 1800

Leu Val Ser Asp Lys Pro Asp Ile Ile Ser Glu Ala Leu Ala Cys
1805 1810 1815

Phe Pro Val Val Trp Cys Trp Asn His Thr Asn Ser Gly Phe Arg
1820 1825 1830

Gln Asn Ser Lys Ile Asp Pro Cys Asn Val His Gly Leu Met Ser

1835	1840	1845
Ser Ser Phe Tyr Gly Lys Val	Ala Ser Ile Leu Asp	His Phe His
1850	1855	1860
Leu Ser Pro Gln Gly Glu Asp	Ser Pro Cys Ser Asn	Glu Ser Ser
1865	1870	1875
Arg Met Glu Ile Thr Arg Lys	Val Val Cys Ile Ile	His Glu Leu
1880	1885	1890
Val Asp Trp Asn Ser Ile Leu	Leu Glu Leu Ser Glu	Val Phe His
1895	1900	1905
Val Asn Ile Ser Leu Val Lys	Thr Val Gln Lys Phe	Trp His Lys
1910	1915	1920
[0165]		
Ile Leu Pro Phe Val Pro Pro	Ser Ile Asn Gln Thr	Arg Asp Ser
1925	1930	1935
Ile Ser Glu Leu Cys Pro Ser	Gly Ser Ile Lys Gln	Val Ala Leu
1940	1945	1950
Gln Ile Ile Glu Lys Leu Lys	Asn Val Asn Phe Thr	Lys Val Thr
1955	1960	1965
Ser Gly Glu Asn Ile Leu Asp	Lys Leu Ser Ser Leu	Asn Lys Ile
1970	1975	1980
Leu Asn Ile Asn Glu Asp Thr	Glu Thr Ser Val Gln	Asn Ile Ile
1985	1990	1995
Ser Ser Asn Leu Glu Arg Thr	Val Gln Leu Ile Ser	Glu Asp Trp
2000	2005	2010

Ser	Leu	Glu	Lys	Ser	Thr	His	Asn	Leu	Leu	Ser	Leu	Phe	Met	Met
2015							2020					2025		

Leu	Gln	Asn	Ala	Asn	Val	Thr	Gly	Ser	Ser	Leu	Glu	Ala	Leu	Ser
2030							2035					2040		

Ser	Phe	Ile	Glu	Lys	Ser	Glu	Thr	Pro	Tyr	Asn	Phe	Glu	Glu	Leu
2045							2050					2055		

Trp	Pro	Lys	Phe	Gln	Gln	Ile	Met	Lys	Asp	Leu	Thr	Gln	Asp	Phe
2060							2065					2070		

Arg	Ile	Arg	His	Leu	Leu	Ser	Glu	Met	Asn	Lys	Gly	Ile	Lys	Ser
2075							2080					2085		

Ile	Asn	Ser	Met	Ala	Leu	Gln	Lys	Ile	Thr	Leu	Gln	Phe	Ala	His
2090							2095					2100		

[0166]

Phe	Leu	Glu	Ile	Leu	Asp	Ser	Pro	Ser	Leu	Lys	Thr	Leu	Glu	Ile
2105							2110					2115		

Ile	Glu	Asp	Phe	Leu	Leu	Val	Thr	Lys	Asn	Trp	Leu	Gln	Glu	Tyr
2120							2125					2130		

Ala	Asn	Glu	Asp	Tyr	Ser	Arg	Met	Ile	Glu	Thr	Leu	Phe	Ile	Pro
2135							2140					2145		

Val	Thr	Asn	Glu	Ser	Ser	Thr	Glu	Asp	Ile	Ala	Leu	Leu	Ala	Lys
2150							2155					2160		

Ala	Ile	Ala	Thr	Phe	Trp	Gly	Ser	Leu	Lys	Asn	Ile	Ser	Arg	Ala
2165							2170					2175		

Gly	Asn	Phe	Asp	Val	Ala	Phe	Leu	Thr	His	Leu	Leu	Asn	Gln	Glu
2180							2185					2190		

Gln Leu Thr Asn Phe Ser Val Val Gln Leu Leu Phe Glu Asn Ile
2195 2200 2205

Leu Ile Asn Leu Ile Asn Asn Leu Ala Gly Asn Ser Gln Glu Ala
2210 2215 2220

Ala Trp Asn Leu Asn Asp Thr Asp Leu Gln Ile Met Asn Phe Ile
2225 2230 2235

Asn Leu Ile Leu Asn His Met Gln Ser Glu Thr Ser Arg Lys Thr
2240 2245 2250

Val Leu Ser Leu Arg Ser Ile Val Asp Phe Thr Glu Gln Phe Leu
2255 2260 2265

Lys Thr Phe Phe Ser Leu Phe Leu Lys Glu Asp Ser Glu Asn Lys
2270 2275 2280

[0167]

Ile Ser Leu Leu Leu Lys Tyr Phe His Lys Asp Val Ile Ala Glu
2285 2290 2295

Met Ser Phe Val Pro Lys Asp Lys Ile Leu Glu Ile Leu Lys Leu
2300 2305 2310

Asp Gln Phe Leu Thr Leu Met Ile Gln Asp Arg Leu Met Asn Ile
2315 2320 2325

Phe Ser Ser Leu Lys Glu Thr Ile Tyr His Leu Met Lys Ser Ser
2330 2335 2340

Phe Ile Leu Asp Asn Gly Glu Phe Tyr Phe Asp Thr His Gln Gly
2345 2350 2355

Leu Lys Phe Met Gln Asp Leu Phe Asn Ala Leu Leu Arg Glu Thr
2360 2365 2370

Ser Met Lys Asn Lys Thr Glu Asn Asn Ile Asp Phe Phe Thr Val
2375 2380 2385

Val Ser Gln Leu Phe Phe His Val Asn Lys Ser Glu Asp Leu Phe
2390 2395 2400

Lys Leu Asn Gln Asp Leu Gly Ser Ala Leu His Leu Val Arg Glu
2405 2410 2415

Cys Ser Thr Glu Met Ala Arg Leu Leu Asp Thr Ile Leu His Ser
2420 2425 2430

Pro Asn Lys Asp Phe Tyr Ala Leu Tyr Pro Thr Leu Gln Glu Val
2435 2440 2445

Ile Leu Ala Asn Leu Thr Asp Leu Leu Phe Phe Ile Asn Asn Ser
2450 2455 2460

[0168]

Phe Pro Leu Arg Asn Arg Ala Thr Leu Glu Ile Thr Lys Arg Leu
2465 2470 2475

Val Gly Ala Ile Ser Arg Ala Ser Glu Glu Ser His Val Leu Lys
2480 2485 2490

Pro Leu Leu Glu Met Ser Gly Thr Leu Val Met Leu Leu Asn Asp
2495 2500 2505

Ser Ala Asp Leu Arg Asp Leu Ala Thr Ser Met Asp Ser Ile Val
2510 2515 2520

Lys Leu Leu Lys Leu Val Lys Lys Val Ser Gly Lys Met Ser Thr
2525 2530 2535

Val Phe Lys Thr His Phe Ile Ser Asn Thr Lys Asp Ser Val Lys

2540	2545	2550
Phe Phe Asp Thr Leu Tyr Ser Ile Met Gln Gln Ser Val Gln Asn		
2555	2560	2565
Leu Val Lys Glu Ile Ala Thr Leu Lys Lys Ile Asp His Phe Thr		
2570	2575	2580
Phe Glu Lys Ile Asn Asp Leu Leu Val Pro Phe Leu Asp Leu Ala		
2585	2590	2595
Phe Glu Met Ile Gly Val Glu Pro Tyr Ile Ser Ser Asn Ser Asp		
2600	2605	2610
Ile Phe Ser Met Ser Pro Ser Ile Leu Ser Tyr Met Asn Gln Ser		
2615	2620	2625
[0169]		
Lys Asp Phe Ser Asp Ile Leu Glu Glu Ile Ala Glu Phe Leu Thr		
2630	2635	2640
Ser Val Lys Met Asn Leu Glu Asp Met Arg Ser Leu Ala Val Ala		
2645	2650	2655
Phe Asn Asn Glu Thr Gln Thr Phe Ser Met Asp Ser Val Asn Leu		
2660	2665	2670
Xaa Glu Glu Ile Leu Gly Cys Leu Val Pro Ile Asn Asn Ile Thr		
2675	2680	2685
Asn Gln Met Asp Phe Leu Tyr Pro Asn Pro Ile Ser Thr His Ser		
2690	2695	2700
Gly Pro Gln Asp Ile Lys Trp Glu Ile Ile His Glu Val Ile Leu		
2705	2710	2715

