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权利要求书 2 页 说明书 104 页 附图 2 页

[54] 发明名称

蜡状芽孢杆菌产生的呕吐毒素的合成酶、编码该酶的基因以及呕吐毒素的检测方法

[57] 摘要

提供蜡状芽孢杆菌(Bacillus cereus)产生的呕吐毒素(催吐素)的简便而且迅速的检测法。 以检体中的催吐素合成酶的存在作为指标，对催吐素进行检测。 通过检测编码催吐素的核酸、或通过使用对该酶特异的抗体的免疫学方法进行催吐素合成酶的存在的检测。

1. 一种含有序列编号1的氨基酸序列的多肽，或含有在序列编号1的氨基酸序列中CRS3或CRS4区域以外的部分经1或多个氨基酸的缺失、取代、添加和/或插入所得的序列、而且具有催吐素合成活性的多肽。

2. 一种含有序列编号3的氨基酸序列的多肽，或含有在序列编号3的氨基酸序列中CRS3或CRS4区域以外的部分经1或多个氨基酸的缺失、取代、添加和/或插入所得的序列、而且保持上述多肽所具有的涉及催吐素合成的功能性结构的多肽。

3. 编码权利要求1所述的任一种多肽的核酸。

4. 编码权利要求2所述的任一种多肽的核酸。

5. 保有权利要求3或4所述的核酸的载体。

6. 用权利要求5所述的载体转化的转化体。

7.被设计成对编码具有催吐素合成活性的多肽的DNA中CRS3和CRS4区域的一部分进行特异扩增的一组核酸。

8. 一种抗体，其特征是对含有序列编号1的氨基酸序列的多肽具有结合性、而对包含序列编号2的氨基酸序列的多肽没有结合性。

9. 一种含有权利要求7所述的一组核酸、DNA扩增用酶以及DNA合成试剂的催吐素检测用试剂盒。

10. 一种含有权利要求8所述的抗体和抗原抗体反应用试剂的催吐素检测用试剂盒。

11. 一种包括研究检体中下述（a）或（b）存在的步骤的催吐素检测方法：

（a）含有序列编号1的氨基酸序列的多肽，或含有在序列编号1的氨基酸序列中CRS3或CRS4区域以外的部分经1或多个氨基酸的缺失、取代、添加和/或插入所得的序列、而且具有催吐素合成活性的多肽，

（b）编码（a）中任一种多肽的核酸。

12. 一种包括以下步骤的催吐素检测方法：

（i）以检体中的DNA为模板，使用权利要求7所述的一组核酸进行DNA扩增反应的步骤，

（ii）对被扩增的DNA进行检测的步骤。

13. 一种包括以下步骤的催吐素检测方法:

(i) 以检体中的 DNA 为模板制备 cDNA 的步骤,

(ii) 使用权利要求 7 所述的一组核酸进行 DNA 扩增反应的步骤,

(iii) 对被扩增的 DNA 进行检测的步骤。

14. 一种包括以下步骤的催吐素检测方法:

(I) 使检体与权利要求 8 所述抗体接触的步骤,

(II) I 的步骤后, 对抗原抗体反应物进行检测的步骤。

15. 权利要求 11~14 任一项所述的催吐素检测方法, 其中作为前处理进行以下步骤:

将检体接种到蜡状芽孢杆菌的增菌培养基中进行培养的步骤。

16. 权利要求 11~14 任一项所述的催吐素检测方法, 其中作为前处理进行以下步骤:

(A) 将检体接种到蜡状芽孢杆菌的增菌培养基中进行培养的步骤,

(B) 对增殖的蜡状芽孢杆菌进行溶菌或破碎的步骤。

蜡状芽孢杆菌产生的呕吐毒素的合成酶、编码该酶的基因以及呕吐毒素的检测方法

技术领域

本发明涉及蜡状芽孢杆菌(Bacillus cereus)产生的呕吐毒素(催吐素)及其检测方法。在临床检查或食品检查等中的催吐素的检测中可以利用本发明。

背景技术

人们都知道混入食品成为食物中毒原因的细菌毒素中黄色葡萄球菌泻肚毒素和蜡状芽孢杆菌呕吐毒素作为耐热性毒素，进行加热处理是无效的。关于在食品卫生上极其重要的黄色葡萄球菌毒素已经确立了检测方法，但关于蜡状芽孢杆菌呕吐毒素的检测到目前为止还没有开发出适当的方法。蜡状芽孢杆菌由于形成能够耐受在 100℃下加热 30 分钟的耐热性芽孢，通过煮沸完全杀死他是困难的，非加热食品本来就存在，即使在加热食品中也存在由蜡状芽孢杆菌呕吐毒素造成的污染的问题。蜡状芽孢杆菌在世界范围内以食物中毒菌闻名，即使在我国由于该菌引起的食物中毒也报告了多起。在 1994 年，从蜡状芽孢杆菌分离、纯化了该呕吐毒素（命名为催吐素，セレウリド），确定了其化学构造（Agat,N.，等 FEMS Microbiol.Lett.121,31-34(1994)）。随之而来开发了利用 HEp－2 细胞检测催吐素的方法（Agat,N.,等 FEMS Microbiol.Lett.121,31-34(1994)）。

弄清楚在食品以及其他检体中有无呕吐毒素（催吐素）在通过 HACCP 进行的食品制造管理上是非常重要的,在世界范围内一直探求其检测法的开发。然而，直到现在简便而迅速地进行蜡状芽孢杆菌的检测以及催吐素检测的方法也没有开发出来。由于利用上述的 HEp－2 细胞的方法也需要熟练的技术，所以简便而且正确的检测，以及多个检体同时处理是困难的。另外，检体为患者的呕吐物、粪便、食品或擦拭样品时，连蜡状芽孢杆菌的鉴定都必须进行经增菌培养、分离培养直至纯培养、确认培养的操作。在各个培养阶段需要的时间都各为 18～24 小时，总共需要的时间约 4 天。

本发明是在以上背景下完成的发明，目的在于提供在催吐素的检

测中可以利用的多肽、核酸等，以及利用他们的简便、而迅速的催吐素的检测法。

发明内容

本发明人鉴于上述目的，进行了不断研究。结果首先发现参与催吐素生物合成的酶，并且在其鉴定中获得了成功。当对编码该酶的基因的碱基序列和不产生催吐素的蜡状芽孢杆菌保有的对应基因进行比较时，发现了在两者之间存在不同序列，直至获得了利用这一不同部分可以进行催吐素的检测的想法。本发明是根据以上想法完成的发明，提供以下构成。

[1] 一种含有序列编号 1 的氨基酸序列的多肽，或含有序列编号 1 的氨基酸序列的一部分被改变后构成的序列、而且具有催吐素合成活性的多肽。

[2] 一种含有序列编号 3 的氨基酸序列的多肽，或含有序列编号 3 的氨基酸序列的一部分被改变后构成的序列、而且保持上述多肽所具有的有关催吐素合成的功能构造的多肽。

[3] 编码[1]所述的任一种多肽的核酸。

[4] 编码[2]所述的任一种多肽的核酸。

[5] 保有[3]或[4]所述核酸的载体。

[6] 用[5]所述载体转化的转化体。

[7] 含有序列 6 的碱基序列中与催吐素合成活性直接有关的区域的至少部分的序列、或含有与上述区域的碱基序列相互补的序列的至少部分的核酸。

[8] 含有序列 7 碱基序列的至少部分、或含有与上述碱基序列互补的序列的至少部分的核酸。

[9] 含有序列 8 的碱基序列中与催吐素合成活性直接有关的区域的碱基序列互补的序列的至少部分的核酸。

[10] 含有与序列编号 9 的碱基序列互补的序列的至少部分的核酸。

[11] 被设计成可以对含有在编码具有催吐素合成活性的多肽的 DNA 中直接与催吐素合成活性有关的区域的至少部分的 DNA 区域进行特异扩增的一组核酸。

[12] 一种将[7]～[10]任一项所述的核酸固定于不溶性支持体后

构成的固相化核酸。

[13] 一种与催吐素合成酶特异结合的抗体。

[14] 一种抗体，其特征是对含有序列编号 1 的氨基酸序列的多肽具有结合性、而对由序列编号 2 的氨基酸序列构成的多肽没有结合性。

[15] 一种含有[7]～[10]任一项所述的核酸、[11]所述的一组核酸或[12]所述的固相化核酸的催吐素检测用试剂盒。

[16] 一种含有[11]所述的一组核酸、DNA 扩增用酶以及 DNA 合成试剂的催吐素检测用试剂盒。

[17] 一种含有[13]或[14]所述抗体和抗原抗体反应用试剂的催吐素检测用试剂盒。

[18] 一种包括研究检体中的（a）或（b）存在的步骤的催吐素检测方法：

（a）含有序列编号 1 的氨基酸序列的多肽，或含有序列编号 1 的氨基酸序列的一部分被改变后构成的序列、而且具有催吐素合成活性的多肽，

（b）编码（a）中任一种多肽的核酸。

[19] 一种包括以下步骤的催吐素检测方法：

（i）以检体中的 DNA 为模板，使用[11]所述的一组核酸进行 DNA 扩增反应的步骤，

（ii）对被扩增的 DNA 进行检测的步骤。

[20] 一种包括以下步骤的催吐素检测方法：

（iii）以检体中的 DNA 为模板制备 cDNA 的步骤，

（iv）使用[11]所述的一组核酸进行 DNA 扩增反应的步骤，

（v）对被扩增的 DNA 进行检测的步骤。

[21] 一种包括以下步骤的催吐素检测方法：

（I）使检体与[13]或[14]所述抗体接触的步骤，

（II）I 的步骤后，对抗原抗体反应物进行检测的步骤。

[22] [18]～[21]中任一项所述的催吐素检测方法，其中作为前处理进行以下步骤：

（A）将检体接种到蜡状芽孢杆菌的增菌培养基中进行培养的步骤。

[23] [18]～[21]中任一项所述的催吐素检测方法，其中作为前处

理进行以下步骤:

（A）将检体接种到蜡状芽孢杆菌的增菌培养基中进行培养的步骤，

（B）对增殖的蜡状芽孢杆菌进行溶菌或破碎的步骤。

另外，本发明中的 DNA 不限于双链 DNA，也可使用包括构成双链的单链 DNA（有义链和反义链）。另外在本发明的 DNA 中包含含有考虑了密码子的简并性的任意的碱基序列的 DNA。另外其形式也没有限定，可以含有 cDNA、基因组 DNA、合成 DNA。

另外，在本发明中所谓多肽指的是广义上的多肽，即包括使用表现为多个氨基酸以肽键连接形成的肽在内的寡肽、狭义多肽以及蛋白质。

在本发明中，将蜡状芽孢杆菌产生的呕吐毒素称为催吐素。

附图的简单说明

图 1 是表示在本发明的实施例中对 PCR 扩增产物进行电泳后的凝胶染色后的状态图。从左边的带开始依次为对 NC7401 株、NC－T 株、NC－G15 株、NC327 株、NC－1－55 株（以上为催吐素产生株）、ATCC14579 株、B-4ac 株、PHLS2668 株、PHLS4433 株、NC1225 株（以上为催吐素非产生株）、苏云金芽孢杆菌（HD73）、以及枯草芽孢杆菌（ATCC21332）的 PCR 反应后的溶液进行电泳后的结果。

图 2 是表示对来自 DNA 浓度不同的样品的 PCR 扩增产物进行电泳后的凝胶染色后的状态图。带编号 1、2、3 和 4 分别为对来自 300ng、30ng、3ng、以及 0.3ng 的样品的 PCR 扩增产物进行电泳后的带。

实施发明的最佳方式

本发明的第 1 个方面涉及到具有催吐素合成活性的多肽（以下也称为「催吐素合成酶」）。本发明中提供的催吐素合成酶含有序列编号 1 的氨基酸序列。就象下面实施例所示那样，该酶是用蜡状芽孢杆菌的 cDNA 文库鉴定的。催吐素合成酶参与催吐素的合成，只出现在产生催吐素的蜡状芽孢杆菌中。因此，检体中该酶的存在可以反映有无催吐素产生。这样一来，催吐素合成酶在作为催吐素检测的指标方面是有用的。

另外，如果获得与催吐素合成酶特异结合的抗体，利用该抗体提供免疫学方法也可以进行该酶的检测、即催吐素的检测。因此，在可

以作为用于制备这样的抗体的免疫源（抗原）利用方面，本发明提供的多肽（催吐素合成酶）也是有用的。

其中作为含有序列编号 1 的氨基酸序列的一部分被改变后构成的氨基酸序列的多肽（以下称为「改变多肽」）只要是具有催吐素合成活性的，可以与上述多肽同样在催吐素的检测等中利用。作为这样的多肽的例子，如关于含有序列编号 1 的氨基酸序列的多肽、保存与催吐素合成活性有关的立体构造的多肽。

这里所谓的「氨基酸序列的一部分被改变」指的是在氨基酸序列中缺失、置换、附加、和/或插入 1 个或数个氨基酸。只要是保持催吐素合成活性，氨基酸序列的改变（变异）位置没有特别限定，也可以在多个位置进行改变。改变的氨基酸数例如可以是相当于总氨基酸的 10％以内的数，优选是相当于总氨基酸的 5％以内的数。更优选的是相当于总氨基酸的 1％以内的数。以上那样改变的多肽可以用众所周知的基因工程的手段进行制作。

象下面叙述的实施例所示的那样，由序列编号 1 的氨基酸序列构成的多肽可以认为是由 4 个结构域构成的。在本发明中为了方便，从 N 末端一侧开始依次将这些结构域称为 CRS1、CRS2、CRS3 和 CRS4。根据本发明人的研究结果，催吐素产生菌中特征性的结构域是 CRS3（1805 位～2824 位的氨基酸序列）和 CRS4（2825 位～3704 位的氨基酸序列）。因此，可以认为这些结构域直接参与催吐素生物合成。由此可以认为为了制备对催吐素合成酶特异的抗体，含有上述特异结构域中的任一个或两者的多肽可以成为特别有效的抗原。本发明也提供含有序列编号 3、序列编号 4、或序列编号 5 记载的氨基酸序列的多肽。另外在这些多肽中，只要是保持他们具有的与催吐素生物合成有关的功能构造，即使一部分氨基酸被改变也可以。

另外，只要是没有特别限定，以下说明中，称之为「催吐素生物合成直接相关的区域」指的都是序列编号 1 的氨基酸序列中 1805 位～3704 位的区域，即 CRS3 和 CRS4（对于 DNA 是编码 CRS3 和 CRS4 的 DNA 区域）。

