(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 March 2006 (16.03.2006)

PCT

(10) International Publication Number
WO 2006/028298 A2

(51) International Patent Classification:
C12N 9/02 (2006.01) *C12P 13/14* (2006.01)
C12P 13/08 (2006.01)

(21) International Application Number: PCT/JP2005/017098

(22) International Filing Date: 9 September 2005 (09.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2004-264458 10 September 2004 (10.09.2004) JP

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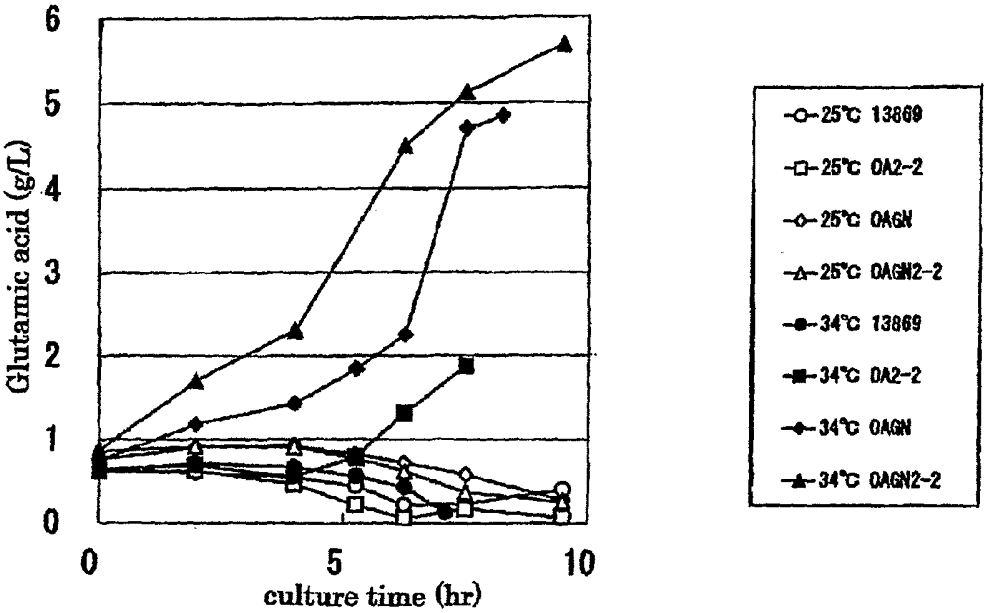
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

[Continued on next page]

(54) Title: L-GLUTAMIC ACID-PRODUCING MICROORGANISM AND A METHOD FOR PRODUCING L-GLUTAMIC ACID



(57) Abstract: A coryneform bacterium which has an L-glutamic acid-producing ability and grows at least at the same growth rate as a non-mutated strain or a wild-type strain and has intracellular α-ketoglutarate dehydrogenase activity which is less than half that of the non-mutated or wild-type strain, and is obtained by introducing a mutation into a coding region or an expression control region of the chromosomal odhA gene encoding the E1o subunit of the α-ketoglutarate dehydrogenase complex.

WO 2006/028298 A2

FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

DESCRIPTION

L-GLUTAMIC ACID-PRODUCING MICROORGANISM AND A METHOD FOR PRODUCING L-GLUTAMIC ACID

Field of the Invention

The present invention relates to an L-glutamic acid-producing microorganism and a method for producing L-glutamic acid using the microorganism. L-glutamic acid is widely used in food industry, for example, as a raw material for production of seasonings.

Brief Description of the Related Art

L-glutamic acid has been conventionally produced on an industrial scale by fermentative methods using L-glutamic acid-producing coryneform bacteria such as those belonging to the genus *Brevibacterium* and *Corynebacterium*. To improve the L-glutamic acid-producing ability of the coryneform bacteria, strains isolated from nature or artificial mutants of such strains are used as the L-glutamic acid-producing coryneform bacteria.

Various technologies for improving the L-glutamic acid-producing ability by enhancing L-glutamic acid biosynthetic enzyme activity using recombinant DNA techniques have been reported. For example, coryneform bacteria with an amplified citrate synthase gene (JP07-121228B), and coryneform bacteria with an amplified glutamate dehydrogenase gene (EP 955368) have been reported.