Phe Leu Asp Lys Ile Leu Ser Gln Asn Ser Thr Glu Ile Gly Ser
2720 2725 2730

Phe Leu Lys Met Val Ile Cys Leu Thr Leu Glu Ala Leu Trp Lys
2735 2740 2745

Asn Leu Lys Lys Asp Asn Trp Asn Val Ser Asn Val Leu Met Thr
2750 2755 2760

Phe Thr Gln His Pro Asn Asn Leu Leu Lys Thr Ile Glu Thr Val
2765 2770 2775

Leu Glu Ala Ser Ser Gly Ile Lys Ser Asp Tyr Glu Gly Asp Leu
2780 2785 2790

Asn Lys Ser Leu Tyr Phe Asp Thr Pro Leu Ser Gln Asn Ile Thr
2795 2800 2805

[0170]

His His Gln Leu Glu Lys Ala Ile His Asn Val Leu Ser Arg Ile
2810 2815 2820

Ala Leu Trp Arg Lys Gly Leu Arg Phe Asn Asn Ser Glu Trp Ile
2825 2830 2835

Thr Ser Thr Arg Thr Leu Phe Gln Pro Leu Phe Glu Ile Phe Ile
2840 2845 2850

Lys Ala Thr Thr Gly Lys Asn Val Thr Ser Glu Lys Glu Glu Arg
2855 2860 2865

Thr Glu Lys Glu Met Ile Asp Phe Pro Tyr Ser Phe Lys Pro Phe
2870 2875 2880

Phe Cys Leu Glu Lys Tyr Leu Gly Gly Leu Phe Val Leu Thr Lys
2885 2890 2895

Tyr Trp Gln Gln Ile Pro Leu Thr Asp Gln Ser Val Val Glu Ile
2900 2905 2910

Cys Glu Val Phe Gln Gln Thr Val Lys Pro Ser Glu Ala Met Glu
2915 2920 2925

Met Leu Gln Lys Val Lys Met Met Val Val Arg Val Leu Thr Ile
2930 2935 2940

Val Ala Glu Asn Pro Ser Trp Thr Lys Asp Ile Leu Cys Ala Thr
2945 2950 2955

Leu Ser Cys Lys Gln Asn Gly Ile Arg His Leu Ile Leu Ser Ala
2960 2965 2970

Ile Gln Gly Val Thr Leu Ala Gln Asp His Phe Gln Glu Ile Glu
2975 2980 2985

[0171]

Lys Ile Trp Ser Ser Pro Asn Gln Leu Asn Cys Glu Ser Leu Ser
2990 2995 3000

Lys Asn Leu Ser Ser Thr Leu Glu Ser Phe Lys Ser Ser Leu Glu
3005 3010 3015

Asn Ala Thr Gly Gln Asp Cys Thr Ser Gln Pro Arg Leu Glu Thr
3020 3025 3030

Val Gln Gln His Leu Tyr Met Leu Ala Lys Ser Leu Glu Glu Thr
3035 3040 3045

Trp Ser Ser Gly Asn Pro Ile Met Thr Phe Leu Ser Asn Phe Thr
3050 3055 3060

Val Thr Glu Asp Val Lys Ile Lys Asp Leu Met Lys Asn Ile Thr
3065 3070 3075

Lys Leu Thr Glu Glu Leu Arg Ser Ser Ile Gln Ile Ser Asn Glu
3080 3085 3090

Thr Ile His Ser Ile Leu Glu Ala Asn Ile Ser His Ser Lys Val
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Leu Phe Ser Ala Leu Thr Val Ala Leu Ser Gly Lys Cys Asp Gln
3110 3115 3120

Glu Ile Leu His Leu Leu Leu Thr Phe Pro Lys Gly Glu Lys Ser
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Trp Ile Ala Ala Glu Glu Leu Cys Ser Leu Pro Gly Ser Lys Val
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Tyr Ser Leu Ile Val Leu Leu Ser Arg Asn Leu Asp Val Arg Ala
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[0172]

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Asn Ser Leu Leu Asp Ile Val Ser Ser Leu Ser Ala Leu Leu Ala
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Lys Ala Gln His Val Phe Glu Tyr Leu Pro Glu Phe Leu His Thr
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Phe Lys Ile Thr Ala Leu Leu Glu Thr Leu Asp Phe Gln Gln Val
3215 3220 3225

Ser Gln Asn Val Gln Ala Arg Ser Ser Ala Phe Gly Ser Phe Gln
3230 3235 3240

Phe Val Met Lys Met Val Cys Lys Asp Gln Ala Ser Phe Leu Ser

3245	3250	3255
Asp Ser Asn Met Phe Ile Asn Leu Pro Arg Val Lys Glu Leu Leu		
3260	3265	3270
Glu Asp Asp Lys Glu Lys Phe Asn Ile Pro Glu Asp Ser Thr Pro		
3275	3280	3285
Phe Cys Leu Lys Leu Tyr Gln Glu Ile Leu Gln Leu Pro Asn Gly		
3290	3295	3300
Ala Leu Val Trp Thr Phe Leu Lys Pro Ile Leu His Gly Lys Ile		
3305	3310	3315
Leu Tyr Thr Pro Asn Thr Pro Glu Ile Asn Lys Val Ile Gln Lys		
3320	3325	3330
[0173]		
Ala Asn Tyr Thr Phe Tyr Ile Val Asp Lys Leu Lys Thr Leu Ser		
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Glu Thr Leu Leu Glu Met Ser Ser Leu Phe Gln Arg Ser Gly Ser		
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Gly Gln Met Phe Asn Gln Leu Gln Glu Ala Leu Arg Asn Lys Phe		
3365	3370	3375
Val Arg Asn Phe Val Glu Asn Gln Leu His Ile Asp Val Asp Lys		
3380	3385	3390
Leu Thr Glu Lys Leu Gln Thr Tyr Gly Gly Leu Leu Asp Glu Met		
3395	3400	3405
Phe Asn His Ala Gly Ala Gly Arg Phe Arg Phe Leu Gly Ser Ile		
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Leu Val Asn Leu Ser Ser Cys Val Ala Leu Asn Arg Phe Gln Ala
3425 3430 3435

Leu Gln Ser Val Asp Ile Leu Glu Thr Lys Ala His Glu Leu Leu
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Gln Gln Asn Ser Phe Leu Ala Ser Ile Ile Phe Ser Asn Ser Leu
3455 3460 3465

Phe Asp Lys Asn Phe Arg Ser Glu Ser Val Lys Leu Pro Pro His
3470 3475 3480

Val Ser Tyr Thr Ile Arg Thr Asn Val Leu Tyr Ser Val Arg Thr
3485 3490 3495

Asp Val Val Lys Asn Pro Ser Trp Lys Phe His Pro Gln Asn Leu
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[0174]