本发明的多肽中，若是存在于自然界中的，可以通过提取纯化等操作作为天然的多肽制备。例如，可以从产生催吐素的蜡状芽孢杆菌的菌体内制备。

另外，本发明的多肽（包括改变多肽）也可以用基因工程手法作为重组多肽制备。即，用编码本发明的多肽的 DNA 转化适当的宿主细胞，通过回收在转化体内表达的多肽进行制备。回收的多肽可以根据目的进行适当纯化。作为重组多肽制备时，可以进行各种修饰。例如，将编码本发明的多肽与其他的适当 DNA 同时插入到载体中，可以得到本发明的多肽和上述另一个 DNA 编码的肽或多肽连接的重组多肽。通过这样的修饰，可以使重组多肽的提取、纯化简便，或附加生物学上的功能。

本发明的多肽也可以通过化学合成制备。例如，可以通过众所周知的肽合成法 - 固相合成法进行合成。

本发明的第 2 个方面提供编码上述本发明的多肽的核酸。作为这样的核酸的具体例子，如具有序列编号 6 或序列编号 7 的碱基序列的 DNA、或序列编号 8 或序列编号 9 的 RNA。或者是这些 DNA 中一部分被改变的 DNA 等。这里的所谓「一部分被改变」指的是构成 DNA 或 RNA 的碱基的一部分被缺失、置换、插入或附加。改变的碱基数可以是例如 1～100 个、优选 1～20 个、更优选 1～10 个。

本发明的核酸可以用作对催吐素进行检测时的样品，即在给予有关有无催吐素存在的指标方面是有用的。另外，为了制备与上述本发明的多肽结合的抗体、即在催吐素的检测中可以利用的抗体的抗原制备过程方面也是有用的。

以上的核酸可以适当利用可与编码催吐素合成酶的基因（具有序列编号 6 的碱基序列的 DNA）特异杂交的探针、引物等从适当的基因组 DNA 文库或 cDNA 文库、或催吐素产生菌的菌体内提取液制备。另外也可以通过以至少编码催吐素合成酶的基因的一部分作为模板，以 dNTP（dATP、dGTP、dCTP、dTTP）作为原料的 PCR 法等进行合成。

为了制备本发明的 DNA 使用的基因组 DNA 文库或 cDNA 文库可以根据常规方法从蜡状芽孢杆菌 NC7401 株制作。

本发明还提供保持上述本发明的 DNA（包括改变 DNA）的载体。只要是可以保持本发明的 DNA 的载体，可以使用任一种载体，但最好是根据目的（克隆、多肽的表达），或考虑宿主细胞的种类之后选择适当的载体。本发明的 DNA 向载体插入可以通过使用限制酶和 DNA 连接酶的众所周知的方法（Molecular Cloning,Third

Edition,1.84,Cold Spring Harbor Laboratory Press,New York）进行。

本发明还提供保持上述本发明的 DNA（包括改变 DNA）的转化体。即涉及到用本发明的 DNA 转化宿主细胞得到的转化体。例如利用磷酸钙法、电穿孔（Potter,H. 等， Proc.Natl.Acad.Sci.U.S.A.81,7161-7165(1984)）、脂转染法（Felgner,P.L. 等， Proc.Natl.Acad.Sci.U.S.A.84,7413-7417(1984)）、微注射（Graessmann,M.& Graessmann,A.， Proc.Natl.Acad.Sci.

U.S.A.73,366-370(1976)）等众所周知的基因导入方法将本发明的 DNA 导入到宿主细胞后进行转化。用上述本发明的载体转化宿主细胞后可以得到本发明的转化体。根据目的可以使用各种各样的宿主细胞，例如可以使用大肠杆菌等原核细胞、酵母等真核细胞。在利用大肠杆菌系时，作为表达载体可以使用 pET-3c 或 pET-8c 等 pET 载体（Novagen 公司）、pBAD 质粒(Invitrogen 公司)、pGEX 质粒(Amersham Pharmacia biotech 公司）等。

通过在适当的条件下对本发明的转化体进行培养，可以大量生产本发明的 DNA 表达产物（多肽），该表达产物可在催吐素合成酶的检测用抗体的制备中利用。另外通过作为与由数个组氨酸构成的 His-Tag、β-D-半乳糖苷酶、GST（谷胱甘肽 S-转移酶）、硫氧还蛋白、麦芽糖结合蛋白质、Myc、Xpress、FLAG 等标记分子的融合蛋白质(肽)表达，可容易进行表达产物的纯化。

本发明的第 3 个方面涉及到催吐素的检测方法，其特征是包括研究检体中是否存在以下（a）或（b）的步骤。（a）：含有序列编号 1 的氨基酸序列的多肽，或含有序列编号 1 的氨基酸序列的一部分被改变后构成的序列、而且具有催吐素合成活性的多肽，或(b)：编码(a)中任一种多肽的核酸。另外，由于检体中催吐素的存在即意味着产生催吐素的蜡状芽孢杆菌的存在，所以本发明中的「催吐素的检测方法」可以作为与「产生催吐素的蜡状芽孢杆菌的检测方法」同义的概念使用。

研究（a）存在的方法没有特别限定，可以利用使用对检测对象的多肽特异的抗体的免疫学方法。

同样，研究（b）存在的方法没有特别限定，例如可以利用使用对

编码检测对象多肽的核酸特异的核酸引物和/或核酸探针的方法，使用设计成对催吐素特异的核酸区域进行特异扩增的一组引物（核酸）的PCR法（聚合酶链式反应）以及其改变法或应用方法（PCR-RFLP限制片段长度多态性)法、RT-PCR（逆转录酶 PCR）法等），Soutern blot杂交法、点杂交法（Southern, E., J. Mol. Biol. 98, 503-517 (1975)），Northern blot法等。

以下给出了本发明提供的催吐素检测方法的更具体的例子。首先，作为利用PCR法等的核酸扩增反应的例子，如包括（i）以检体中的DNA为模板，使用一组核酸进行DNA扩增反应的步骤，该组核酸被设计成可以对含有编码催吐素合成活性的多肽的DNA(例如由序列编号6的碱基序列构成的DNA）中，与催吐素合成活性直接相关的至少一部分的DNA区域（例如由序列编号7的碱基序列构成的DNA区域）进行特异扩增，以及（ii）对被扩增的DNA进行检测的步骤的方法。另外作为利用RT－PCR法的方法，如包括（iii）以检体中的mRNA为模板制备cDNA的步骤，（iv）使用一组核酸进行DNA扩增反应的步骤，该组核酸被设计成可以对含有编码催吐素合成活性的多肽的DNA中与催吐素合成活性直接有关的至少一部分DNA区域进行特异扩增，以及(v)对被扩增的DNA进行检测的步骤的方法。

由于必须是可通过PCR法等扩增得到的大小，所以由一组引物规定的扩增区域最好是约4,000bp以下。另外，当扩增区域过小时，由于对扩增产物和引物的二聚体难于进行区别，所以扩增区域最好是50bp以上。另外，为了有效进行扩增，扩增区域优选100bp～1,000bp大小。

作为在PCR法等中使双链核酸热变性时的温度，例如可以是约90℃～约95℃，作为使引物杂交的退火温度，例如可以为约37℃～约65℃，而作为聚合反应时的温度例如可以为50℃～约80℃。在PCR法以及其变更方法等中可以将这些热变性、退火、聚合作为一个循环反复进行直至扩增到可以检测到扩增产物为止。扩增产物的检测可以利用琼脂糖凝胶电泳进行。即，通过对酶反应液进行琼脂糖凝胶电泳，可以确认扩增的核酸片段的存在及其长度。由该电泳结果可以判定在检体中是否存在含有引物识别的序列的核酸，由此可以判定有无催吐素存在，即有无产生催吐素的蜡状芽孢杆菌的存在。在扩增产物的检测

中不限定于琼脂糖凝胶电泳，也可以利用其他电泳或各种层析。

作为在本发明的催吐素检测方法中能够利用的核酸（引物或探针用），只要是在对编码催吐素合成酶的基因进行特异检测中可以利用的，没有特别限定，例如至少含有序列编号 6 的碱基序列中与催吐素合成活性直接有关的区域的一部分序列的核酸、或与上述区域的碱基序列互补的序列的一部分的核酸。这里所谓「与催吐素合成活性直接有关的区域」如上所述，具体指的是编码 CRS3 和 CRS4 的区域，即具有序列编号 7 的碱基序列的区域。在用检体中的 mRNA 作为检测对象时，在催吐素检测方法中也同样可以利用至少含有与序列编号 8 的碱基序列中与催吐素合成活性直接有关区域的碳基序列互补的序列的一部分的核酸。更具体讲，如至少含有与序列编号 9 的碱基序列互补的序列的一部分的核酸。

至于探针、引物，可以根据解析方法使用合适的 DNA 片段或 RNA 片段。探针、引物的碱基长度只要是能够发挥各自功能的长度就可以，如果考虑到选择性或检测灵敏度和再现性，作为引物的碱基长度为 10bp 以上、优选在 15bp 以上，具体来说如 10～30bp 左右，优选 15～25bp 程度。

另外，对于引物，只要是可以与扩增对象特异杂交、能够扩增目的 DNA 片段，即使与作为模板的序列多少有些错配也可以。错配的程度可以是 1～n 个，优选 1～5 个，更优选 1～3 个。对于探针也同样，在对检测没有影响的范围内，即使对检测对象的序列多少有点错配也可以。

以下给出了在运用 PCR 法等伴随特定 DNA 区域的扩增的方法的催吐素检测方法中能够利用的核酸（引物组）的具体例子。

引物组 1

有义链用引物：5'-GGTGAATTGTGTCTGGGAGG-3'（序列编号 10）

反义链用引物：5'-ATTTTTATTAAGAGGCAATG-3'（序列编号 11）

引物组 2

有义链用引物：5'-GTCAAGATAAGAGGCTTCCGAATT-3'（序列编号 12）

反义链用引物：5'-AATGGAATGACCACCAAGCT-3'（序列编号 13）

引物组 3

有义链用引物：5'-AGGAAGTTCCGTTTGTGGAC-3'（序列编号 14）

反义链用引物：5'-CACATAACCTTTTGCAACTC-3'（序列编号 15）

引物组 4

有义链用引物：5'-GGCGAACTATGTGTTGGTGG-3'（序列编号 16）

反义链用引物：5'-TAAAGAGTCACCACCATAAG-3'（序列编号 17）

引物组 5

有义链用引物：5'-ACGTCAGGCAGTACTGGAAA-3'（序列编号 18）

反义链用引物：5'-TTCGATGCGGAATCCACGAA-3'（序列编号 19）

本发明中的核酸（引物、探针）可以通过磷酸二酯法等众所周知的方法合成。另外，作为探针使用时的标记物质、标记方式可以采用众所周知的物质。作为标记物质如 ^{32}P 等放射性同位素、异硫氰酸荧光素、异硫氰酸四甲基罗丹明等荧光物质，作为标记方法如使用 T4DNA 聚合酶或 Klenow 片段的 3'末端标记法、切口移位法、随机引物法（Molecular Cloning,Third Edition,Chapter 9,Cold Spring Harbor Laboratory Press,New York）等。

以下就利用免疫学方法的催吐素的检测方法进行说明。作为利用免疫学方法的催吐素的检测方法，如包括 I）使检体与对催吐素合成酶特异的抗体接触的步骤，（II）I 的步骤后，抗原抗体反应物的检出步骤在内的方法。这里的所谓「对催吐素合成酶特异的抗体」指的是具有与催吐素合成酶特异结合性的抗体，作为具体例子，如对含有序列编号 1 的氨基酸序列的多肽具有结合性、而对由序列编号 2 的氨基酸序列构成的多肽没有结合性的抗体。可以使用的抗体的类别没有特别限定，例如可以使用属于 IgG 类、IgM 类等的抗体。另外也可以使用 Fab、Fab'、F（ab'）2，scFv、dsFv 等抗体片段。

作为测定方法，如 ELISA（酶联免疫吸附定量法）法、放射免疫分析、FACS、免疫沉淀法、免疫印迹等定性的或定量的方法。另外作为抗原抗体反应的种类可以采用使检体中的催吐素合成酶和另外添加的催吐素合成酶与催吐素合成酶特异的抗体竞争反应的方法（竞争法），以及不使他们进行竞争反应的方法（非竞争法）。

作为对催吐素合成酶特异的抗体优选使用单克隆抗体。由于单克隆抗体的特异性高，所以可以进行高灵敏度测定。另外，利用使用对催吐素合成酶特异的而且识别互不相同的抗原表位的 2 种抗体的夹层法在灵敏度、特异性方面更好。

抗体可以进行固相化后使用。作为固相化使用的不溶性支持体，可以使用聚苯乙烯树脂、聚碳酸酯树脂、硅树脂、尼龙树脂等树脂或玻璃等对水不溶性的物质，其材料没有特别限定。抗体向这些不溶性支持体的负载可以通过物理吸附或化学吸附进行。

作为在免疫学测定法中可使用的标记物质，过氧化物酶、碱性磷酸酶、β－D－半乳糖苷酶、葡萄糖氧化酶、葡萄糖－6－磷酸脱氢酶、以及微过氧化物酶等酶、异硫氰酸荧光素（FITC）、异硫氰酸四甲基罗丹明（TRITC）、以及铕等荧光物质、氨基苯二酰肼、异氨基苯二酰肼、以及吖啶鎓衍生物等化学发光物质、NAD等辅酶、生物素以及^{131}I和^{125}I等放射性物质等可以作为标记物质使用。特别是作为标记物质使用生物素，使用荧光色素或酶标记的抗生物素蛋白（例如抗生物素蛋白过氧化物酶）反应的方法，可以进行更高灵敏度的测定。

与催吐素合成酶特异结合的单克隆抗体可以通过常规方法获得。以下给出了一个单克隆抗体的制作方法的例子。首先取得催吐素合成酶，作为抗原免疫小鼠等动物。然后从被免疫的动物摘出抗体产生细胞，使该细胞与骨髓瘤细胞融合得到杂交瘤细胞。接下来，使该杂交瘤单克隆化后，选择产生与催吐素合成酶特异结合的克隆。

作为抗原可以使用从产生催吐素的蜡状芽孢杆菌的菌体内分离、纯化的催吐素合成酶。另外也可以使用利用用编码催吐素合成酶的碱基序列，通过来自大肠杆菌的表达体系得到的重组多肽。

作为免疫方法，例如可以采用将上述抗原与弗氏完全或不完全佐剂混合，进行乳化，注射到小鼠等的腹腔内、皮下或肌肉，隔一定时间注射一次，进行数次注射的方法。作为免疫的动物可以使用小鼠以及大鼠、仓鼠、兔、豚鼠、鸡、绵羊、山羊等。免疫完成后，取出免疫的动物的脾脏，取得抗体产生细胞。也可以从淋巴节、末梢血液等采取抗体产生细胞。