In the production of substances by fermentation, it is necessary to maintain sufficient growth of bacterial cells to sufficiently produce a target substance. Accordingly, it is necessary to breed a strain with enhanced biosynthesis of a target substance without causing a decrease in bacterial growth. In the production of L-glutamic acid, it has been reported that it is advantageous to decrease α-ketoglutarate dehydrogenase activity (JP06-237779A, and WO95/34672). However, there have been no reports of decreasing the α-ketoglutarate dehydrogenase activity while maintaining a sufficient level of L-glutamic acid production.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a technology to improve the L-glutamic acid-producing ability of coryneform bacteria for fermentative production of L-glutamic acid. When the α-ketoglutarate dehydrogenase gene is disrupted, energy generated through the TCA cycle is decreased, leading to retardation of the bacterial growth. As a result, sufficient yield of L-glutamic acid may not be obtained.

Therefore, a mutant strain having a decreased ability to degrade L-glutamic acid while maintaining an ordinary growth rate would be useful for efficient production of L-glutamic acid. Mutant strains were obtained that have a decreased α-ketoglutarate dehydrogenase activity and maintain almost the same growth rate as a wild-type strain, by introducing mutations into a chromosomal odhA gene that encodes the E1o subunits of the α-ketoglutarate dehydrogenase complex of coryneform bacterium. L-glutamic acid was found to be efficiently produced by using such mutant strains.

It is an object of the present invention to provide an L-glutamic acid-producing coryneform bacterium, comprising

a) intracellular α-ketoglutarate dehydrogenase activity which is less than half that of a non-mutated or wild-type strain, and

b) a mutation in a coding region or an expression control region of a chromosomal odhA gene encoding the E1o subunit of the α-ketoglutarate dehydrogenase complex,

wherein said bacterium grows almost at the same growth rate as a non-mutated or wild-type strain.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said odhA gene encodes a protein selected from the group consisting of:

(A) a protein comprising an amino acid sequence of SEQ ID NO: 10,

(B) a protein comprising an amino acid sequence of SEQ ID NO: 10, whereby one or several amino acids in said protein are substituted, deleted, inserted, or added, and wherein said protein has an activity of the E1o subunit of the α-ketoglutarate dehydrogenase complex.

(C) a protein comprising amino acids 37 to 1257 of SEQ ID NO: 10, and

(D) a protein comprising amino acids 37 to 1257 of SEQ ID NO: 10, whereby one or several amino acids in said protein are substituted, deleted, inserted, or added, and wherein said protein has an activity of the E1o subunit of the α-ketoglutarate dehydrogenase complex.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said several amino acids are 2 to 20 amino acids.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said odhA gene is selected from the group consisting of:

(a) a gene comprising nucleotides 443 to 4213 of SEQ ID NO: 9,

(b) a gene that is able to hybridize under stringent conditions to a polynucleotide comprising nucleotides 443 to 4213 of SEQ ID NO: 9 or a probe prepared from a polynucleotide comprising nucleotides 443 to 4213 of SEQ ID NO: 9, and wherein said gene encodes a protein which has the activity of the E1o subunit of the α-ketoglutarate dehydrogenase complex,

(c) a gene comprising nucleotides 551 to 4213 of SEQ ID NO: 9, and

(d) a gene that is able to hybridize under stringent conditions to a polynucleotide comprising nucleotides 551 to 4213 of SEQ ID NO: 9 or a probe prepared from a polynucleotide comprising nucleotides 551 to 4213 of SEQ ID NO: 9, and wherein said gene encodes a protein which has the activity of the E1o subunit of the α-ketoglutarate dehydrogenase complex.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said mutation is introduced into a region encoding a thiamine pyrophosphate binding region.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said mutation comprises deletion of an amino acid selected from the group consisting of Gly at position 686, Leu at position 687, Gly at position 688, Asn at position 713, Asn at position 714, and combinations thereof in the amino acid sequence shown in SEQ ID NO: 10.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said mutation is introduced into the region comprising nucleotides 2534 to 2548 of SEQ ID NO: 9.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said mutation comprises deletion of one or more amino acids in the region comprising amino acids 698 to 702 of SEQ ID NO: 10.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said mutation comprises replacement of an amino acid selected from the group consisting of Lys at position 698, Leu at position 699, Arg at position 700, Tyr at position 702, and combinations thereof in the amino acid sequence shown in SEQ ID NO: 10.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said mutation is introduced into the region comprising nucleotides 1094 to 1111 of SEQ ID NO: 9.