Pro Ala Asp Gly Phe Lys Tyr Asn Tyr Val Phe Ala Pro Leu Gln
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Asp Met Ile Glu Arg Ala Ile Ile Leu Val Gln Thr Gly Gln Glu
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Ala Leu Glu Pro Ala Ala Gln Thr Gln Ala Ala Pro Tyr Pro Cys
3545 3550 3555

His Thr Ser Asp Leu Phe Leu Asn Asn Val Gly Phe Phe Phe Pro
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Leu Ile Met Met Leu Thr Trp Met Val Ser Val Ala Ser Met Val
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Arg Lys Leu Val Tyr Glu Gln Glu Ile Gln Ile Glu Glu Tyr Met
3590 3595 3600

Arg Met Met Gly Val His Pro Val Ile His Phe Leu Ala Trp Phe
3605 3610 3615

Leu Glu Asn Met Ala Val Leu Thr Ile Ser Ser Ala Thr Leu Ala
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Ile Val Leu Lys Thr Ser Gly Ile Phe Ala His Ser Asn Thr Phe
3635 3640 3645

Ile Val Phe Leu Phe Leu Leu Asp Phe Gly Met Ser Val Val Met
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Leu Ser Tyr Leu Leu Ser Ala Phe Phe Ser Gln Ala Asn Thr Ala
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Ala Leu Cys Thr Ser Leu Val Tyr Met Ile Ser Phe Leu Pro Tyr
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[0175]

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Phe Phe Ile Thr Phe Leu Glu Gly Gln Glu Thr Gly Ile Gln Trp
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Asn Asn Met Tyr Gln Ala Leu Glu Gln Gly Gly Met Thr Phe Gly
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Trp Val Cys Trp Met Ile Leu Phe Asp Ser Ser Leu Tyr Phe Leu
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Cys Gly Trp Tyr Leu Ser Asn Leu Ile Pro Gly Thr Phe Gly Leu
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Arg Lys Pro Trp Tyr Phe Pro	Phe Thr Ala Ser Tyr	Trp Lys Ser
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Val Gly Phe Leu Val Glu Lys	Arg Gln Tyr Phe Leu	Ser Ser Ser
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Leu Phe Phe Phe Asn Glu Asn	Phe Asp Asn Lys Gly	Ser Ser Leu
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Gln Asn Arg Glu Gly Glu Leu	Glu Gly Ser Ala Pro	Gly Val Thr
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Leu Val Ser Val Thr Lys Glu	Tyr Glu Gly His Lys	Ala Val Val
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Gln Asp Leu Ser Leu Thr Phe	Tyr Arg Asp Gln Ile	Thr Ala Leu
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[0176]

Leu Gly Thr Asn Gly Ala Gly	Lys Thr Thr Ile Ile	Ser Met Leu
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Thr Gly Leu His Pro Pro Thr	Ser Gly Thr Ile Ile	Ile Asn Gly
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Lys Asn Leu Gln Thr Asp Leu	Ser Arg Val Arg Met	Glu Leu Gly
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Val Cys Pro Gln Gln Asp Ile	Leu Leu Asp Asn Leu	Thr Val Arg
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Glu His Leu Leu Leu Phe Ala	Ser Ile Lys Ala Pro	Gln Trp Thr
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Lys Lys Glu Leu His Gln Gln	Val Asn Gln Thr Leu	Gln Asp Val
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Gly Leu Lys Arg Lys Leu Ser	Leu Gly Ile Ala Phe	Met Gly Met
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Cys Ser Arg His Ser Leu Trp	Asp Ile Leu Leu Lys	Tyr Arg Glu
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Gly Arg Thr Ile Ile Phe Thr	Thr His His Leu Asp	Glu Ala Glu
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[0177]		
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Cys Cys Gly Pro Pro Phe Cys	Leu Lys Glu Ala Tyr	Gly Gln Gly
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Asp Leu Lys Asp Met Ala Cys	Val Thr Ser Leu Ile	Lys Ile Tyr
4085	4090	4095
Ile Pro Gln Ala Phe Leu Lys	Asp Ser Ser Gly Ser	Glu Leu Thr
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Tyr Thr Ile Pro Lys Asp Thr	Asp Lys Ala Cys Leu	Lys Gly Leu
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Phe Gln Ala Leu Asp Glu Asn Leu His Gln Leu His Leu Thr Gly
4130 4135 4140

Tyr Gly Ile Ser Asp Thr Thr Leu Glu Glu Val Phe Leu Met Leu
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Leu Gln Asp Ser Asn Lys Lys Ser His Ile Ala Leu Gly Thr Glu
4160 4165 4170

Ser Glu Leu Gln Asn His Arg Pro Thr Gly His Leu Ser Gly Tyr
4175 4180 4185

Cys Gly Ser Leu Ala Arg Pro Ala Thr Val Gln Gly Val Gln Leu
4190 4195 4200

Leu Arg Ala Gln Val Ala Ala Ile Leu Ala Arg Arg Leu Arg Arg
4205 4210 4215

[0178]

Thr Leu Arg Ala Gly Lys Ser Thr Leu Ala Asp Leu Leu Leu Pro
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Val Leu Phe Val Ala Leu Ala Met Gly Leu Phe Met Val Arg Pro
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Leu Ala Thr Glu Tyr Pro Pro Leu Arg Leu Thr Pro Gly His Tyr
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Gln Arg Ala Glu Thr Tyr Phe Phe Ser Ser Gly Gly Asp Asn Leu
4265 4270 4275

Asp Leu Thr Arg Val Leu Leu Arg Lys Phe Arg Asp Gln Asp Leu
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Pro Cys Ala Asp Leu Asn Pro Arg Gln Lys Asn Ser Ser Cys Trp
4295 4300 4305

Arg Thr Asp Pro Phe Ser His Pro Glu Phe Gln Asp Ser Cys Gly
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Cys Leu Lys Cys Pro Asn Arg Ser Ala Ser Ala Pro Tyr Leu Thr
4325 4330 4335

Asn His Leu Gly His Thr Leu Leu Asn Leu Ser Gly Phe Asn Met
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Glu Glu Tyr Leu Leu Ala Pro Ser Glu Lys Pro Arg Leu Gly Gly
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Trp Ser Phe Gly Leu Lys Ile Pro Ser Glu Ala Gly Gly Ala Asn
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Gly Asn Ile Ser Lys Pro Pro Thr Leu Ala Lys Val Trp Tyr Asn
4385 4390 4395

[0179]

Gln Lys Gly Phe His Ser Leu Pro Ser Tyr Leu Asn His Leu Asn
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Asn Leu Ile Leu Trp Gln His Leu Pro Pro Thr Val Asp Trp Arg
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Ala Leu Cys Ile Val Leu Gly Phe Ser Ile Leu Ser Ala Ser Ile
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Gly Ser Ser Val Val Arg Asp Arg Val Ile Gly Ala Lys Arg Leu
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Gln His Ile Ser Gly Leu Gly Tyr Arg Met Tyr Trp Phe Thr Asn
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Val Ala Val Ile Val Ala Phe Gln Leu Thr Ala Phe Thr Phe Arg
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Lys Asn Leu Ala Ala Thr Ala Leu Leu Leu Ser Leu Phe Gly Tyr
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Ala Thr Leu Pro Trp Met Tyr Leu Met Ser Arg Ile Phe Ser Ser
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Ser Asp Val Ala Phe Ile Ser Tyr Val Ser Leu Asn Phe Ile Phe
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[0180]

Gly Leu Cys Thr Met Pro Ile Thr Ile Met Pro Arg Leu Leu Ala
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Ile Ile Ser Lys Ala Lys Asn Leu Gln Asn Ile Tyr Asp Val Leu
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Lys Trp Val Phe Thr Ile Phe Pro Gln Phe Cys Leu Gly Gln Gly
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Leu Val Glu Leu Cys Tyr Asn Gln Ile Lys Tyr Asp Leu Thr His
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Asn Phe Gly Ile Asp Ser Tyr Val Ser Pro Phe Glu Met Asn Phe
4640 4645 4650