使用的骨髓瘤细胞的种类没有特别限定，选择与免疫使用的动物的相关的合适的种类。最好是使用来自与抗体产生细胞同种动物的骨髓瘤细胞，例如当使用小鼠时可以使用骨髓瘤细胞株PAI。细胞融合，例如可以通过按照一定比例将抗体产生细胞与骨髓瘤细胞混合，然后加入聚乙二醇后搅拌处理进行细胞融合。另外也可以使用用电脉冲进行细胞融合。

在只选择进行了细胞融合的杂交瘤时，可以运用使用一般的 HAT 培养基（按给定比例含有次黄嘌呤、氨基蝶呤、胸腺嘧啶的选择培养基）的方法。含有杂交瘤的培养液为了以后的选择，可以在 96 孔板中培育。

然后取各个容器内的培养上清，通过使用催吐素合成酶的 ELISA 法等选择产生抗催吐素合成酶的抗体的杂交瘤。抗体阳性的容器内的杂交瘤通过有限稀释法进行克隆，可以得到单克隆化的杂交瘤细胞株。

通过对杂交瘤的培养液进行纯化可以得到所期望的抗体。另外使杂交瘤增殖到所期望的数以上后，将他们移植到动物（例如小鼠）的腹腔内，使其在腹水内增殖，通过纯化腹水，也可以获得所期望的抗体。在上述培养液的纯化或腹水的纯化中适合采用使用蛋白 G、蛋白 A 等的亲和层析。另外，也可以使用将抗原固相化的亲和层析。另外也可以使用离子交换层析、凝胶过滤层析、硫铵分级、以及离心分离等方法。这些方法可以单独或任意组合使用。

通过以上方法得到的抗体是否特异识别催吐素合成酶，例如可以通过使用将催吐素合成酶固相化的板的 ELISA 法进行确认。

在本发明的催吐素检测方法中可以将利用的核酸（引物或探针）固定于不溶性支持体后使用。同样，在本发明的催吐素检测方法中也可以将可利用的抗体固定于不溶性支持体后使用。可以将固定化中使用的不溶性支持体事先加工成片状、颗粒状等，使用这些固定化核酸或固定化抗体可以简便地进行检体中的催吐素的检测。

本发明的另一个方面提供在催吐素检测中可以利用的试剂盒。即，使用在催吐素的检测中可以利用的核酸（含有一组的核酸、固相化核酸）构建催吐素检测用试剂盒。在催吐素检测用试剂盒中除了这些核酸之外，还可以含有核酸扩增用酶（例如 PCR 法中使用的 DNA 合成酶）以及作为底物的核酸（dATP、dCTP、dGTP、dTTP）、反应用的试剂等。另外，作为标准物质可以含有催吐素合成酶（可以是部分纯化品）、催吐素产生菌株的菌体内提取物（可以是进行了部分纯化提取物）。

利用以上的催吐素检测用试剂盒，以检体中的核酸作为靶可以检测催吐素，也可以构建以检体中的多肽、即催吐素合成酶作为靶，用

于对催吐素进行检测的试剂盒。在这样的试剂盒中含有对上述的催吐素合成酶特异的抗体（包括固相化抗体）。此外，也可以构建包含与该抗体结合的第二抗体、抗原抗体反应用试剂（缓冲液、发色底物、发色试剂、发色反应终止液等）等的试剂盒。另外作为标准物质可以含有催吐素合成酶（可以是部分纯化品）、催吐素产生菌株的菌体内提取物（可以是进行了部分纯化的提取物）。

提供给本发明的催吐素检测方法的检体没有特别限定，作为检体例如可以使用各种食品、人或动物的呕吐物或粪便、或擦拭样品等。这些检体可以预先进行用溶菌酶等酶处理、加压处理、加热处理或超声处理等。通过这些处理，检体中的菌体被溶菌或破碎。但是当预料在采取检体时，检体中的蜡状芽孢杆菌的细胞膜破碎时，就不必进行溶菌处理等。

对于从检查对象采取的样品最好是用蜡状芽孢杆菌的增殖培养基（选择培养基）预先进行培养。通过采用该培养步骤，可以进行可靠性更高的检测。

另外，检查对象为液状时，可以将采取的样品用于直接溶菌等处理或培养步骤，当检查对象为固体状时，优选是用适当的溶剂对菌体进行提取后，用于这些处理。

以下用实施例对本发明进行更详细说明。

〈实施例 1〉从蜡状芽孢杆菌基因组 DNA 文库克隆呕吐毒素（催吐素）合成酶基因

使用来自蜡状芽孢杆菌 NC7401 株（保管在名古屋市卫生研究所、国立医药品食品卫生研究所）的 EMBL3（Promega 公司生产）制作噬菌体文库。对得到的约 400 个白色蚀斑进行筛选，作为在不借助于核糖体的氨基酸合成酶中特异存在的区域，用 BSC I（GGAATTCCTTAAAIGCIGGAGGAGCITATGTGCCGCTT GATCC：序列编号 20）以及 II（GGAATTCCTTTIGGITTICCIGTTGTICCI GAIGTGTAAAT：序列编号 21）作为引物（Kathrin,M.，等，FEMS Microbiol.Lett.135,295-303(1996)）特异扩增的 DNA 片段通过 Southern 杂交法进行分析。另外对通过作为模板使用 NC7401 株的染色体 DNA，作为引物使用 BSC I 和 II 的 PCR 法扩增的 DNA 片段用标记物标记试剂盒（Roch Diagnostics 公司生产）进行标记的探针进行分

析。分析结果，选择多个表达量大的插入 DNA，分别用限制性内切酶 SaI1 切出，亚克隆到克隆载体 pHSG299（宝酒造株式会社生产）的多克隆位点。

〈实施例 2〉呕吐毒素（催吐素）合成酶 cDNA 的序列分析

亚克隆的各个 DNA 片段的序列通过使用自动测序仪（Applied Biosystems 公司生产）循环测序反应进行分析。考虑到重复的序列后，通过对各个 DNA 片段的序列信息进行分析，决定催吐素合成酶的全长 DNA 序列以及氨基酸序列（序列编号 1）。当对该序列进行详细研究时，发现催吐素合成酶由合成各个氨基酸的的 4 个结构域构成，N 末端一侧的 2 个结构域虽然也广泛地存在于不产生催吐素的蜡状芽孢杆菌株中，但 C 末端一侧的 2 个结构域是产生催吐素的菌株所特异的。

〈实施例 3〉利用 PCR 法进行催吐素的检测

（3－1）检体的制备

从图 1 的表表示的芽孢杆菌（催吐素产生株和非产生株各 5 株）按照以下顺序制备检体。作为对照组使用苏云金芽孢杆菌（Bacillus thuringienesis）、以及枯草芽孢杆菌（Bacillus subtilis）。

将各个菌体分别接种到适当的增菌培养基（LB 培养基），于 37℃下在好氧条件下培养过夜，通过离心操作从培养后的 1.5ml 培养基中回收菌体。将回收的菌体用 10mMTris－HCl 缓冲液（pH7.5）清洗一次后，悬浮于 0.5ml 溶解了终浓度为 1mg/ml 的溶菌酶的同一缓冲液中。在该状态下于 37℃下放置 10 分钟，使其溶菌。然后，向溶菌液中添加等量被上述缓冲液饱和的酚，进行充分搅拌。离心处理后，回收上层液，进行醇沉淀处理，使核酸成分沉淀。将得到的沉淀物溶解于 1ml 上述缓冲液，作为以下检测方法中的检体。

（3－2）PCR 用引物的合成

以序列编号 6 给出的催吐素合成酶的碱基序列信息为基础，选择对催吐素产生株特异的序列，化学合成以下所示引物（寡核苷酸）。

有义链用引物：5'-GGTGAATTGTGTCTGGGAGG-3'（序列编号 10）

反义链用引物：5'-ATTTTTATTAAGAGGCAATG-3'（序列编号 11）

（3－3）PCR 法

向上述各个检体 3μl 加入灭菌蒸馏水 16.05μl、10×反应用缓冲液 3μl、dNTP 溶液 4.8μl、有义链用引物 1.5μl、反义链用引物

1.5μl、以及耐热性 DNA 聚合酶 0.150μl，将总量调整到约 30μl 的反应液。而 10×反应用缓冲液的组成为 500mM KCl、100mM Tris－HCl（pH8.3）、15mM $MgCl_2$、0.1%（w/v）明胶，dNTP 溶液是使终浓度各为 1.25mM 的 dATP、dCTP、dGTP 和 dTTP 混合的溶液。另外各个引物是（3－2）中得到的化学合成纯化品的水溶液（50DU/ml）。至于耐热性 DNA 聚合酶使用 TaqDNA 聚合酶（5unit/ml: Perkin Elmer Cetus 公司生产）。

PCR 反应条件如下。即热变性: 94℃ 1 分钟，退火: 55℃ 1 分钟，聚合反应: 72℃ 1 分钟。由热变性开始经退火直至聚合反应的过程作为 1 个循环，共进行 35 次循环。另外，使用 DNA Thermal Cycler（Perkin Elmer Cetus 公司生产）进行 PCR 反应。

（3－4）PCR 扩增产物的检测

为了检测由 PCR 反应液扩增的 DNA 片段，在以下条件下进行琼脂糖电泳。作为琼脂糖凝胶使用凝胶浓度为 2%（w/v）的凝胶。使用溴乙锭（0.5μg/ml）进行电泳后的凝胶染色。电泳条件为加 100V 电压，电泳 30 分钟。其他的电泳条件以及操作方法根据 Molecular Cloning, Third Edition, Cold Spring Harbor Laboratory Press, New York 记载的方法。

图 1 表示染色后的凝胶。在图 1 中，从左边的带开始依次为对 NC7401 株、NC－T 株、NC－G15 株、NC327 株、NC－1－55 株（以上为产生催吐素株）、ATCC14579 株、B-4ac 株、PHLS2668 株、PHLS4433 株、NC1225 株（以上为不产生催吐素的菌株）、苏云金芽孢杆菌（HD73）、以及枯草芽孢杆菌（ATCC21332）的 PCR 反应后的溶液进行电泳后的结果。就象图 1 所表示的那样，可知在催吐素产生菌株（带 1～5）可以得到约 450bp 的 PCR 扩增产物。而在催吐素非产生菌株和苏云金芽孢杆菌 HD73、以及枯草芽孢杆菌 ATCC21332 中没有检测到相当于该 PCR 扩增产物的带。由以上结果可以确认通过本实施例的方法可特异进行催吐素产生菌株的检测、即催吐素的检测。

〈实施例 4〉 利用 PCR 法进行催吐素产生菌的微量检测

（4－1）检体的 DNA 量的计算

使用图 1 表示的蜡状芽孢杆菌 NC7401 株，用实施例的（3－1）给出的方法制备检体，得到纯化 DNA 标准品。然后通过测定波长 260nm

的吸光度计算出该标准品中的 DNA 量。

（4－2）PCR 扩增产物的检测

以（4－1）求出的 DNA 量作为参考，对检体进行稀释，制备分别含有 300ng（分子数：约 1×10^{2}）、30ng（分子数：约 1×10^{1}）、3ng（分子数：约 1）、0.3ng（分子数：约 1×10^{-1}）的样品。利用这些样品通过实施例 3 的（3－2）和（3－3）给出的方法进行 PCR，然后用（3－4）给出的方法进行 PCR 扩增产物的检测。图 2 给出了对 PCR 扩增产物电泳后的凝胶进行染色后的状态。道编号 1、2、3 和 4 数分别对应来自 300ng、3ng、3ng 以及 0.3 的样品的 PCR 扩增产物进行电泳后的道。道 3，即使在使用含有 3ng 的 DNA 的样品时也可以确认目的带。这意味着可以对相当于蜡状芽孢杆菌染色体的 1～数个分子的 DNA 量进行检测，由此可认为理论上如果在检体中存在大约几个催吐素产生蜡状芽孢杆菌，也可以其存在、即催吐素进行检测。

本发明并不受上述发明的实施方式以及实施例的说明的任何限定。只要是没有脱离开专利申请范围的记载，本领域技术人员容易想到的范围中种种变化方式都包括在本发明中。

产业上利用的可能性

本发明提供蜡状芽孢杆菌产生的呕吐毒素（催吐素）的氨基酸序列以及碱基序列。利用这些序列，使用核酸探针或抗体有可能进行催吐素的检测。通过使用对催吐素特异的抗体或核酸探针，对催吐素可以简便而且迅速地进行检测。在实施例中给出的本发明的检测方法的一个例子中，对检体中的核酸进行扩增的反应所需要的时间约 3 小时，直至获得后来的检测结果大约为 30 分钟，可以在极短的时间内对到目前为止不能检测的催吐素进行检测。

另外利用本发明的方法可以对催吐素进行高灵敏度检测。这意味着可以对少量检体进行检测，以及可以使检体的前处理简便化。另外通过本发明的催吐素检测方法不仅可以对催吐素直接进行检测，而且可以对催吐素合成酶的有无进行研究，由研究结果判别催吐素是否存在于检体中。作为在蜡状芽孢杆菌中产生催吐素的菌株的共通的特征，认为是具有在本发明中鉴定的催吐素合成酶活性，即催吐素产生株必然有催吐素合成酶基因。然而，由于不知道在其他生物种中是否产生与催吐素同源的毒素，所以通过将催吐素合成酶或编码该酶的基

因作为检测对象，可以有选择地或特异地对检体中的催吐素的存在（催吐素产生菌的存在）进行检测。因此，可以得到可靠性高的结果，适用于食品检查、临床检查。

序列表

<110> 股份有限公司生物控制研究所
OHTA, Michio
AGATA, Norio

<120> 催吐素合成酶，其基因，和催吐素的检测方法

<130> P0202401

<150> JP P2002-142398
<151> 2002-05-17

<160> 21

<170> PatentIn version 3.1

<210> 1
<211> 3704
<212> PRT
<213> 蜡状芽孢杆菌

<400> 1

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Gly Gly Met Met Glu Met Lys Arg Val Glu Glu His Asp His Ile His
20 25 30