It is a further object of the present invention to provide the coryneform bacterium as described above, wherein said mutation comprises deletion of one or more amino acids in the region comprising amino acids 218 to 224 of SEQ ID NO: 10.

It is a further object of the present invention to provide a method for producing L-glutamic acid comprising:

a) culturing the coryneform bacterium according to claim 1 in a culture medium and

b) collecting L-glutamic acid from the culture medium and/or the bacterium.

It is a further object of the present invention to provide a gene encoding mutant α-ketoglutarate dehydrogenase selected from the group consisting:

(a) a gene comprising nucleotides 443 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, or a gene comprising nucleotides 443 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48,

(b) a gene that is able to hybridize under stringent conditions to a polynucleotide comprising nucleotides 443 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, a polynucleotide comprising nucleotides 443 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48, a probe prepared from nucleotides 443 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, or a probe prepared from nucleotides 443 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48, and wherein said gene encodes a protein which has α-ketoglutarate dehydrogenase activity which is less than half that of a wild-type or non-mutated strain by forming a complex with E2o and E3 subunits,

(c) a gene comprising nucleotides 551 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, or a gene comprising nucleotides 551 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48, and

(d) a gene that is able to hybridize under stringent conditions to a polynucleotide comprising nucleotides 551 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, a polynucleotide comprising nucleotides 551 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48, a probe prepared from nucleotides 551 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, or a probe prepared from nucleotides 551 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48, and wherein said gene encodes a protein which has α-ketoglutarate dehydrogenase activity which is less than half that of a wild-type or non-mutated strain by forming a complex with E2o and E3 subunits.

It is a further object of the present invention to provide a mutant α-ketoglutarate dehydrogenase selected from the group consisting of:

(a) a protein selected from the group consisting of SEQ ID NO: 12, 14, 16, 45, 47, and 49,

(b) a protein selected from the group consisting of SEQ ID NO: 12, 14, 16, 45, 47, and 49, whereby one or several amino acids in said protein are substituted, deleted, or added, and wherein said protein exhibits α-ketoglutarate dehydrogenase activity which is less than half that of a wild-type or non-mutated strain by forming a complex with E2o and E3 subunits,

(c) a protein comprising amino acids 37 to 1256 of an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 45, 47, and 49, a protein comprising amino acids 37 to 1255 of an amino acid sequence of SEQ ID NO: 14, or a protein comprising amino acids 37 to 1254 of an amino acid sequence of SEQ ID NO: 16, and

(d) a protein comprising amino acids 37 to 1257 of an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 45, 47, and 49, a protein comprising amino acids 37 to 1255 of an amino acid sequence of SEQ ID NO: 14, or a protein comprising amino acids 37 to 1254 of an amino acid sequence of SEQ ID NO: 16, whereby one or several amino acids in said protein are substituted, deleted, or added, and wherein said protein exhibits α-ketoglutarate dehydrogenase activity which is less than half that of a wild-type or non-mutated strain by forming a complex with E2o and E3 subunits.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the construction of plasmid pBS3.

Fig. 2 is shows the construction of plasmid pBS4S.

Fig. 3 shows the construction of plasmid pBSOAGN.

Fig. 4 shows the construction of plasmid pBSOA2-2.

Fig. 5 shows the change in L-glutamic acid concentration when each strain is cultured.

Fig. 6 shows the growth rate of each strain.

Fig. 7 shows the change in the amount of residual sugar when each strain is cultured.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Hereinafter, the present invention will be described in detail.

<1> Coryneform bacterium of the present invention

The coryneform bacterium of the present invention has an L-glutamic acid-producing ability, and grows almost at the same growth rate as a non-mutated strain or a wild-type strain. The corynebacterium of the present invention has intracellular α-ketoglutarate dehydrogenase (hereinafter, also referred to as "α-KGDH") activity which is less than half that of a non-mutated strain or the wild-type strain, by introduction of mutations into a coding region or an expression control region of the odhA gene, which encodes the E1o subunit of α-KGDH complex.

α-KGDH is also called oxoglutarate dehydrogenase or 2-oxoglutarate dehydrogenase.

In the present invention, examples of coryneform bacterium include conventional coryneform bacterium, and also include bacteria that had been classified into the genus *Brevibacterium* but are currently is classified into the genus *Corynebacterium* (Int. J. Syst. Bacteriol., 41, 255(1991)), as well as the *Brevibacterium* bacteria that are very close to *Corynebacterium* bacteria. Examples of such coryneform bacterium include the following.