Leu Gly Trp Ile Phe Val Gln Leu Ala Ser Gln Gly Thr Val Leu

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Arg Gly His Ser Thr Leu Gln Gly Thr Val Lys Ser Ser Lys Asp		
4685	4690	4695
Thr Asp Val Glu Lys Glu Glu Lys Arg Val Phe Glu Gly Arg Thr		
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Asn Gly Asp Ile Leu Val Leu Tyr Asn Leu Ser Lys His Tyr Arg		
4715	4720	4725
Arg Phe Phe Gln Asn Ile Ile Ala Val Gln Asp Ile Ser Leu Gly		
4730	4735	4740
[0181]		
Ile Pro Lys Gly Glu Cys Phe Gly Leu Leu Gly Val Asn Gly Ala		
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Gly Lys Ser Thr Thr Phe Lys Met Leu Asn Gly Glu Val Ser Leu		
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Thr Ser Gly His Ala Ile Ile Arg Thr Pro Met Gly Asp Ala Val		
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Asp Leu Ser Ser Ala Gly Thr Ala Gly Val Leu Ile Gly Tyr Cys		
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Pro Gln Gln Asp Ala Leu Asp Glu Leu Leu Thr Gly Trp Glu His		
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Leu Tyr Tyr Tyr Cys Ser Leu Arg Gly Ile Pro Arg Gln Cys Ile		
4820	4825	4830

Pro Glu Val Ala Gly Asp Leu Ile Arg Arg Leu His Leu Glu Ala
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His Ala Asp Lys Pro Val Ala Thr Tyr Ser Gly Gly Thr Lys Arg
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Lys Leu Ser Thr Ala Leu Ala Leu Val Gly Lys Pro Asp Ile Leu
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Leu Leu Asp Glu Pro Ser Ser Gly Met Asp Pro Cys Ser Lys Arg
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Tyr Leu Trp Gln Thr Ile Met Lys Glu Val Arg Glu Gly Cys Ala
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Ala Val Leu Thr Ser His Ser Met Glu Glu Cys Glu Ala Leu Cys
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[0182]

Thr Arg Leu Ala Ile Met Val Asn Gly Ser Phe Lys Cys Leu Gly
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Ser Pro Gln His Ile Lys Asn Arg Phe Gly Asp Gly Tyr Thr Val
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Lys Val Trp Leu Cys Lys Glu Ala Asn Gln His Cys Thr Val Ser
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Asp His Leu Lys Leu Tyr Phe Pro Gly Ile Gln Phe Lys Gly Gln
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His Leu Asn Leu Leu Glu Tyr His Val Pro Lys Arg Trp Gly Cys
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Leu Ala Asp Leu Phe Lys Val Ile Glu Asn Asn Lys Thr Phe Leu
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Asn Ile Lys His Tyr Ser Ile Asn Gln Thr Thr Leu Glu Gln Val
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Phe Ile Asn Phe Ala Ser Glu Gln Gln Gln Thr Leu Gln Ser Thr
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20

25

30

Tyr Ser Val Pro Glu Glu Thr Asp Lys Gly Ser Phe Val Gly Asn Ile

35

40

45

Ala Lys Asp Leu Gly Leu Gln Pro Gln Glu Leu Ala Asp Gly Gly Val
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Arg Ile Val Ser Arg Gly Arg Met Pro Leu Phe Ala Leu Asn Pro Arg
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Ser Gly Ser Leu Ile Thr Ala Arg Arg Ile Asp Arg Glu Glu Leu Cys
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Ala Gln Ser Met Pro Cys Leu Val Ser Phe Asn Ile Leu Val Glu Asp
100 105 110

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Asn Thr Pro Gln Phe Gln Leu Glu Glu Leu Glu Phe Lys Met Asn Glu
130 135 140

[0196]

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Glu Met Val Leu Gln Ser Pro Leu Asp Arg Glu Glu Glu Ala Val His
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His Leu Ile Leu Thr Ala Ser Asp Gly Gly Glu Pro Val Arg Ser Gly
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Thr Leu Arg Ile Tyr Ile Gln Val Val Asp Ala Asn Asp Asn Pro Pro
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[0197]

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Gly Tyr Asn Ile Thr Ile Thr Ala Ile Asp Gln Gly Thr Pro Ala Leu

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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
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[0199]

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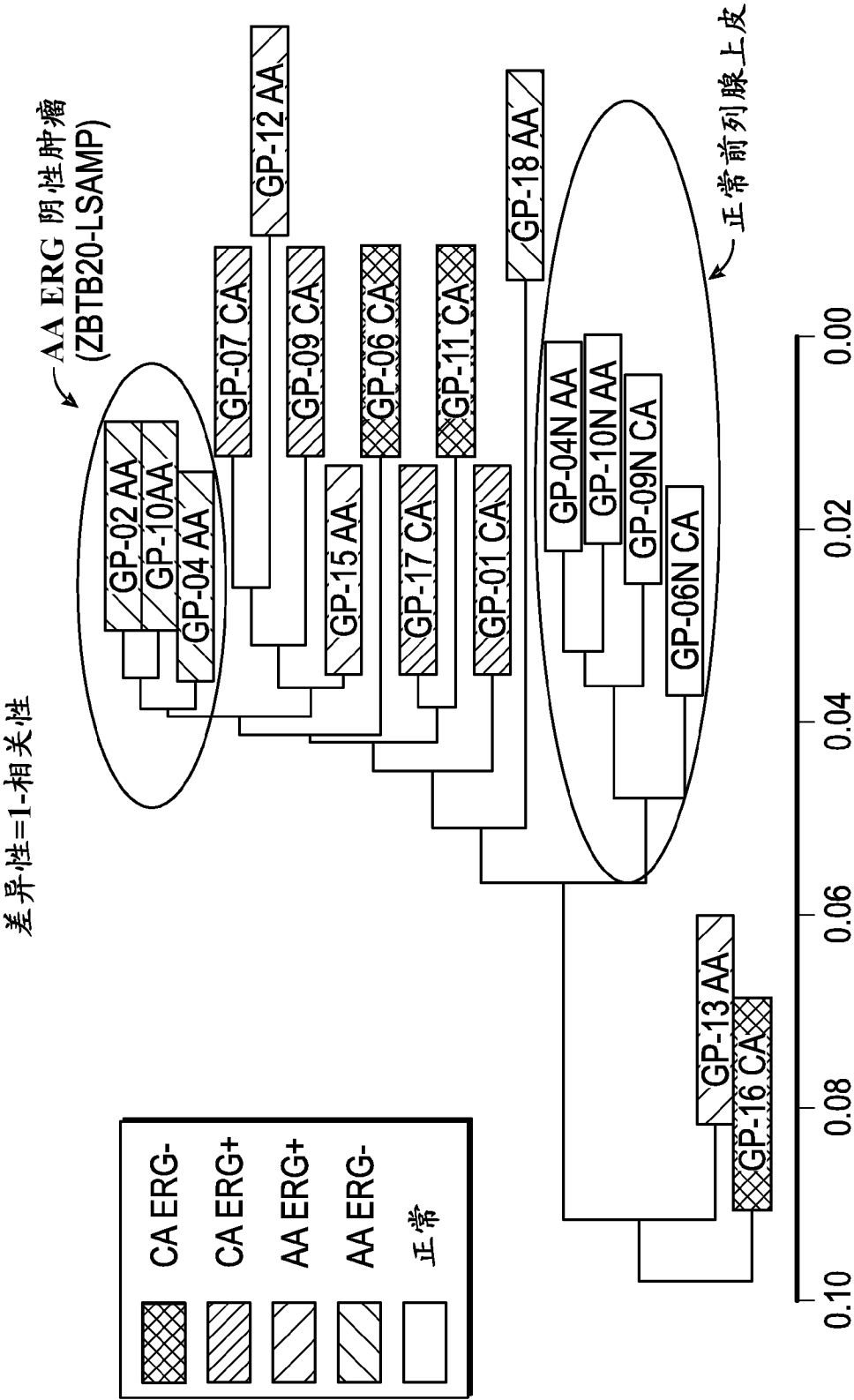