Val Leu Asn Glu Ile Glu Asn Glu Cys Glu Arg Arg Tyr Gly Arg Ser
35 40 45

Asn Ile Ala Ile Met Leu Glu Lys His Gly Val His Glu Gln Pro Leu
50 55 60

His Ile Glu Asp Leu Phe His Glu Val Glu Met Gln Glu His Ser Arg
65 70 75 80

Val Ser Arg His Glu Thr Val Leu Met Thr Asp Lys Gln Cys Ile Asp
85 90 95

Glu Ser Gly Lys Pro Leu Ala Leu Arg Phe Gly Glu Pro Leu His Leu
100 105 110

Asp Asp Cys Thr Pro Lys Thr Leu Gln Glu Ile Leu Lys Arg Ala Ala
115 120 125

Lys Gln Ala Lys Asp Lys Gly Met Thr Phe Val Tyr Glu Asp Gly His
130 135 140

Glu Glu Tyr Leu Ser Tyr Gln Glu Met Leu Ala Asp Ala Glu Arg Leu
145 150 155 160

Leu Lys Gly Leu Arg Asn Leu Gly Ile Gln Pro Gly Glu Ser Ile Leu
165 170 175

Phe Gln Phe Lys Asp Asn Lys His Phe Val Thr Ala Phe Trp Ala Cys
180 185 190

Ile Leu Gly Gly Phe Leu Pro Thr Pro Leu Gly Thr Ala Pro Ile Tyr
195 200 205

Ser Glu Gln Asn Ala Gln Val Leu Lys Leu Tyr Asn Thr Trp Gln Leu
210 215 220

Leu Glu Gln Pro Ile Ile Leu Thr Glu Phe Glu Leu Lys Glu Glu Ile
225 230 235 240

Ala Ala Ile Arg Thr Thr Leu Gln Arg Gln Glu Ile Val Ile His Ser
245 250 255

Ile Glu Asn Val Met Asp Thr Ala Arg Asp Thr Asn Trp Phe Pro Cys
260 265 270

Thr Glu Asp Thr Ile Val Leu Asn Leu Leu Thr Ser Gly Ser Thr Gly
275 280 285

Val Pro Lys Cys Val Gln His Lys Ser Lys Ser Ile Ile Ala Arg Thr
290 295 300

Val Ser Asn Cys Ile Asp Arg Gln Leu Asp Glu Lys Glu Val Ser Leu
305 310 315 320

Asn Trp Met Pro Leu Asp His Val Gly Gly Ile Val Met Cys His Ile
325 330 335

Arg Asp Thr Tyr Leu Met Cys Gln Gln Val Asn Cys Leu Ile Ser Ala
340 345 350

Phe Ile Glu Asn Pro Leu Asn Trp Leu His Trp Ile Asp Ala Tyr Ser
355 360 365

Ala Thr Phe Thr Trp Ala Pro Asn Phe Ala Phe Ser Leu Ile Asn Gln
370 375 380

Tyr Glu Glu Glu Ile Lys Ser Ser Ser Trp Asn Leu Ser Ser Met Arg
385 390 395 400

Tyr Ile Val Asn Gly Gly Glu Ala Val Ile Ser Ser Val Gly Met Lys
405 410 415

Phe Leu Glu Leu Leu Gln Gln His Gln Leu Pro Ser Asn Cys Leu Ile
420 425 430

```
Pro Thr Phe Gly Met Ser Glu Val Ser Ser Gly Ile Ile Glu Cys His
        435                 440                 445

Ser Phe Tyr Thr Gln Thr Thr Asn Thr Gly Met Leu Tyr Val Asp Lys
    450                 455                 460

Asn Ser Leu Asp Gly Asn Leu Gln Phe Thr Tyr Glu Gly His Gln Asn
465                 470                 475                 480

Ala Ile Val Phe Thr Glu Val Gly Arg Pro Met Pro Gly Ile Gly Ile
                485                 490                 495

Arg Ile Val Asp Glu Asp Asn Gln Cys Leu Ser Glu Asp Arg Ile Gly
            500                 505                 510

Arg Phe Gln Ile His Gly Pro Thr Val Met Asn Gly Tyr Phe Lys Asn
        515                 520                 525

Asp Glu Ala Asn Ala Glu Ser Phe Thr Glu Asp Gly Trp Phe Asp Ser
    530                 535                 540

Gly Asp Leu Gly Phe Ile His Asn Gly Asn Leu Val Ile Thr Gly Arg
545                 550                 555                 560

Lys Lys Asp Met Ile Val Val His Gly Ala Asn Tyr Tyr Asn Tyr Glu
                565                 570                 575

Ile Glu Ala Leu Val Glu Gln Val Pro Gly Val Glu Thr Thr Phe Val
            580                 585                 590

Cys Ala Thr Ser Val Lys Ser Ala Glu Gly Ala Glu Glu Leu Ala Ile
        595                 600                 605
```

```
Phe Phe Val Pro Val Ile Asn His Val Ser Val Met Phe Ala Thr Met
    610                 615                 620

Gln Gln Ile Lys Glu Ile Val Ala Arg Lys Met Gly Ile Thr Pro Lys
625                 630                 635                 640

Val Ile Ile Pro Ile Gln Lys Glu Ala Phe Phe Lys Thr Asp Ser Gly
                645                 650                 655

Lys Ile Thr Arg Asn Ala Phe Gln Lys Gln Phe Glu Asn Gly Ala Tyr
            660                 665                 670

Arg Glu Ile Thr Gln Lys Ile Asp Cys His Leu Gln Asn Glu Lys Thr
        675                 680                 685

Leu Ser Gln Trp Phe Tyr Arg Glu Lys Leu Val Glu Ser Lys Leu Gly
    690                 695                 700

Lys Ser Val Ser Ser Gln Lys Glu Thr Tyr Val Phe Phe Arg Gln Gly
705                 710                 715                 720

Lys Ser Phe His His Val Leu Lys Glu Lys Leu Thr Gln His Ser Val
                725                 730                 735

Val Ile Val Asp Val Gly Glu Thr Phe Gly Glu Ile His Pro Asn His
            740                 745                 750

Tyr Gln Ile Asn Pro Lys Asn Lys Met Asp Tyr Val Arg Leu Phe Glu
        755                 760                 765

Glu Leu Ala Lys Arg Asn Val Glu Asp Gln Val Phe His Leu Leu His
    770                 775                 780
```

```
Ala Trp Asn Tyr Cys Asp Thr Val Pro Thr Phe Arg Ser Val Glu Asp
785                 790                 795                 800

Leu Ala Asn Ala Gln Tyr Leu Gly Val Phe Ser Val Met Phe Ala Leu
                805                 810                 815

Gln Ala Ile Met His Ala Lys Leu Pro Leu Arg Arg Val Thr Val Ile
            820                 825                 830

Ala Thr Asn Ser Val Gly Leu Glu Ala Lys Glu Met Asn Tyr Ser Cys
        835                 840                 845

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

Leu Gln Val Lys Tyr Ile Asp Ile Glu Gly Lys Asp Ile Gln Phe Asp
865                 870                 875                 880

Thr Glu Thr Val Trp Lys Glu Leu Gln Gln Gln Glu Thr Ile Pro Val
                885                 890                 895

Val Leu Tyr Arg Asp Glu Lys Arg Tyr Lys Ile Gly Leu Glu Lys Val
            900                 905                 910

Pro Met Leu Glu Gln Lys Glu Lys Asn Ile Pro Phe Gln Gln Gln Gly
        915                 920                 925

Phe Tyr Ile Ile Thr Gly Gly Leu Gly Gly Leu Gly Thr Leu Val Ala
    930                 935                 940

Lys Leu Leu Leu Glu Arg Tyr Ser Ala Asn Val Leu Leu Leu Gly Arg
945                 950                 955                 960
```

Thr Glu Ile Glu Thr Asn Ala Glu Lys Met Arg Leu Leu Asp Ser Leu
965 970 975

Lys Glu Tyr Glu Gln Tyr Gly Gly Thr Val Gln Tyr Lys Met Cys Asn
980 985 990

Val Met Asp Leu Asp Ala Met Arg Lys Val Val His Ser Gln Glu Glu
995 1000 1005

Arg Leu Gln Gln Lys Val Asn Gly Ile Ile His Leu Ala Gly Ile
1010 1015 1020

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

Ala Met Phe Glu Ala Lys Val Tyr Ala Ser Trp Val Leu His Glu
1040 1045 1050

Ile Val Lys Glu Arg Gln Asp Cys Leu Tyr Ile Thr Thr Ser Ser
1055 1060 1065

Ala Arg Thr Leu Leu Pro Gly Met Thr Ile Ser Ala Tyr Cys Ser
1070 1075 1080

Ala Asn Arg Phe Val Glu Asn Phe Ala Tyr Tyr Gln Arg Ser Gln
1085 1090 1095

Asn Val Asn Ser Tyr Cys Phe Ser Trp Ser Phe Trp Asn Glu Ile
1100 1105 1110

Gly Met Gly Thr Asn Leu Leu Ile Lys Asn Ala Leu Ile Ala Lys
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Gly Phe Glu Leu Ile Asp Asp Gln Lys Gly Ile Tyr Ser Leu Leu
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Ala Gly Leu Lys Gly Asn Glu Pro Asn Val Phe Val Gly Ile Asn
1145 1150 1155

His Glu Lys Glu Glu Met Ala His Leu Ile Gly Thr Glu Glu Gln
1160 1165 1170

Glu Thr Glu Glu Leu Thr Ile Tyr Ile Thr Pro Glu Tyr Leu His
1175 1180 1185

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1190 1195 1200

Gly Leu Glu Lys Glu Ile Val Ile Leu Pro Lys Leu Pro Leu Asp
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Glu Tyr Gly Lys Val Asp Gln Thr Arg Leu Ala His Ala Ser Asp
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Ser Arg Phe Gly Lys Lys Gln His Ile Val Pro Arg Asn Asp Ile
1235 1240 1245

Glu Glu Lys Ile Ala Phe Ile Trp Glu Gly Leu Leu Asn Lys Lys
1250 1255 1260

Asp Ile Ser Val Leu Asp His Phe Phe Glu Leu Gly Gly Asp Ser
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Leu Lys Ala Thr Glu Met Ile Ser Ala Leu Lys Lys Asn Phe Ala
1280 1285 1290

Val Thr Ile Thr Gln Gln Glu Phe Phe Gln Ser Ser Thr Val Glu
1295 1300 1305

Glu Leu Ala Ser Leu Val Glu Lys Lys Leu Ser Arg Thr Arg Thr
1310 1315 1320

His Glu Met Asp Ile Val Thr Phe Ser Asp Arg Gly Asn Val Val
1325 1330 1335

Glu Met Ser Ser Ala Gln Lys Arg Gln Trp Phe Leu Tyr Glu Met
1340 1345 1350

Asp Arg Glu Asn Pro Tyr Tyr Asn Asn Thr Leu Val Ile Arg Leu
1355 1360 1365

Thr Gly Glu Ile His Leu Pro Ile Leu Arg Ser Ser Ile Ile Glu
1370 1375 1380

Leu Val Asn Lys His Glu Thr Leu Arg Thr Thr Phe Val Met Val
1385 1390 1395

Asp Gly Ile Pro Ser Gln Ile Ile Ala Asp Glu Glu Leu Val Glu
1400 1405 1410

Ile Glu Glu Ile Asp Leu Lys His Leu Ser Ala Glu Glu Thr Leu
1415 1420 1425

Gln Lys Leu Glu Gly Leu Arg Gln Arg Glu Ala Asn Thr Ala Phe
1430 1435 1440

Lys Ile Glu Asn Ser Ala Phe Arg Ala Lys Val Ile Leu Ile Asp
1445 1450 1455

Glu Lys Arg Val Glu Ile Leu Leu Ser Val His His Ile Val Ser
1460 1465 1470

Asp Gly Trp Ser Met Gly Ile Leu Val Lys Asp Ile Ala Glu Ile
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Tyr Glu Asp Ile Arg Gln Trp Gly Glu Ser Lys Gln Glu Pro Leu
1490 1495 1500

Pro Ile Glu Tyr Ala Asp Tyr Thr Leu Trp Gln Asn Glu Phe Met
1505 1510 1515

Lys Gly Glu Glu Phe Ser Lys Gln Leu Ser Tyr Trp Lys Glu Lys
1520 1525 1530

Leu Ala Glu Asp Ile Pro Val Leu Asp Leu Pro Leu Asp Lys Pro
1535 1540 1545

Arg Pro Pro Ile Gln Thr Tyr Arg Gly Lys Val Lys Thr Phe Thr
1550 1555 1560

Leu His Glu Asn Met Thr Arg Met Leu Lys Glu Ile Cys Gln Glu
1565 1570 1575

Glu Glu Cys Thr Leu Phe Met Leu Leu Leu Ser Ala Phe Ser Ser
1580 1585 1590

Leu Leu His Arg Tyr Thr Gly Gln Glu Asp Leu Val Val Gly Ser
1595 1600 1605

Leu Val Ala Asn Arg Asn Arg Glu Gln Ile Glu Lys Leu Ile Gly
1610 1615 1620

Phe Phe Val Asn Thr Leu Pro Leu Arg Ile Asn Leu His Arg Glu
1625 1630 1635

Met Gln Phe Thr Glu Leu Leu Ser Gln Val Lys Lys Thr Thr Ile
1640 1645 1650

Asp Ala Tyr Asp His Gln Asp Val Pro Phe Glu Leu Leu Val Asp
1655 1660 1665

Glu Leu Gln Ile Glu Arg Asp Ser Ser Arg Asn Ala Leu Phe Gln
1670 1675 1680

Val Leu Phe Val Leu Gln Asn Ala Gln Leu Gln Ala Val Asp Leu
1685 1690 1695

Glu Lys Ala Thr Met Glu Leu Glu Ile Leu Asp Ser Asp Thr Ala
1700 1705 1710

Lys Phe Asp Met Ser Val Gln Ile Phe Glu Leu Glu Asp Thr Leu
1715 1720 1725

Ser Ile Lys Leu Glu Tyr Asn Thr Asp Leu Phe Phe Asp Asp Thr
1730 1735 1740

Ile Glu Arg Phe Leu Ala His Tyr Glu Thr Ile Leu Ala Ser Val
1745 1750 1755

Ile His Asn Gln Lys Ala Lys Ile Gly Glu Leu Ser Ile Leu Pro
1760 1765 1770

Gln Ser Glu Tyr Thr Lys Leu Val Ser Glu Trp Asn Glu Lys Ser
1775 1780 1785

Ala Thr Tyr Asn Gly Asn Gln Cys Ile His Glu Leu Phe Glu Ala
1790 1795 1800

Ala Val His Lys Thr Pro Ser Ala Thr Ala Leu Ile Tyr Arg Asn
1805 1810 1815

Lys Glu Met Thr Tyr Glu Asp Val Asn Ala Gln Ala Asn Ala Leu
1820 1825 1830

Ala His Lys Leu Arg Asp Ala Gly Val Gly Pro Asn Gln Val Val
1835 1840 1845

Gly Val Leu Cys Asp Arg Ser Phe Glu Met Val Val Gly Ile Leu
1850 1855 1860

Ala Val Leu Lys Ala Gly Gly Ala Tyr Leu Pro Ile Asp Thr Ala
1865 1870 1875

Tyr Pro Met Gln Arg Thr Glu Tyr Val Leu Gln Asn Ser Glu Ala
1880 1885 1890

Thr Ile Leu Leu Thr Lys Glu Cys Tyr Leu Lys Glu Ser Leu Asp
1895 1900 1905

Phe Glu Gly Glu Val Phe Tyr Leu Asp Asp Ala Arg Leu Phe Glu
1910 1915 1920

Gly Asp Arg Arg Asp Leu Gln Asn Ile Asn Asn Pro Thr Asn Leu
1925 1930 1935

Ala Tyr Ile Ile Tyr Thr Ser Gly Ser Thr Gly Asn Pro Lys Gly
1940 1945 1950

Val Met Val Ala His Gln Ser Val Val Asn Leu Leu Leu Asp Leu
1955 1960 1965

Gln Glu Lys Tyr Pro Val Leu Ala Glu Asp Lys His Leu Leu Lys
1970 1975 1980

Thr Thr Tyr Thr Phe Asp Val Ser Val Ala Glu Ile Phe Gly Trp
1985 1990 1995

Phe His Ala Gly Gly Thr Leu Val Ile Ala Gly His Gly Asp Glu
2000 2005 2010

Lys Asp Pro Glu Lys Leu Ile Gln Leu Ile Gln Cys His Lys Val
2015 2020 2025

Thr His Ile Asn Phe Val Pro Ser Met Leu His Ala Met Leu Gln
2030 2035 2040

Ala Leu Asp Glu Lys Asp Phe Ala Ile Met Asn Arg Leu Lys Tyr
2045 2050 2055

Ile Ile Val Ala Gly Glu Ala Val Ser Pro Glu Leu Cys Asn Arg
2060 2065 2070

Leu Tyr Ala His Cys Pro Asn Val Lys Leu Glu Asn Leu Tyr Gly
2075 2080 2085

Pro Thr Glu Gly Thr Ile Tyr Ala Thr Gly Phe Ser Ile His Lys
2090 2095 2100

Glu Met Asn Val Ala Asn Val Pro Ile Gly Lys Pro Leu Ser His
2105 2110 2115

Val Glu Thr Tyr Ile Leu Asp Gln Asn Asn Gln Ile Val Pro Ile
2120 2125 2130

Gly Val Pro Gly Glu Leu Cys Leu Gly Gly Ile Cys Val Ala Lys
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Gly Tyr Met Lys Glu Pro Val Leu Thr Glu Glu Lys Phe Val Val
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Asn Pro Met Lys Gln Ser Glu Arg Met Tyr Arg Thr Gly Asp Leu
2165 2170 2175