图 1

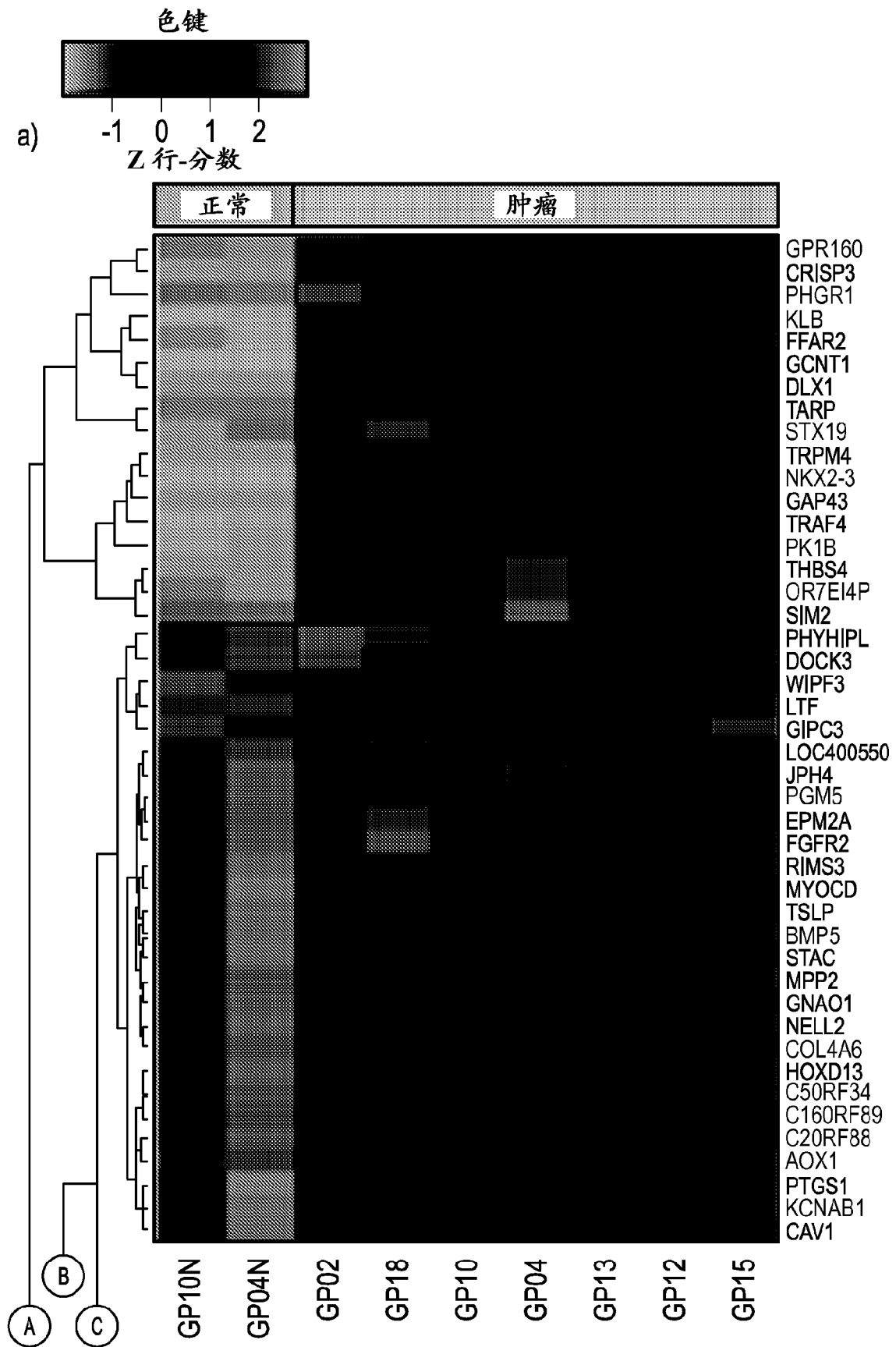


图 2

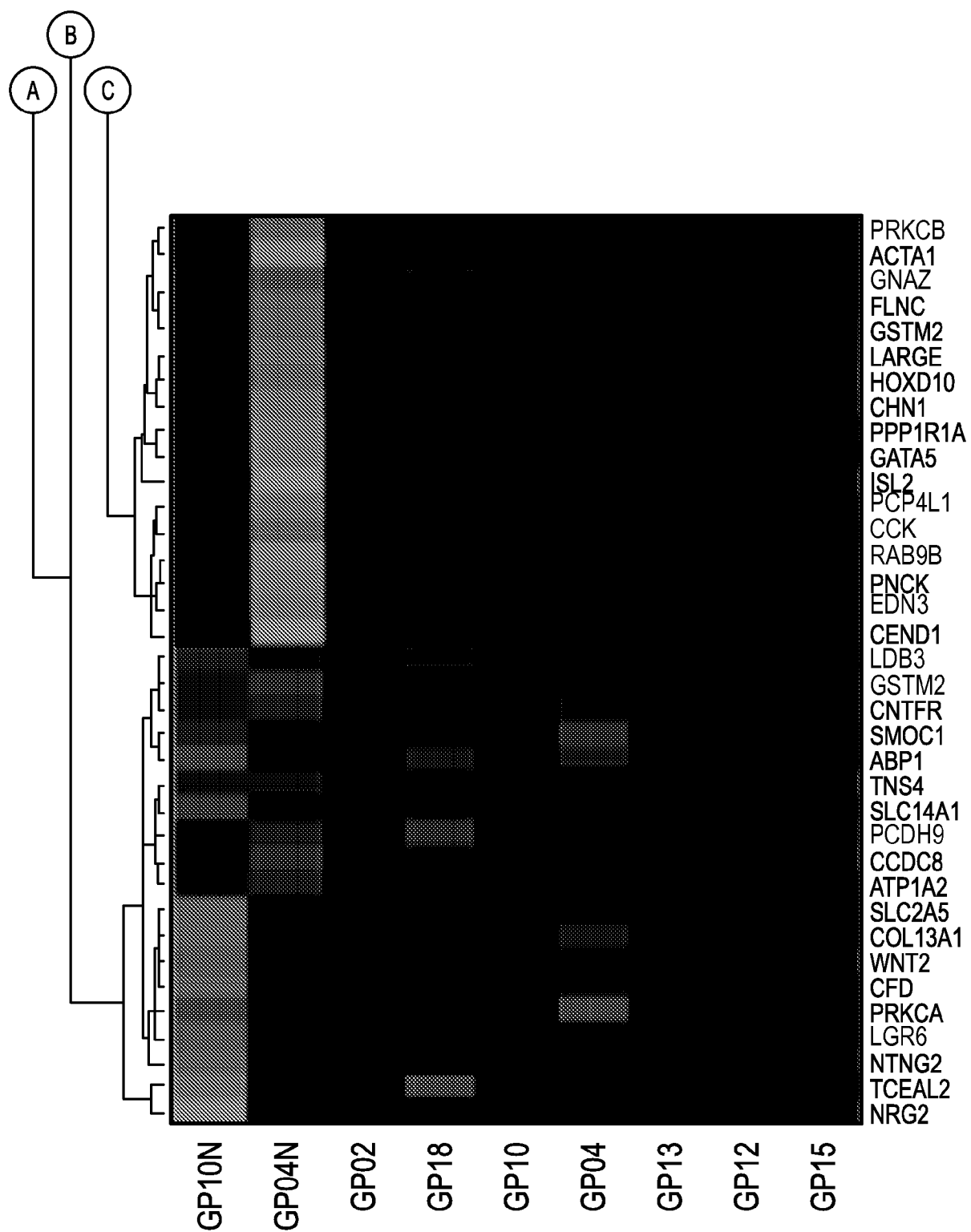


图 2(续)

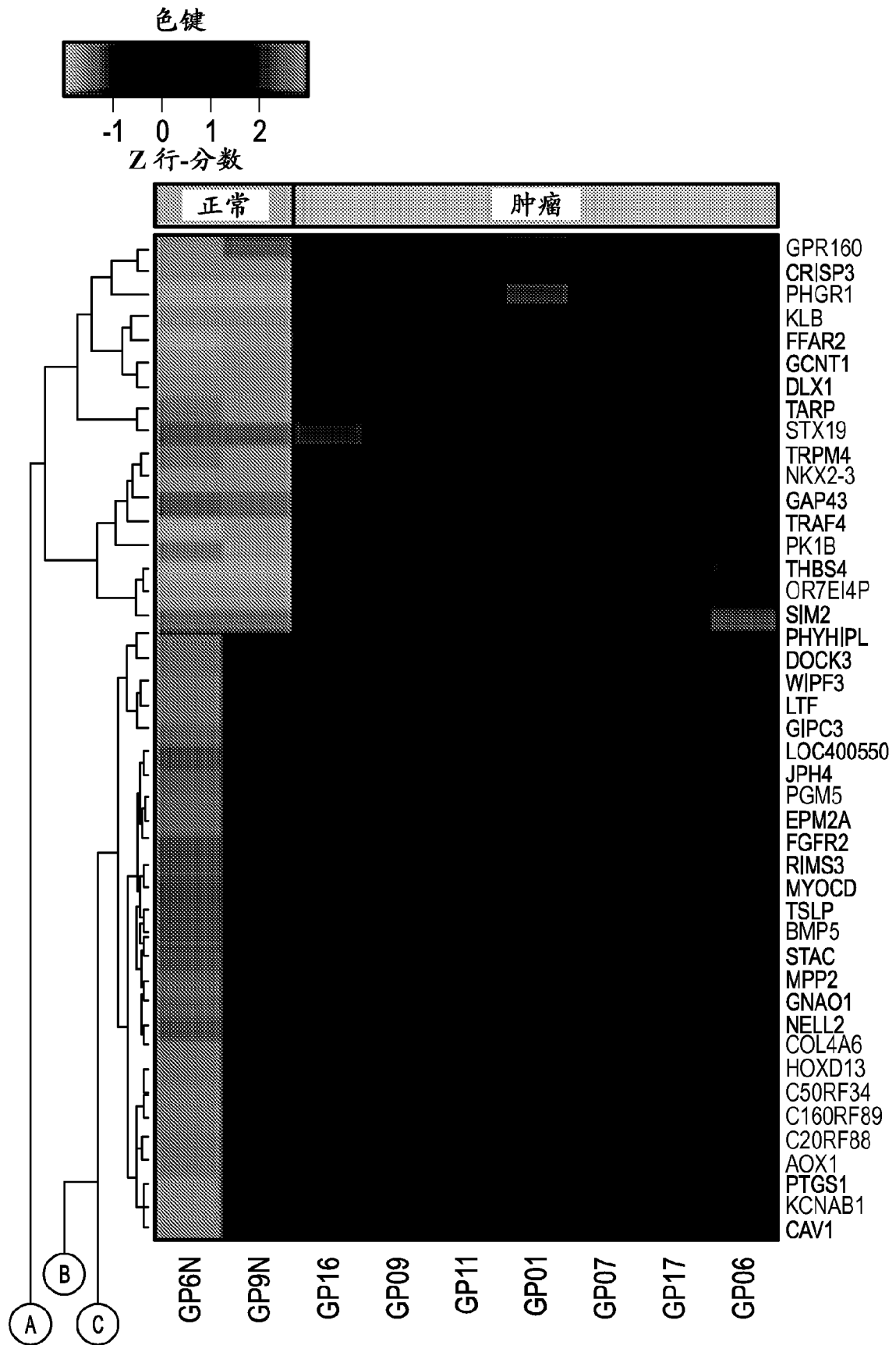


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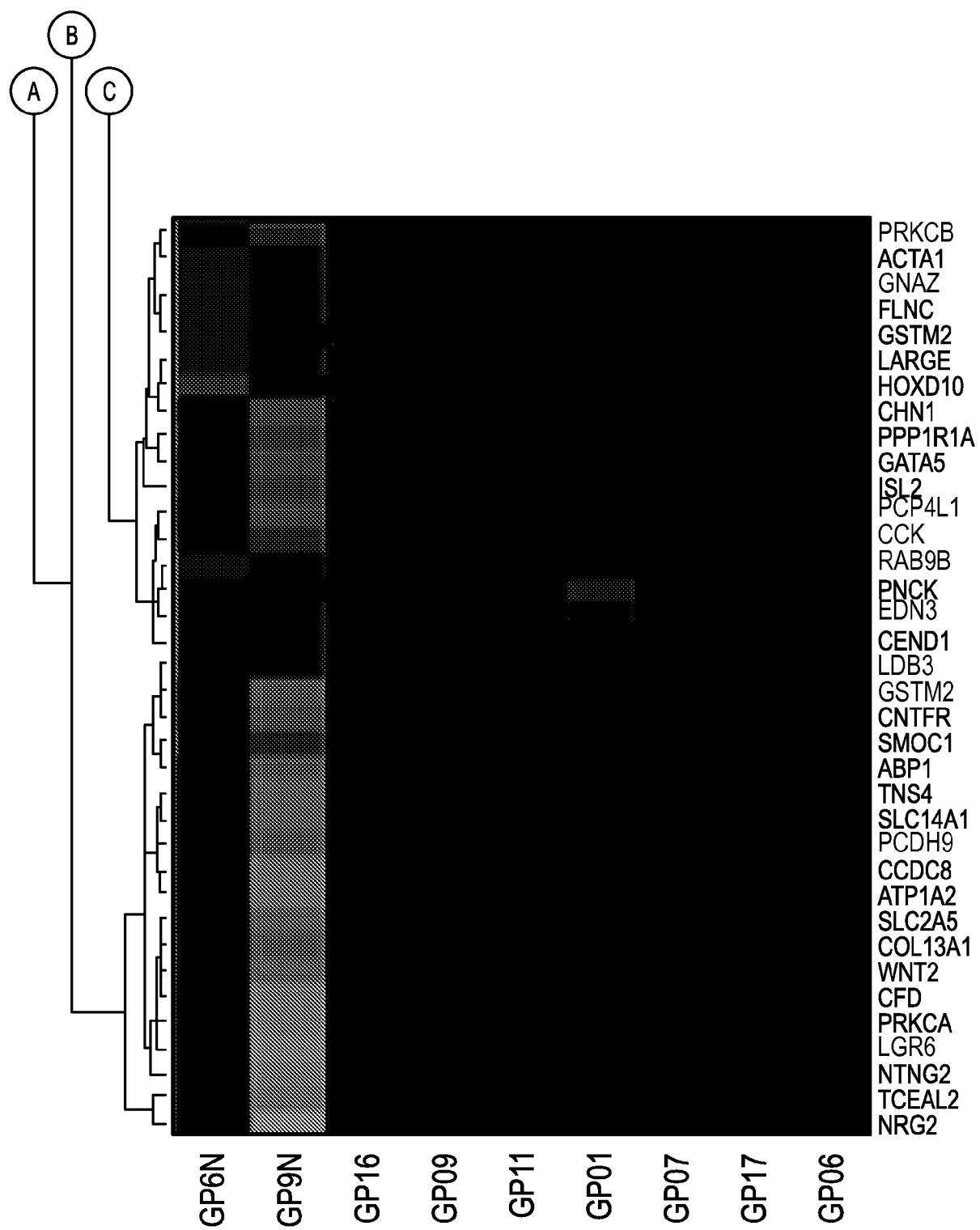