Val Arg Trp Leu Ala Asp Gly Asn Ile Glu Tyr Leu Gly Arg Ile
2180 2185 2190

Asp Asn Glu Val Lys Ile Arg Gly Phe Arg Ile Glu Leu Gly Glu
2195 2200 2205

Ile Glu Ala Ala Ile Ala Ala Leu Glu Asp Val Val Gln Thr Ile
2210 2215 2220

Val Thr Thr Met Thr Asp His Lys Gly Ala Asn Lys Ile Val Ala
2225 2230 2235

Tyr Val Val Ser Glu Lys Tyr Asp Glu Glu Arg Ile Arg Glu His
2240 2245 2250

Val Lys Lys Thr Leu Pro Gln Tyr Met Val Pro Ser Tyr Phe Val
2255 2260 2265

Ser Met Lys Ala Leu Pro Leu Asn Lys Asn Gly Lys Val Asp Arg
2270 2275 2280

Lys Glu Leu His Ser Val Asp Leu Tyr Glu Thr Ser Met Asp Thr
2285 2290 2295

Val Ile Val Gly Pro Arg Asn Glu Lys Glu Ala Met Leu Ser Val
2300 2305 2310

Ile Trp Gln Glu Leu Leu Gly Leu Glu Asn Ile Ser Val His Asp
2315 2320 2325

Asn Phe Phe Lys Leu Gly Gly His Ser Ile Asn Ala Thr Gln Leu
2330 2335 2340

Val Ser Lys Ile Tyr Ser Val Cys Arg Val Arg Met Pro Leu Lys
2345 2350 2355

Asn Val Phe Glu Tyr Thr Thr Leu Ala Thr Met Ala Arg Val Leu
2360 2365 2370

Glu Glu Leu Leu Val Ser Ala Val Asp Glu Val Ala Val Thr Thr
2375 2380 2385

Glu Arg Ile Pro Lys Ile Leu Pro Arg Thr Tyr Tyr Asp Leu Ser
2390 2395 2400

Tyr Ser Gln Glu Arg Ile Tyr Phe Leu Ser Thr Met Glu Lys Glu
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Thr Asn Tyr Tyr Asn Ile Leu Gly Ala Trp Asp Ile Tyr Gly Lys
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Leu Asp Val Thr Leu Phe Glu Lys Ala Ile Gln Leu Leu Met Lys
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Lys His His Ser Leu Arg Ala Thr Phe Glu Ile Val Asp Gly Lys
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Pro Val Gln Ile Ile His Asp Asp Met Glu Ile Pro Val Gln Phe
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Ile Asp Leu Thr Val Met Pro Glu Gly Leu Arg Ile Glu Glu Val
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Asp Glu Leu Met Leu Lys Glu Ser Lys Arg Val Tyr Asn Leu Ala
2495 2500 2505

Asn Gly Pro Leu Met His Cys Thr Ile Val Lys Ile Lys Glu Gly
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Glu His Val Leu Leu Ile Gly Gln His His Ile Ile Ser Asp Gly
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Trp Ser Leu Gly Ile Phe Val Lys Glu Leu Asn Glu Met Tyr Asp
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Ala Phe Val Gln His Lys Pro Val Ala Glu Thr Pro Ser Thr Ile
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Ser Ile Met Asp Phe Thr Ala Trp His Asn Ser Lys Val Asp Glu
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Asp Gln Asp Asp Arg Gln Tyr Trp Leu Gln Arg Phe Glu Gly Glu
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Leu Pro Thr Leu Glu Leu Pro Thr Asp Arg Gln Arg Pro Leu Leu
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Lys Thr Tyr His Gly Asp Thr Leu Ser Tyr Lys Val Asn Ser Gln
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Leu His Gln Lys Leu Lys Asp Phe Ser His Ala Asn Gly Val Thr
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Met Phe Met Thr Leu Leu Thr Ala Tyr Asn Ile Met Leu Asn Lys
2645 2650 2655

Leu Thr Asn Glu Thr Asp Ile Val Val Gly Ser Pro Val Ala Gly
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Arg Asn Glu Pro Glu Ser Lys Asp Leu Ile Gly Met Phe Val Asn
2675 2680 2685

Thr Leu Ala Leu Arg Ser His Leu Gly Asp Asn Pro Thr Val Asp
2690 2695 2700

Val Leu Leu Lys Gln Ile Lys Gln Asn Thr Leu Glu Ala Tyr Asn
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His Gln Asp Tyr Pro Phe Asp Lys Leu Val Asp Asp Leu Asp Pro
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His Arg Asp Leu Ser Arg Thr Pro Ile Phe Gln Val Met Met Gly
2735 2740 2745

Tyr Met Asn Met Pro Leu Met Val Ala Phe Arg Glu Ala Glu Val
2750 2755 2760

Arg Glu Arg Phe Val Arg His Lys Val Ala Arg Phe Asp Leu Thr
2765 2770 2775

Leu His Val Phe Glu Asp Glu Asp Gln Met Lys Ile Phe Phe Glu
2780 2785 2790

Tyr Asn Thr Asp Leu Phe Asp Glu Ser Thr Ile Met Arg Trp Gln
2795 2800 2805

Asn His Phe Glu Thr Leu Leu Gln Glu Ile Val Ser Asn Pro Thr
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Lys Arg Ile Ser Glu Leu Asn Ile Leu Thr Asn Glu Glu Lys Tyr
2825 2830 2835

Glu Ile Leu Glu Met Asn Asn Asn Ser Thr Glu Tyr Pro Gln His
2840 2845 2850

Glu Ser Val Ala Glu Ile Phe Arg Glu Thr Lys Ile Lys His Gln
2855 2860 2865

Ala Lys Leu Ala Ile Thr Tyr Lys Asp Arg Lys Leu Thr Tyr Ala
2870 2875 2880

Glu Leu Ser Glu Lys Ala Asn Ala Leu Ala His Thr Leu Lys Arg
2885 2890 2895

Arg Gly Val Ala Gln His Asp Val Val Gly Ile Val Ala Glu Arg
2900 2905 2910

Ser Pro Glu Thr Ile Ile Gly Ile Leu Ala Ile Leu Lys Val Gly
2915 2920 2925

Ala Ile Tyr Leu Pro Ile Asp Pro Lys Leu Pro Gln Leu Thr Leu
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Glu His Ile Trp Arg Asp Ser Gly Ala Lys Val Leu Leu Gly Lys
2945 2950 2955

Asn Glu Thr Thr Val Glu Val Gly Lys Glu Val Pro Phe Val Asp
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Ile Glu Gly Asp Lys Gly Lys Gln Glu Glu Leu Val Cys Pro Ile
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Ser Pro Glu Asp Thr Ala Tyr Ile Met Tyr Thr Ser Gly Ser Thr
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Gly Lys Pro Lys Gly Val Met Val Thr His Arg Asn Ile Val Arg
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Leu Val Lys Asn Thr Asn Phe Val Ser Leu Gln Glu Gln Asp Val
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Ile Trp Gly Ala Leu Leu Asn Gly Leu Thr Leu His Leu Val Glu
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Asp Tyr Val Ile Leu Asp Gly Glu Ala Leu Gln Glu Glu Ile Gln
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Gln Asn Lys Ala Thr Ile Met Trp Val Ser Ala Pro Leu Phe Asn
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Gln Leu Ala Asp Gln Asn Pro Ala Met Phe Thr Gly Ile Lys Gln
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Leu Leu Ile Gly Gly Asp Val Leu Ser Pro Lys His Ile Asn Lys
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Val Met Asp His Cys Ala Pro Ile Asn Ile Ile Asn Gly Tyr Gly
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Pro Thr Glu Asn Thr Thr Phe Ser Thr Ser Phe Val Ile Asp Gln
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Met Tyr Gln Asp Ser Ile Pro Ile Gly Thr Pro Ile Ala Asn Ser
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Ser Ala Tyr Ile Leu Asp Val His Gln Asn Ile Gln Pro Ile Gly
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Val Val Gly Glu Leu Cys Val Gly Gly Asp Gly Val Ala Lys Gly
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Tyr Val Asn Leu Glu Gln Leu Thr Glu Glu Arg Phe Ile Ala Asp
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Pro Phe Leu Lys Gly Ser Thr Met Tyr Arg Thr Gly Asp Tyr Val
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Lys Leu Leu Pro Asn Gly Asn Ile Gln Tyr Ile Gly Arg Val Asp
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Asn Glu Val Lys Ile Arg Gly Phe Arg Ile Glu Leu Glu Ala Ile
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Met Asn Thr Leu Lys Gln Cys Glu Ser Ile Lys Asp Val Ile Val
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Val Val Gln Glu Gln Asn Gly Tyr Lys Thr Leu Val Ala Tyr Val
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Val Gly Glu Glu Ser Leu Ser Ile Glu Thr Val Arg Ala Tyr Ala
3290 3295 3300

Lys Lys His Leu Ala Glu Tyr Met Val Pro Ser Gln Phe Ile Phe
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Ile Glu Glu Ile Pro Leu Ser Ile Asn Gly Lys Val Gln Tyr Ser
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Lys Leu Pro Lys Val Gln Glu Val Leu His Lys Lys Val Glu Thr
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Leu Leu Pro Glu Asn Arg Leu Glu Glu Ile Ile Leu Arg Val Tyr
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Arg Asp Val Leu Glu Lys Glu Asp Phe Gly Val Thr Asp Ser Phe
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Phe Ala Tyr Gly Gly Asp Ser Leu Leu Ser Ile Gln Val Val Ser
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Met Leu Lys Lys Glu Glu Ile Ala Val Asp Pro Lys Met Ile Phe
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Met His Thr Thr Val Arg Glu Leu Ala Lys Ala Cys Glu Asn Arg
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Pro Val Met Glu Glu Thr Lys Arg Thr Glu Lys Asp Tyr Leu Ile
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Gln Met Arg Glu Gly Ser Glu Glu Asp Ser Cys Ile Ile Phe Ala
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Pro Pro Ala Gly Gly Thr Val Leu Gly Tyr Ile Glu Leu Ala Arg
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Tyr Phe Glu Gly Ile Gly Asn Val Tyr Gly Leu Gln Ala Pro Gly
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Leu Tyr Asp Asp Glu Glu Pro Thr Phe Leu Asp Tyr Asp Glu Leu
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Val Glu Val Phe Leu Arg Ser Ile Glu Gly Thr Tyr Arg Pro Gly
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Gln Asp Tyr Leu Gly Gly His Ser Leu Gly Gly His Ile Ala Phe
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Gly Met Cys Cys Glu Leu Ile Lys Gln Gly Lys Ala Pro Lys Gly
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Leu Leu Ile Leu Asp Thr Thr Pro Ser Leu Gln Val Val Lys Gly
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Ala Lys Asp Glu Lys Ile Ala Glu Glu Asp Phe Lys Met Met Val
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Leu Ala Ala Gly Ile Gly Asn Met Met Gly Val Asp Pro Glu Glu
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Leu Lys Gln Leu Ser Tyr Glu Glu Ala Lys Thr Arg Val Val Ala
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Val Ala Gln Lys Asp Glu Lys Leu Lys Thr Phe Ile Asn Glu Thr
3605 3610 3615

Tyr Leu Asp Lys Tyr Leu Lys Leu Gln Ile His Ser Leu Leu Met
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Ser Arg Thr Leu Glu Leu Glu Lys Thr Gln Leu Asp Ile Pro Ile
3635 3640 3645

Lys Val Phe Lys Thr Gln Phe His Thr Glu Glu Leu Val Glu Arg
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Phe Asp Ala Trp His Asn Tyr Thr Asn Gln Ala Cys Thr Phe Ile
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Asp Ile Pro Gly Thr His Thr Thr Met Met Arg Leu Pro His Val
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Asn Ile Ala Ile Met Leu Glu Lys His Gly Val His Glu Gln Pro Leu
50 55 60