图 2(续)

b)

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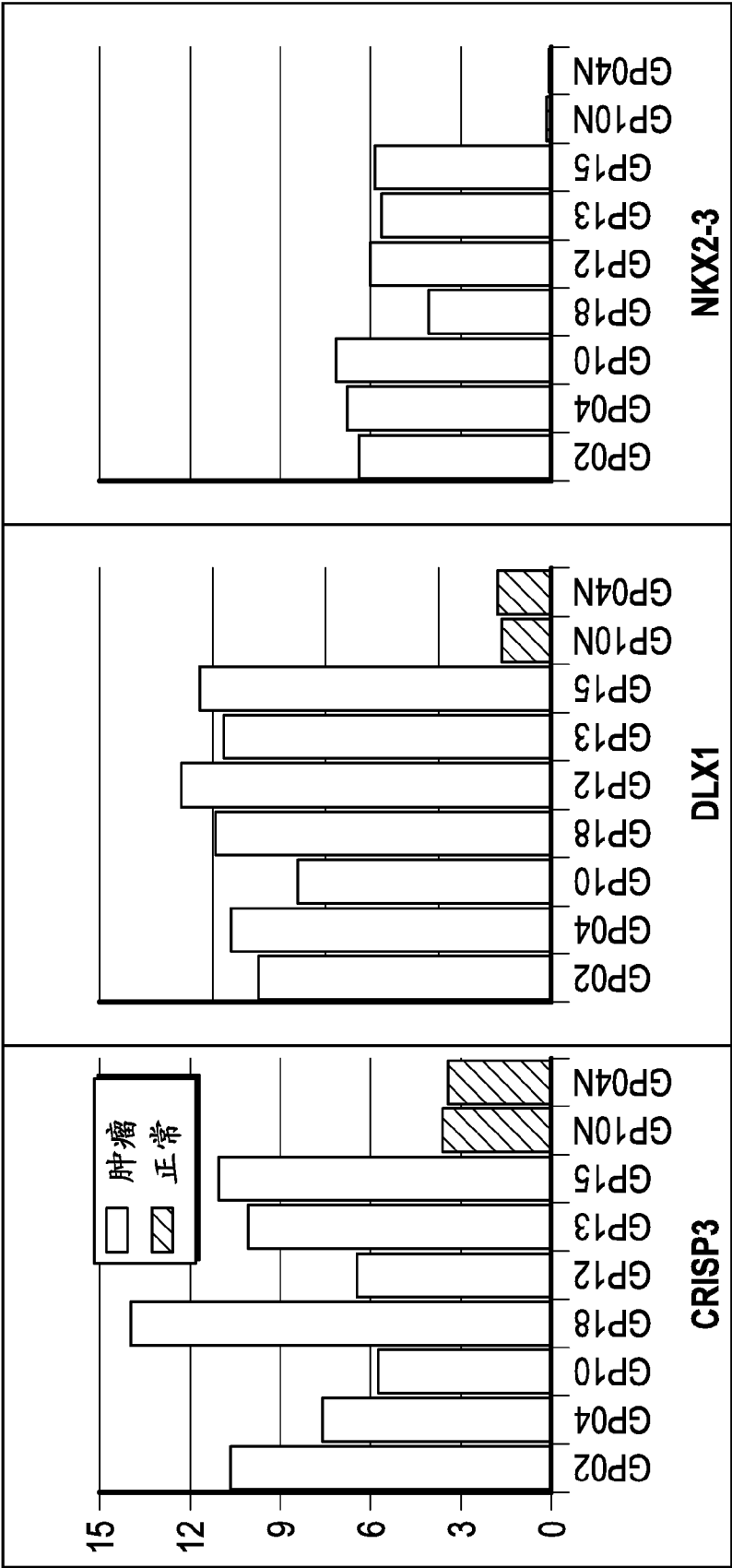


图 2

高加索美国人

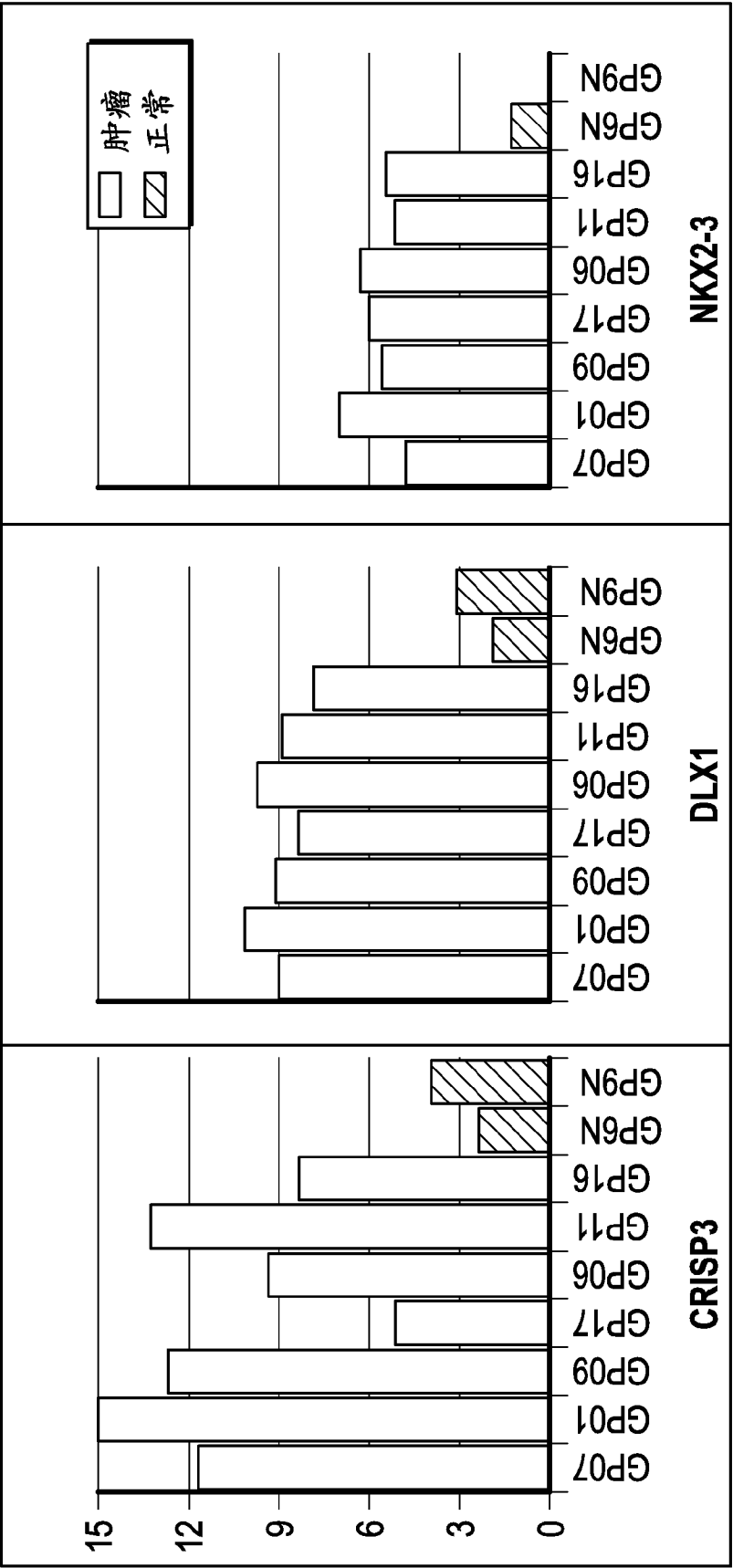


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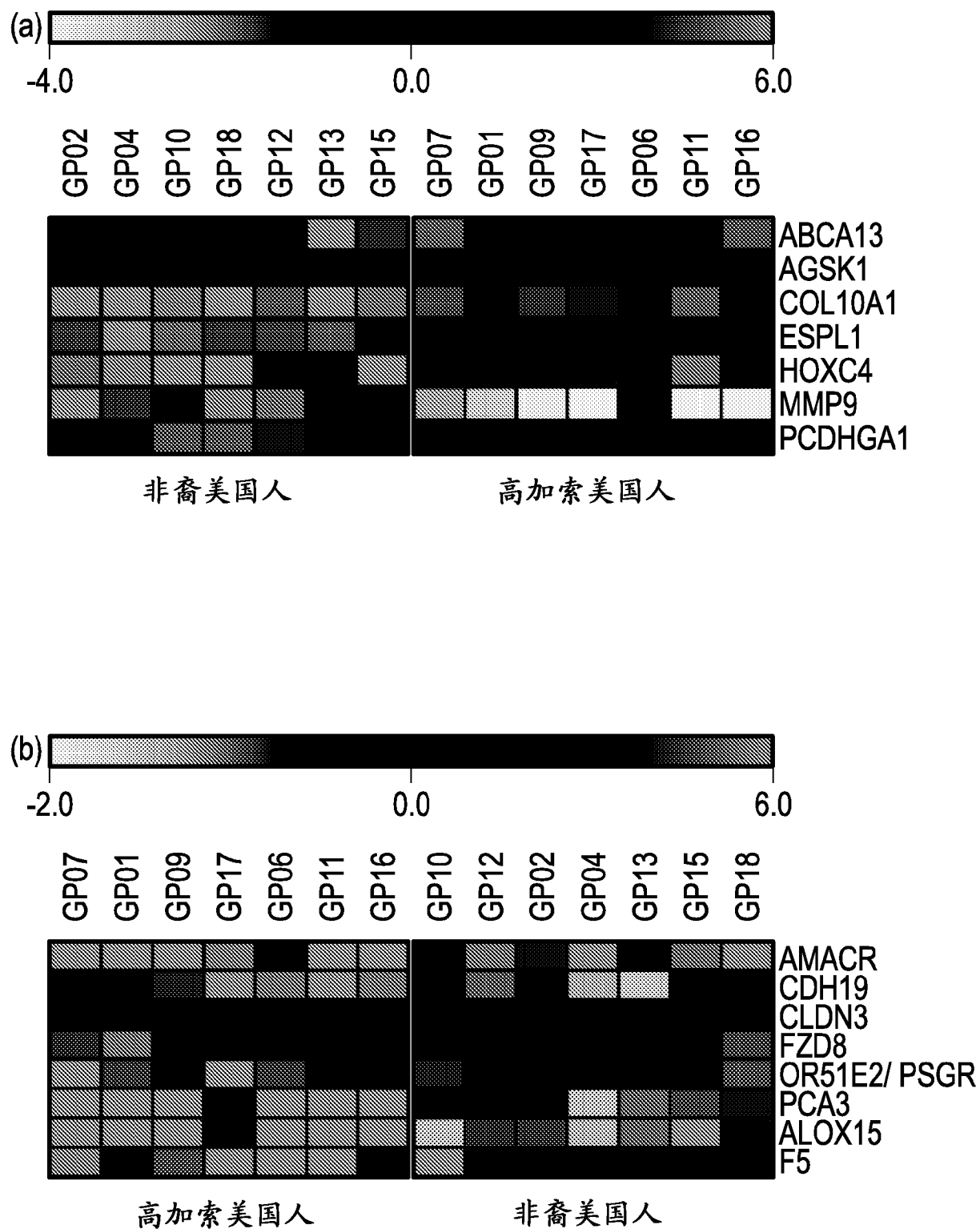


图 3

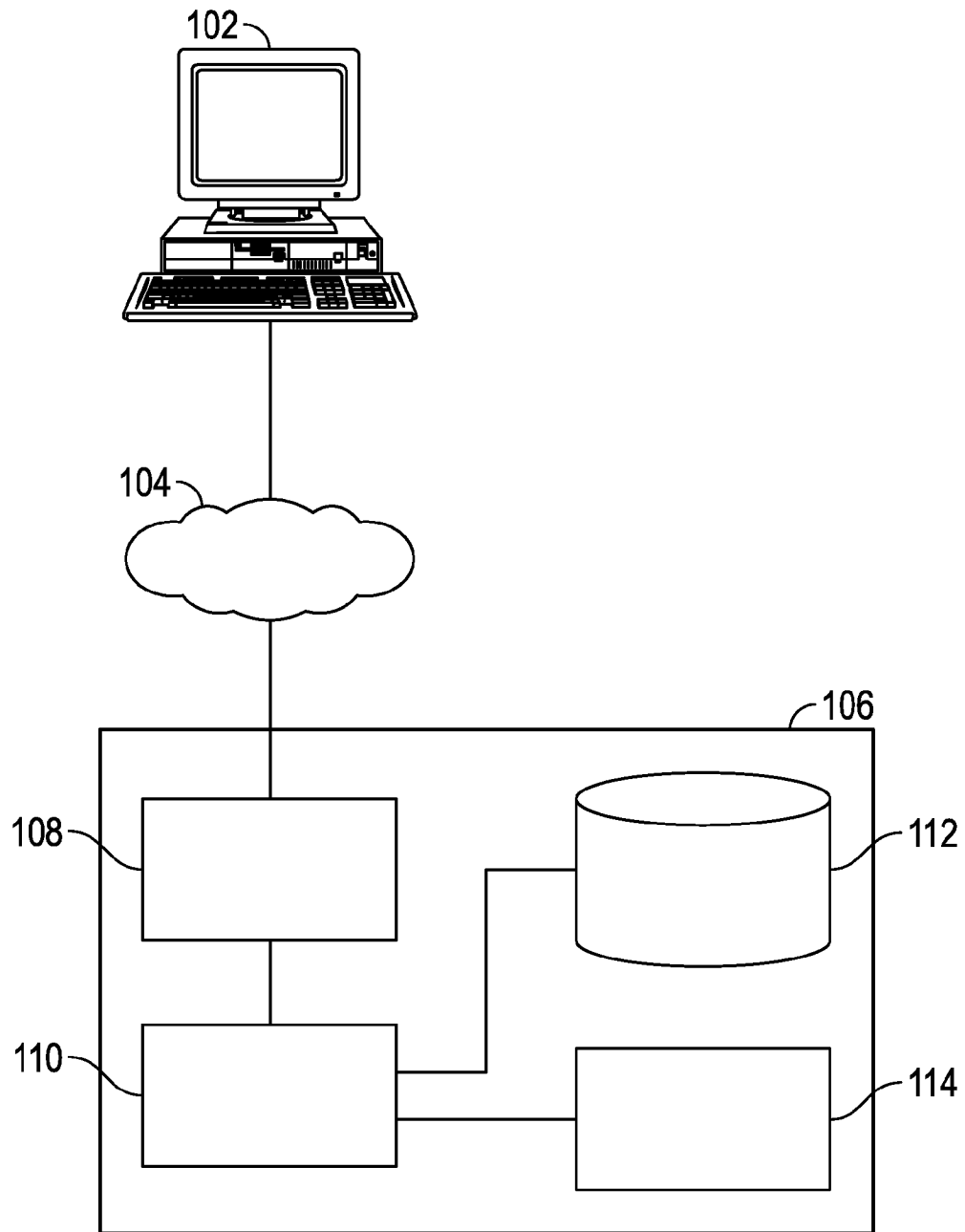


图 4