His Ile Glu Asp Leu Phe His Glu Val Glu Met Gln Glu His Ser Arg
65 70 75 80

Val Ser Arg His Glu Thr Val Leu Met Thr Asp Lys Gln Cys Ile Asp
85 90 95

Glu Ser Gly Lys Pro Leu Ala Leu Arg Phe Gly Glu Pro Leu His Leu
100 105 110

Asp Asp Cys Thr Pro Lys Thr Leu Gln Glu Ile Leu Lys Arg Ala Ala
115 120 125

Lys Glu Ala Lys Asp Lys Gly Met Thr Phe Val Tyr Glu Asp Gly His
130 135 140

Glu Glu Tyr Leu Ser Tyr Gln Glu Met Leu Ala Asp Ala Glu Arg Leu
145 150 155 160

Leu Lys Gly Leu Arg Asn Leu Gly Ile Gln Pro Gly Glu Ser Ile Leu
165 170 175

Phe Gln Phe Lys Asp Asn Lys His Phe Val Thr Ala Phe Trp Ala Cys
180 185 190

Ile Leu Gly Gly Phe Leu Pro Thr Pro Leu Gly Thr Ala Pro Ile Tyr
195 200 205

Ser Glu Gln Asn Ala Gln Val Leu Lys Leu Tyr Asn Thr Trp Gln Leu

210 215 220

Leu Glu Gln Pro Ile Ile Leu Thr Glu Phe Glu Leu Lys Glu Glu Ile
225 230 235 240

Ala Ala Ile Arg Thr Thr Leu Gln Arg Gln Glu Ile Val Ile His Ser
245 250 255

Ile Glu Asn Val Met Asp Thr Ala Arg Asp Thr Asn Trp Phe Pro Cys
260 265 270

Thr Glu Asp Thr Ile Val Leu Asn Leu Leu Thr Ser Gly Ser Thr Gly
275 280 285

Val Pro Lys Cys Val Gln His Lys Ser Lys Ser Ile Ile Ala Arg Thr
290 295 300

Val Ser Asn Cys Ile Asp Arg Gln Leu Asp Glu Lys Glu Val Ser Leu
305 310 315 320

Asn Trp Met Pro Leu Asp His Val Gly Gly Ile Val Met Cys His Ile
325 330 335

Arg Asp Thr Tyr Leu Met Cys Gln Gln Val Asn Cys Leu Ile Ser Ala
340 345 350

Phe Ile Glu Asn Pro Leu Asn Trp Leu His Trp Ile Asp Ala Tyr Ser
355 360 365

Ala Thr Phe Thr Trp Ala Pro Asn Phe Ala Phe Ser Leu Ile Asn Gln
370 375 380

Tyr Glu Glu Glu Ile Lys Ser Ser Ser Trp Asn Leu Ser Ser Met Arg

385 390 395 400

Tyr Ile Val Asn Gly Gly Glu Ala Val Ile Ser Ser Val Gly Met Lys
405 410 415

Phe Leu Gln Leu Leu Gln Gln His Gln Leu Pro Ser Asn Cys Leu Ile
420 425 430

Pro Thr Phe Gly Met Ser Glu Val Ser Ser Gly Ile Ile Glu Cys His
435 440 445

Ser Phe Tyr Thr Gln Thr Thr Asn Thr Gly Met Leu Tyr Val Asp Lys
450 455 460

Asn Ser Leu Asp Gly Asn Leu Gln Phe Thr Tyr Glu Gly His Gln Asn
465 470 475 480

Ala Ile Val Phe Thr Glu Val Gly Arg Pro Met Pro Gly Ile Gly Ile
485 490 495

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

565 570 575

Ile Glu Ala Leu Val Glu Gln Val Pro Gly Val Glu Thr Thr Phe Val
580 585 590

Cys Ala Thr Ser Val Lys Ser Ala Glu Gly Ala Glu Glu Leu Ala Ile
595 600 605

Phe Phe Val Pro Val Ile Asn His Val Ser Val Met Phe Ala Thr Met
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Gln Gln Ile Lys Gln Ile Val Ala Arg Lys Met Gly Ile Thr Pro Lys
625 630 635 640

Val Ile Ile Pro Ile Gln Lys Glu Ala Phe Phe Lys Thr Asp Ser Gly
645 650 655

Lys Ile Thr Arg Asn Ala Phe Gln Lys Gln Phe Glu Asn Gly Ala Tyr
660 665 670

Arg Glu Ile Thr Gln Lys Ile Asp Cys His Leu Gln Asn Glu Lys Thr
675 680 685

Leu Ser Gln Trp Phe Tyr Arg Glu Lys Leu Val Glu Ser Lys Leu Gly
690 695 700

Lys Ser Val Ser Ser Gln Lys Glu Thr Tyr Val Phe Phe Arg Gln Gly
705 710 715 720

Lys Ser Phe His His Val Leu Lys Glu Lys Leu Thr Gln His Ser Val
725 730 735

Val Ile Val Asp Val Gly Glu Thr Phe Gly Glu Ile His Pro Asn His

740 745 750

Tyr Glu Ile Asn Pro Lys Asn Lys Met Asp Tyr Val Arg Leu Phe Glu
755 760 765

Glu Leu Ala Lys Arg Asn Val Glu Asp Gln Val Phe His Leu Leu His
770 775 780

Ala Trp Asn Tyr Cys Asp Thr Val Pro Thr Phe Arg Ser Val Glu Asp
785 790 795 800

Leu Ala Asn Ala Gln Tyr Leu Gly Val Phe Ser Val Met Phe Ala Leu
805 810 815

Gln Ala Ile Met His Ala Lys Leu Pro Leu Arg Arg Val Thr Val Ile
820 825 830

Ala Thr Asn Ser Val Gly Leu Glu Ala Lys Glu Met Asn Tyr Ser Cys
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Ser Thr Leu Glu Gly Tyr Val Lys Thr Leu Pro Ala Glu Phe Glu Asn
850 855 860

Leu Glu Val Lys Tyr Ile Asp Ile Glu Gly Lys Asp Ile Gln Phe Asp
865 870 875 880

Thr Glu Thr Val Trp Lys Glu Leu Gln Gln Gln Glu Thr Ile Pro Val
885 890 895

Val Leu Tyr Arg Asp Glu Lys Arg Tyr Lys Ile Gly Leu Glu Lys Val
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Pro Met Leu Glu Gln Lys Glu Lys Asn Ile Pro Phe Gln Gln Gln Gly

915 920 925

Phe Tyr Ile Ile Thr Gly Gly Leu Gly Gly Leu Gly Thr Leu Val Ala
930 935 940

Lys Leu Leu Leu Glu Arg Tyr Ser Ala Asn Val Leu Leu Leu Gly Arg
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Thr Glu Ile Glu Thr Asn Ala Glu Lys Met Arg Leu Leu Asp Ser Leu
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Lys Glu Tyr Glu Gln Tyr Gly Gly Thr Val Gln Tyr Lys Met Cys Asn
980 985 990

Val Met Asp Leu Asp Ala Met Arg Lys Val Val His Ser Gln Glu Glu
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Arg Leu Gln Gln Lys Val Asn Gly Ile Ile His Leu Ala Gly Ile
1010 1015 1020

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

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Asn Val Asn Ser Tyr Cys Phe Ser Trp Ser Phe Trp Asn Glu Ile
1100 1105 1110

Gly Met Gly Thr Asn Leu Leu Ile Lys Asn Ala Leu Ile Ala Lys
1115 1120 1125

Gly Phe Gln Leu Ile Asp Asp Gln Lys Gly Ile Tyr Ser Leu Leu
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Ala Gly Leu Lys Gly Asn Glu Pro Asn Val Phe Val Gly Ile Asn
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His Glu Lys Glu Glu Met Ala His Leu Ile Gly Thr Glu Glu Gln
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Glu Thr Gln Gln Leu Thr Ile Tyr Ile Thr Pro Glu Tyr Leu His
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Ile Leu Glu Glu Val Phe Ser Ile Leu Asn Arg Glu Glu Phe Gly
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Gly Leu Glu Lys Glu Ile Val Ile Leu Pro Lys Leu Pro Leu Asp
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Glu Tyr Gly Lys Val Asp Gln Thr Arg Leu Ala His Ala Ser Asp
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Ser Arg Phe Gly Lys Lys Gln His Ile Val Pro Arg Asn Asp Ile
1235 1240 1245

Glu Gln Lys Ile Ala Phe Ile Trp Glu Gly Leu Leu Asn Lys Lys

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Asp Ile Ser Val Leu Asp His Phe Phe Glu Leu Gly Gly Asp Ser
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Leu Lys Ala Thr Gln Met Ile Ser Ala Leu Lys Lys Asn Phe Ala
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Val Thr Ile Thr Gln Gln Glu Phe Phe Gln Ser Ser Thr Val Glu
1295 1300 1305

Glu Leu Ala Ser Leu Val Glu Lys Lys Leu Ser Arg Thr Arg Thr
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His Glu Met Asp Ile Val Thr Phe Ser Asp Arg Gly Asn Val Val
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Glu Met Ser Ser Ala Gln Lys Arg Gln Trp Phe Leu Tyr Glu Met
1340 1345 1350

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

1415 1420 1425

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

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Leu Leu His Arg Tyr Thr Gly Gln Glu Asp Leu Val Val Gly Ser
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Leu Val Ala Asn Arg Asn Arg Glu Gln Ile Glu Lys Leu Ile Gly
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Phe Phe Val Asn Thr Leu Pro Leu Arg Ile Asn Leu His Arg Glu
1625 1630 1635

Met Gln Phe Thr Glu Leu Leu Ser Gln Val Lys Lys Thr Thr Ile
1640 1645 1650

Asp Ala Tyr Asp His Gln Asp Val Pro Phe Glu Leu Leu Val Asp
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Glu Leu Glu Ile Glu Arg Asp Ser Ser Arg Asn Ala Leu Phe Gln
1670 1675 1680

Val Leu Phe Val Leu Gln Asn Ala Gln Leu Gln Ala Val Asp Leu
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Glu Lys Ala Thr Met Glu Leu Glu Ile Leu Asp Ser Asp Thr Ala
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Lys Phe Asp Met Ser Val Gln Ile Phe Glu Leu Glu Asp Thr Leu
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Ser Ile Lys Leu Glu Tyr Asn Thr Asp Leu Phe Phe Asp Asp Thr
1730 1735 1740

Ile Glu Arg Phe Leu Ala His Tyr Glu Thr Ile Leu Ala Ser Val

1745 1750 1755

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

Asn Asn Pro Thr Asn Leu Ala Tyr Ile Ile Tyr Thr Ser Gly Ser Thr
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Gly Asn Pro Lys Gly Val Met Val Ala His Gln Ser Val Val Asn Leu
145 150 155 160

Leu Leu Asp Leu Gln Glu Lys Tyr Pro Val Leu Ala Glu Asp Lys His
165 170 175

Leu Leu Lys Thr Thr Tyr Thr Phe Asp Val Ser Val Ala Glu Ile Phe
180 185 190

Gly Trp Phe His Ala Gly Gly Thr Leu Val Ile Ala Gly His Gly Asp
195 200 205

Glu Lys Asp Pro Glu Lys Leu Ile Gln Leu Ile Gln Cys His Lys Val
210 215 220

Thr His Ile Asn Phe Val Pro Ser Met Leu His Ala Met Leu Gln Ala
225 230 235 240

Leu Asp Glu Lys Asp Phe Ala Ile Met Asn Arg Leu Lys Tyr Ile Ile
245 250 255

Val Ala Gly Glu Ala Val Ser Pro Glu Leu Cys Asn Arg Leu Tyr Ala
260 265 270

His Cys Pro Asn Val Lys Leu Glu Asn Leu Tyr Gly Pro Thr Glu Gly
275 280 285

Thr Ile Tyr Ala Thr Gly Phe Ser Ile His Lys Glu Met Asn Val Ala
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Asn Val Pro Ile Gly Lys Pro Leu Ser His Val Glu Thr Tyr Ile Leu
305 310 315 320

Asp Glu Asn Asn Gln Ile Val Pro Ile Gly Val Pro Gly Glu Leu Cys
325 330 335

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

Tyr Leu Gly Arg Ile Asp Asn Gln Val Lys Ile Arg Gly Phe Arg Ile
385 390 395 400

Glu Leu Gly Glu Ile Glu Ala Ala Ile Ala Ala Leu Glu Asp Val Val
405 410 415

Gln Thr Ile Val Thr Thr Met Thr Asp His Lys Gly Ala Asn Lys Ile
420 425 430

Val Ala Tyr Val Val Ser Glu Lys Tyr Asp Glu Glu Arg Ile Arg Glu
435 440 445

His Val Lys Lys Thr Leu Pro Gln Tyr Met Val Pro Ser Tyr Phe Val
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Ser Met Lys Ala Leu Pro Leu Asn Lys Asn Gly Lys Val Asp Arg Lys
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Gln Leu His Ser Val Asp Leu Tyr Glu Thr Ser Met Asp Thr Val Ile
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Val Gly Pro Arg Asn Glu Lys Glu Ala Met Leu Ser Val Ile Trp Gln
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Glu Leu Leu Gly Leu Glu Asn Ile Ser Val His Asp Asn Phe Phe Lys
515 520 525

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

Thr Leu Ala Thr Met Ala Arg Val Leu Glu Glu Leu Leu Val Ser Ala
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Val Asp Glu Val Ala Val Thr Thr Glu Arg Ile Pro Lys Ile Leu Pro
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Arg Thr Tyr Tyr Asp Leu Ser Tyr Ser Gln Gln Arg Ile Tyr Phe Leu
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Ser Thr Met Glu Lys Glu Thr Asn Tyr Tyr Asn Ile Leu Gly Ala Trp
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Asp Ile Tyr Gly Lys Leu Asp Val Thr Leu Phe Glu Lys Ala Ile Gln
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Leu Leu Met Lys Lys His His Ser Leu Arg Ala Thr Phe Glu Ile Val
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Asp Gly Lys Pro Val Gln Ile Ile His Asp Asp Met Glu Ile Pro Val
660 665 670

Gln Phe Ile Asp Leu Thr Val Met Pro Glu Gly Leu Arg Ile Glu Glu
675 680 685

Val Asp Glu Leu Met Leu Lys Glu Ser Lys Arg Val Tyr Asn Leu Ala
690 695 700

Asn Gly Pro Leu Met His Cys Thr Ile Val Lys Ile Lys Glu Gly Glu
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His Val Leu Leu Ile Gly Gln His His Ile Ile Ser Asp Gly Trp Ser
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Leu Gly Ile Phe Val Lys Glu Leu Asn Glu Met Tyr Asp Ala Phe Val
740 745 750

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

Phe Thr Ala Trp His Asn Ser Lys Val Asp Glu Asp Gln Asp Asp Arg
770 775 780

Gln Tyr Trp Leu Gln Arg Phe Glu Gly Glu Leu Pro Thr Leu Glu Leu
785 790 795 800

Pro Thr Asp Arg Gln Arg Pro Leu Leu Lys Thr Tyr His Gly Asp Thr
805 810 815

Leu Ser Tyr Lys Val Asn Ser Gln Leu His Gln Lys Leu Lys Asp Phe
820 825 830

Ser His Ala Asn Gly Val Thr Met Phe Met Thr Leu Leu Thr Ala Tyr
835 840 845

Asn Ile Met Leu Asn Lys Leu Thr Asn Glu Thr Asp Ile Val Val Gly
850 855 860

Ser Pro Val Ala Gly Arg Asn Glu Pro Glu Ser Lys Asp Leu Ile Gly
865 870 875 880

Met Phe Val Asn Thr Leu Ala Leu Arg Ser His Leu Gly Asp Asn Pro
885 890 895

Thr Val Asp Val Leu Leu Lys Gln Ile Lys Gln Asn Thr Leu Glu Ala
900 905 910

Tyr Asn His Glu Asp Tyr Pro Phe Asp Lys Leu Val Asp Asp Leu Asp
915 920 925

Pro His Arg Asp Leu Ser Arg Thr Pro Ile Phe Gln Val Met Met Gly
930 935 940

Tyr Met Asn Met Pro Leu Met Val Ala Phe Arg Glu Ala Glu Val Arg
945 950 955 960

Glu Arg Phe Val Arg His Lys Val Ala Arg Phe Asp Leu Thr Leu His
965 970 975

Val Phe Glu Asp Glu Asp Gln Met Lys Ile Phe Phe Glu Tyr Asn Thr
980 985 990

Asp Leu Phe Asp Glu Ser Thr Ile Met Arg Trp Gln Asn His Phe Glu
995 1000 1005

Thr Leu Leu Gln Glu Ile Val Ser Asn Pro Thr Lys Arg Ile Ser
1010 1015 1020

Glu Leu Asn Ile Leu Thr Asn Glu Glu Lys Tyr Glu Ile Leu Glu
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Met Asn Asn Asn Ser Thr Glu Tyr Pro Gln His Glu Ser Val Ala
1040 1045 1050

Glu Ile Phe Arg Glu Thr Lys Ile Lys His Gln Ala Lys Leu Ala
1055 1060 1065

Ile Thr Tyr Lys Asp Arg Lys Leu Thr Tyr Ala Glu Leu Ser Glu
1070 1075 1080

Lys Ala Asn Ala Leu Ala His Thr Leu Lys Arg Arg Gly Val Ala
1085 1090 1095

Glu His Asp Val Val Gly Ile Val Ala Glu Arg Ser Pro Glu Thr
1100 1105 1110

Ile Ile Gly Ile Leu Ala Ile Leu Lys Val Gly Ala Ile Tyr Leu
1115 1120 1125

Pro Ile Asp Pro Lys Leu Pro Gln Leu Thr Leu Gln His Ile Trp
1130 1135 1140

Arg Asp Ser Gly Ala Lys Val Leu Leu Gly Lys Asn Glu Thr Thr
1145 1150 1155

Val Glu Val Gly Lys Glu Val Pro Phe Val Asp Ile Glu Gly Asp
1160 1165 1170

Lys Gly Lys Gln Glu Glu Leu Val Cys Pro Ile Ser Pro Glu Asp
1175 1180 1185

Thr Ala Tyr Ile Met Tyr Thr Ser Gly Ser Thr Gly Lys Pro Lys
1190 1195 1200

Gly Val Met Val Thr His Arg Asn Ile Val Arg Leu Val Lys Asn
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Thr Asn Phe Val Ser Leu Gln Glu Gln Asp Val Leu Leu Gln Thr
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Gly Ser Leu Thr Phe Asp Ala Ala Thr Phe Glu Ile Trp Gly Ala
1235 1240 1245

Leu Leu Asn Gly Leu Thr Leu His Leu Val Glu Asp Tyr Val Ile
1250 1255 1260

Leu Asp Gly Glu Ala Leu Gln Glu Glu Ile Gln Gln Asn Lys Ala
1265 1270 1275

Thr Ile Met Trp Val Ser Ala Pro Leu Phe Asn Gln Leu Ala Asp
1280 1285 1290

Glu Asn Pro Ala Met Phe Thr Gly Ile Lys Gln Leu Leu Ile Gly
1295 1300 1305

Gly Asp Val Leu Ser Pro Lys His Ile Asn Lys Val Met Asp His
1310 1315 1320

Cys Ala Pro Ile Asn Ile Ile Asn Gly Tyr Gly Pro Thr Glu Asn
1325 1330 1335

Thr Thr Phe Ser Thr Ser Phe Val Ile Asp Gln Met Tyr Gln Asp
1340 1345 1350

Ser Ile Pro Ile Gly Thr Pro Ile Ala Asn Ser Ser Ala Tyr Ile
1355 1360 1365

Leu Asp Val His Gln Asn Ile Gln Pro Ile Gly Val Val Gly Glu
1370 1375 1380

Leu Cys Val Gly Gly Asp Gly Val Ala Lys Gly Tyr Val Asn Leu
1385 1390 1395

Glu Glu Leu Thr Glu Glu Arg Phe Ile Ala Asp Pro Phe Leu Lys
1400 1405 1410

Gly Ser Thr Met Tyr Arg Thr Gly Asp Tyr Val Lys Leu Leu Pro
1415 1420 1425

Asn Gly Asn Ile Gln Tyr Ile Gly Arg Val Asp Asn Gln Val Lys
1430 1435 1440

Ile Arg Gly Phe Arg Ile Glu Leu Glu Ala Ile Met Asn Thr Leu
1445 1450 1455

Lys Gln Cys Glu Ser Ile Lys Asp Val Ile Val Val Val Gln Glu
1460 1465 1470

Gln Asn Gly Tyr Lys Thr Leu Val Ala Tyr Val Val Gly Glu Glu
1475 1480 1485

Ser Leu Ser Ile Glu Thr Val Arg Ala Tyr Ala Lys Lys His Leu
1490 1495 1500

Ala Glu Tyr Met Val Pro Ser Gln Phe Ile Phe Ile Glu Glu Ile
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Pro Leu Ser Ile Asn Gly Lys Val Gln Tyr Ser Lys Leu Pro Lys
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Val Gln Glu Val Leu His Lys Lys Val Glu Thr Leu Leu Pro Glu
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Asn Arg Leu Glu Glu Ile Ile Leu Arg Val Tyr Arg Asp Val Leu
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Glu Lys Glu Asp Phe Gly Val Thr Asp Ser Phe Phe Ala Tyr Gly
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Gly Asp Ser Leu Leu Ser Ile Gln Val Val Ser Met Leu Lys Lys
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Glu Glu Ile Ala Val Asp Pro Lys Met Ile Phe Met His Thr Thr
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Val Arg Glu Leu Ala Lys Ala Cys Glu Asn Arg Pro Val Met Glu
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Glu Thr Lys Arg Thr Glu Lys Asp Tyr Leu Ile Gln Met Arg Glu
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Gly Ser Glu Glu Asp Ser Cys Ile Ile Phe Ala Pro Pro Ala Gly
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Gly Thr Val Leu Gly Tyr Ile Glu Leu Ala Arg Tyr Phe Glu Gly
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Ile Gly Asn Val Tyr Gly Leu Gln Ala Pro Gly Leu Tyr Asp Asp
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Glu Glu Pro Thr Phe Leu Asp Tyr Asp Glu Leu Val Gln Val Phe
1685 1690 1695

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

Lys Ile Ala Glu Glu Asp Phe Lys Met Met Val Leu Ala Ala Gly
1760 1765 1770

Ile Gly Asn Met Met Gly Val Asp Pro Glu Glu Leu Lys Gln Leu
1775 1780 1785

Ser Tyr Glu Glu Ala Lys Thr Arg Val Val Ala Val Ala Gln Lys
1790 1795 1800

Asp Glu Lys Leu Lys Thr Phe Ile Asn Glu Thr Tyr Leu Asp Lys
1805 1810 1815

Tyr Leu Lys Leu Gln Ile His Ser Leu Leu Met Ser Arg Thr Leu
1820 1825 1830

Glu Leu Glu Lys Thr Gln Leu Asp Ile Pro Ile Lys Val Phe Lys
1835 1840 1845

Thr Glu Phe His Thr Glu Glu Leu Val Glu Arg Phe Asp Ala Trp
1850 1855 1860

His Asn Tyr Thr Asn Gln Ala Cys Thr Phe Ile Asp Ile Pro Gly
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35 40 45

Asp Arg Ser Phe Glu Met Val Val Gly Ile Leu Ala Val Leu Lys Ala
50 55 60

Gly Gly Ala Tyr Leu Pro Ile Asp Thr Ala Tyr Pro Met Gln Arg Thr
65 70 75 80

Glu Tyr Val Leu Gln Asn Ser Glu Ala Thr Ile Leu Leu Thr Lys Glu
85 90 95

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

Asn Asn Pro Thr Asn Leu Ala Tyr Ile Ile Tyr Thr Ser Gly Ser Thr
130 135 140

Gly Asn Pro Lys Gly Val Met Val Ala His Gln Ser Val Val Asn Leu
145 150 155 160

Leu Leu Asp Leu Gln Glu Lys Tyr Pro Val Leu Ala Glu Asp Lys His
165 170 175

Leu Leu Lys Thr Thr Tyr Thr Phe Asp Val Ser Val Ala Glu Ile Phe
180 185 190

Gly Trp Phe His Ala Gly Gly Thr Leu Val Ile Ala Gly His Gly Asp
195 200 205

Glu Lys Asp Pro Glu Lys Leu Ile Gln Leu Ile Gln Cys His Lys Val
210 215 220

Thr His Ile Asn Phe Val Pro Ser Met Leu His Ala Met Leu Gln Ala
225 230 235 240

Leu Asp Glu Lys Asp Phe Ala Ile Met Asn Arg Leu Lys Tyr Ile Ile
245 250 255

Val Ala Gly Glu Ala Val Ser Pro Glu Leu Cys Asn Arg Leu Tyr Ala
260 265 270

His Cys Pro Asn Val Lys Leu Glu Asn Leu Tyr Gly Pro Thr Glu Gly
275 280 285

Thr Ile Tyr Ala Thr Gly Phe Ser Ile His Lys Glu Met Asn Val Ala
290 295 300

Asn Val Pro Ile Gly Lys Pro Leu Ser His Val Glu Thr Tyr Ile Leu
305 310 315 320

Asp Gln Asn Asn Gln Ile Val Pro Ile Gly Val Pro Gly Glu Leu Cys
325 330 335

Leu Gly Gly Ile Cys Val Ala Lys Gly Tyr Met Lys Glu Pro Val Leu
340 345 350

Thr Glu Glu Lys Phe Val Val Asn Pro Met Lys Gln Ser Glu Arg Met
355 360 365

Tyr Arg Thr Gly Asp Leu Val Arg Trp Leu Ala Asp Gly Asn Ile Glu
370 375 380

Tyr Leu Gly Arg Ile Asp Asn Gln Val Lys Ile Arg Gly Phe Arg Ile
385 390 395 400

Glu Leu Gly Glu Ile Glu Ala Ala Ile Ala Ala Leu Glu Asp Val Val
405 410 415

Gln Thr Ile Val Thr Thr Met Thr Asp His Lys Gly Ala Asn Lys Ile
420 425 430

Val Ala Tyr Val Val Ser Glu Lys Tyr Asp Glu Glu Arg Ile Arg Glu
435 440 445

His Val Lys Lys Thr Leu Pro Gln Tyr Met Val Pro Ser Tyr Phe Val
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Ser Met Lys Ala Leu Pro Leu Asn Lys Asn Gly Lys Val Asp Arg Lys
465 470 475 480

Gln Leu His Ser Val Asp Leu Tyr Glu Thr Ser Met Asp Thr Val Ile
485 490 495

Val Gly Pro Arg Asn Glu Lys Glu Ala Met Leu Ser Val Ile Trp Gln
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Glu Leu Leu Gly Leu Glu Asn Ile Ser Val His Asp Asn Phe Phe Lys
515 520 525

Leu Gly Gly His Ser Ile Asn Ala Thr Gln Leu Val Ser Lys Ile Tyr
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Ser Val Cys Arg Val Arg Met Pro Leu Lys Asn Val Phe Gln Tyr Thr
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Thr Leu Ala Thr Met Ala Arg Val Leu Glu Glu Leu Leu Val Ser Ala
565 570 575

Val Asp Glu Val Ala Val Thr Thr Glu Arg Ile Pro Lys Ile Leu Pro
580 585 590

Arg Thr Tyr Tyr Asp Leu Ser Tyr Ser Gln Gln Arg Ile Tyr Phe Leu
595 600 605

Ser Thr Met Glu Lys Glu Thr Asn Tyr Tyr Asn Ile Leu Gly Ala Trp
610 615 620

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

Leu Leu Met Lys Lys His His Ser Leu Arg Ala Thr Phe Glu Ile Val
645 650 655

Asp Gly Lys Pro Val Gln Ile Ile His Asp Asp Met Glu Ile Pro Val
660 665 670

Glu Phe Ile Asp Leu Thr Val Met Pro Glu Gly Leu Arg Ile Glu Glu
675 680 685

Val Asp Glu Leu Met Leu Lys Glu Ser Lys Arg Val Tyr Asn Leu Ala
690 695 700

Asn Gly Pro Leu Met His Cys Thr Ile Val Lys Ile Lys Glu Gly Glu
705 710 715 720

His Val Leu Leu Ile Gly Gln His His Ile Ile Ser Asp Gly Trp Ser
725 730 735

Leu Gly Ile Phe Val Lys Glu Leu Asn Glu Met Tyr Asp Ala Phe Val
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Gln His Lys Pro Val Ala Glu Thr Pro Ser Thr Ile Ser Ile Met Asp
755 760 765

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

Thr Val Asp Val Leu Leu Lys Gln Ile Lys Gln Asn Thr Leu Glu Ala
900 905 910

Tyr Asn His Gln Asp Tyr Pro Phe Asp Lys Leu Val Asp Asp Leu Asp
915 920 925

Pro His Arg Asp Leu Ser Arg Thr Pro Ile Phe Gln Val Met Met Gly
930 935 940

Tyr Met Asn Met Pro Leu Met Val Ala Phe Arg Glu Ala Glu Val Arg
945 950 955 960

Glu Arg Phe Val Arg His Lys Val Ala Arg Phe Asp Leu Thr Leu His
965 970 975

Val Phe Glu Asp Glu Asp Gln Met Lys Ile Phe Phe Glu Tyr Asn Thr
980 985 990

Asp Leu Phe Asp Glu Ser Thr Ile Met Arg Trp Gln Asn His Phe Glu
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Thr Leu Leu Glu Glu Ile Val Ser Asn Pro Thr Lys
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35 40 45

Ile Thr Tyr Lys Asp Arg Lys Leu Thr Tyr Ala Glu Leu Ser Glu Lys
50 55 60

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

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

Ile Leu Ala Ile Leu Lys Val Gly Ala Ile Tyr Leu Pro Ile Asp Pro
100 105 110

Lys Leu Pro Gln Leu Thr Leu Gln His Ile Trp Arg Asp Ser Gly Ala
115 120 125

Lys Val Leu Leu Gly Lys Asn Glu Thr Thr Val Glu Val Gly Lys Glu
130 135 140

Val Pro Phe Val Asp Ile Glu Gly Asp Lys Gly Lys Gln Glu Glu Leu
145 150 155 160

Val Cys Pro Ile Ser Pro Glu Asp Thr Ala Tyr Ile Met Tyr Thr Ser
165 170 175

Gly Ser Thr Gly Lys Pro Lys Gly Val Met Val Thr His Arg Asn Ile
180 185 190

Val Arg Leu Val Lys Asn Thr Asn Phe Val Ser Leu Gln Glu Gln Asp
195 200 205

Val Leu Leu Gln Thr Gly Ser Leu Thr Phe Asp Ala Ala Thr Phe Glu
210 215 220

Ile Trp Gly Ala Leu Leu Asn Gly Leu Thr Leu His Leu Val Glu Asp
225 230 235 240

Tyr Val Ile Leu Asp Gly Glu Ala Leu Gln Glu Glu Ile Gln Gln Asn
245 250 255

Lys Ala Thr Ile Met Trp Val Ser Ala Pro Leu Phe Asn Gln Leu Ala
260 265 270

Asp Glu Asn Pro Ala Met Phe Thr Gly Ile Lys Gln Leu Leu Ile Gly
275 280 285

Gly Asp Val Leu Ser Pro Lys His Ile Asn Lys Val Met Asp His Cys
290 295 300

Ala Pro Ile Asn Ile Ile Asn Gly Tyr Gly Pro Thr Glu Asn Thr Thr
305 310 315 320

Phe Ser Thr Ser Phe Val Ile Asp Gln Met Tyr Gln Asp Ser Ile Pro
325 330 335

Ile Gly Thr Pro Ile Ala Asn Ser Ser Ala Tyr Ile Leu Asp Val His
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Gln Asn Ile Gln Pro Ile Gly Val Val Gly Glu Leu Cys Val Gly Gly
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Asp Gly Val Ala Lys Gly Tyr Val Asn Leu Glu Gln Leu Thr Glu Glu
370 375 380

Arg Phe Ile Ala Asp Pro Phe Leu Lys Gly Ser Thr Met Tyr Arg Thr
385 390 395 400

Gly Asp Tyr Val Lys Leu Leu Pro Asn Gly Asn Ile Gln Tyr Ile Gly
405 410 415

Arg Val Asp Asn Gln Val Lys Ile Arg Gly Phe Arg Ile Glu Leu Glu
420 425 430

Ala Ile Met Asn Thr Leu Lys Gln Cys Glu Ser Ile Lys Asp Val Ile
435 440 445

Val Val Val Gln Glu Gln Asn Gly Tyr Lys Thr Leu Val Ala Tyr Val
450 455 460

Val Gly Glu Glu Ser Leu Ser Ile Glu Thr Val Arg Ala Tyr Ala Lys
465 470 475 480

Lys His Leu Ala Glu Tyr Met Val Pro Ser Gln Phe Ile Phe Ile Glu
485 490 495

Glu Ile Pro Leu Ser Ile Asn Gly Lys Val Gln Tyr Ser Lys Leu Pro
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Lys Val Glu Glu Val Leu His Lys Lys Val Glu Thr Leu Leu Pro Glu
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Asn Arg Leu Glu Glu Ile Ile Leu Arg Val Tyr Arg Asp Val Leu Glu
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Lys Glu Asp Phe Gly Val Thr Asp Ser Phe Phe Ala Tyr Gly Gly Asp
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Ser Leu Leu Ser Ile Gln Val Val Ser Met Leu Lys Lys Glu Glu Ile
565 570 575

Ala Val Asp Pro Lys Met Ile Phe Met His Thr Thr Val Arg Glu Leu
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Ala Lys Ala Cys Glu Asn Arg Pro Val Met Glu Glu Thr Lys Arg Thr
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Glu Lys Asp Tyr Leu Ile Gln Met Arg Glu Gly Ser Glu Glu Asp Ser
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Cys Ile Ile Phe Ala Pro Pro Ala Gly Gly Thr Val Leu Gly Tyr Ile
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Glu Leu Ala Arg Tyr Phe Glu Gly Ile Gly Asn Val Tyr Gly Leu Gln
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Ala Pro Gly Leu Tyr Asp Asp Glu Glu Pro Thr Phe Leu Asp Tyr Asp
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Glu Leu Val Gln Val Phe Leu Arg Ser Ile Glu Gly Thr Tyr Arg Pro
675 680 685

Gly Gln Asp Tyr Leu Gly Gly His Ser Leu Gly Gly His Ile Ala Phe
690 695 700

Gly Met Cys Cys Glu Leu Ile Lys Gln Gly Lys Ala Pro Lys Gly Leu
705 710 715 720

Leu Ile Leu Asp Thr Thr Pro Ser Leu Gln Val Val Lys Gly Ala Lys
725 730 735

Asp Glu Lys Ile Ala Glu Glu Asp Phe Lys Met Met Val Leu Ala Ala
740 745 750

Gly Ile Gly Asn Met Met Gly Val Asp Pro Glu Glu Leu Lys Gln Leu
755 760 765

Ser Tyr Glu Glu Ala Lys Thr Arg Val Val Ala Val Ala Gln Lys Asp
770 775 780

Glu Lys Leu Lys Thr Phe Ile Asn Glu Thr Tyr Leu Asp Lys Tyr Leu
785 790 795 800

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

Lys Thr Glu Leu Asp Ile Pro Ile Lys Val Phe Lys Thr Gln Phe His
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Thr Glu Glu Leu Val Glu Arg Phe Asp Ala Trp His Asn Tyr Thr Asn
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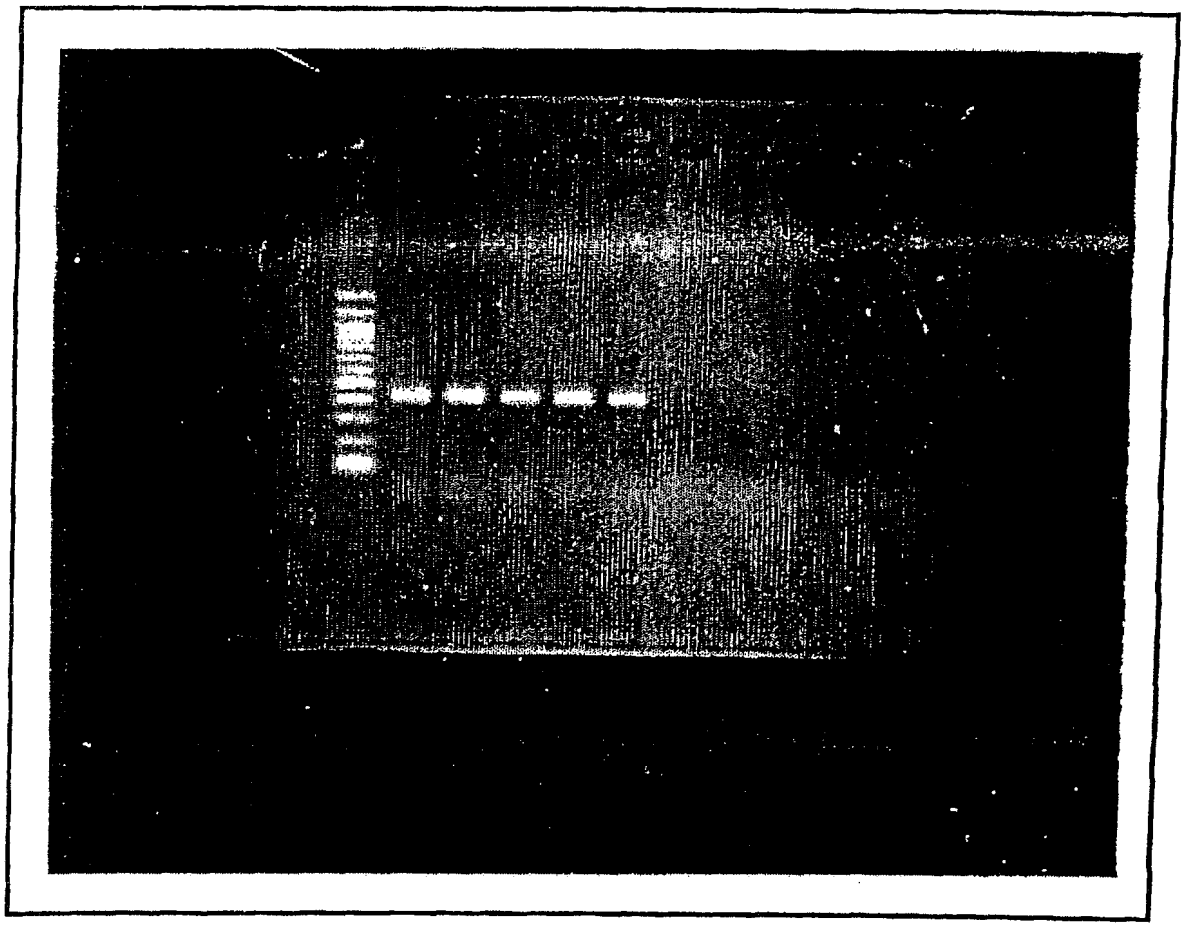

图 1

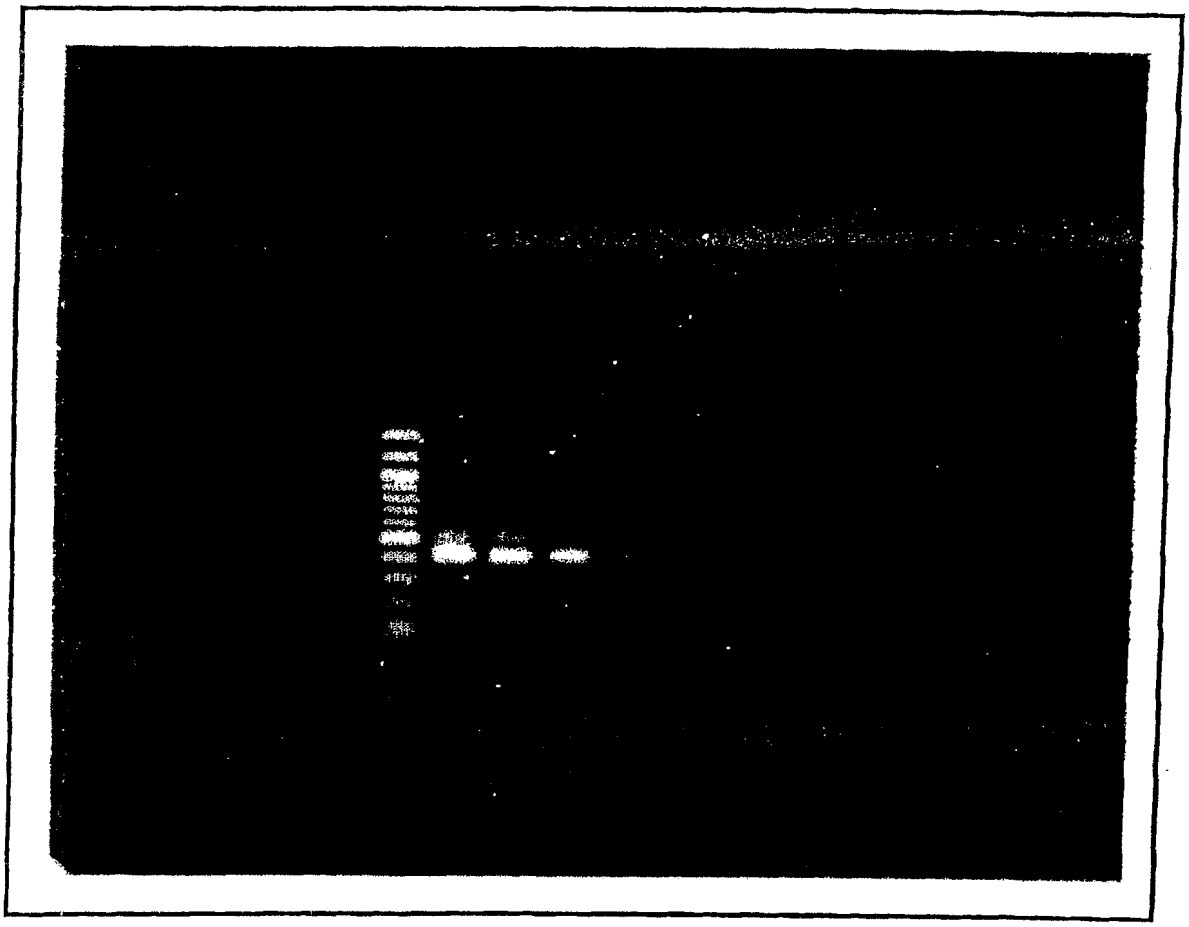

图 2

专利名称(译)	蜡状芽孢杆菌产生的呕吐毒素的合成酶、编码该酶的基因以及呕吐毒素的检测方法		
公开(公告)号	CN100359005C	公开(公告)日	2008-01-02
申请号	CN03811266.3	申请日	2003-05-16
[标]发明人	太田美智男 安形则雄		
发明人	太田美智男 安形则雄		
IPC分类号	C12N9/00 C12N15/09 C07K16/40 C12N5/10 C12N1/15 C12N1/19 C12N1/21 C12Q1/68 G01N33/53 G01N33/566 G01N33/569 C07K14/32		
CPC分类号	C07K16/40 C07K14/32 C12N9/00 C12N15/52 G01N33/53 G01N33/5302		
代理人(译)	曹雯 王景朝		
审查员(译)	马秋娟		
优先权	2002142398 2002-05-17 JP		
其他公开文献	CN1653173A		
外部链接	Espacenet SIPO		

摘要(译)

提供蜡状芽孢杆菌(Bacillus cereus)产生的呕吐毒素(催吐素)的简便而且迅速的检测法。以检体中的催吐素合成酶的存在作为指标，对催吐素进行检测。通过检测编码催吐素的核酸、或通过使用对该酶特异的抗体的免疫学方法进行催吐素合成酶的存在的检测。

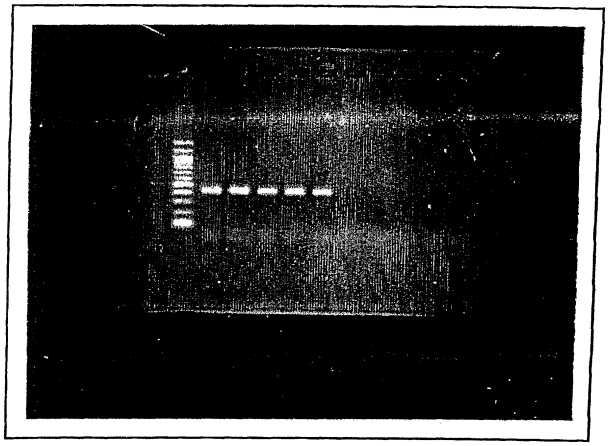

图 1