Corynebacterium acetoacidophilum
Corynebacterium acetoglutamicum
Corynebacterium alkanolyticum
Corynebacterium callunae
Corynebacterium glutamicum
Corynebacterium lilium
Corynebacterium melassecola
Corynebacterium thermoaminogenes (Corynebacterium efficiens)
Corynebacterium herculis
Brevibacterium divaricatum
Brevibacterium flavum
Brevibacterium immariophilum
Brevibacterium lactofermentum (Corynebacterium glutamicum)
Brevibacterium roseum
Brevibacterium saccharolyticum
Brevibacterium thiogenitalis
Brevibacterium ammoniagenes
Brevibacterium album
Brevibacterium cerinum
Microbacterium ammoniaphilum

Specific examples of the coryneform bacteria are as follows.

Corynebacterium acetoacidophilum ATCC13870
Corynebacterium acetoglutamicum ATCC15806

Corynebacterium alkanolyticum ATCC21511
Corynebacterium callunae ATCC15991
Corynebacterium glutamicum ATCC13020, ATCC13032, ATCC13060, ATCC13869
Corynebacterium lilium ATCC15990
Corynebacterium melassecola ATCC17965
Corynebacterium thermoaminogenes AJ12340 (FERM BP-1539)
Corynebacterium herculis ATCC13868
Brevibacterium divaricatum ATCC14020
Brevibacterium flavum ATCC13826, ATCC14067, AJ12418 (FERM BP-2205)
Brevibacterium immariophilum ATCC14068
Brevibacterium lactofermentum (*Corynebacterium glutamicum*) ATCC13869
Brevibacterium roseum ATCC13825
Brevibacterium saccharolyticum ATCC14066
Brevibacterium thiogenitalis ATCC19240
Brevibacterium ammoniagenes ATCC6871, ATCC6872
Brevibacterium album ATCC15111
Brevibacterium cerinum ATCC15112
Microbacterium ammoniaphilum ATCC15354

These strains are available from the American Type Culture Collection (ATCC, Address: P.O. Box 1549, Manassas, VA 20108, United States of America). That is, each strain is given a unique registration number which is listed in the catalogue of the ATCC. Strains can be ordered using this registration number. The AJ12340 strain was deposited at National Institute of Bioscience and Human Technology, Agency of Industrial Science and Technology, Ministry of International Trade and Industry (currently International Patent Organism Depositary, National Institute of Advanced Industrial Science and Technology at Tsukuba Central 6, 1-1, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken 305-5466, Japan) on October 27, 1989 under the provisions of the Budapest Treaty and given an accession number of FERM BP-1539. The AJ12418 strain was deposited at National Institute of Bioscience and Human Technology, Agency of Industrial Science and Technology, Ministry of International Trade and Industry on January 5, 1989 under the provisions of the Budapest Treaty and given an accession number of FERM BP-2205.

In the present invention, "L-glutamic acid-producing ability" means an ability to cause accumulation of a sufficient amount of L-glutamic acid in a medium when the coryneform bacterium of the present invention is cultured in the medium. The L-glutamic acid-producing ability may be either a property of a parent strain from which the coryneform bacterium of the present invention is bred or a property imparted or enhanced by a mutation, gene recombination, etc. Furthermore, the L-glutamic acid-producing ability may be imparted by introducing a mutation into the odhA gene which encodes the E1o subunit of α-ketoglutarate dehydrogenase complex.

Examples of the methods for imparting the L-glutamic acid-producing ability include enhancing expression of a gene encoding an L-glutamic acid biosynthetic enzyme. Examples of the enzymes involved in L-glutamic acid biosynthesis include glutamate dehydrogenase, glutamine synthetase, glutamate synthetase, isocitrate dehydrogenase, aconitate hydratase, citrate synthase, phosphoenolpyruvate carboxylase, pyruvate carboxylase, pyruvate dehydrogenase, pyruvate kinase, phosphoenolpyruvate synthase, enolase, phosphoglyceromutase, phosphoglycerate kinase, glyceraldehyde-3-phophate dehydrogenase, triose phosphate isomerase, fructose bisphosphate aldolase, phosphofructokinase, and glucose phosphate isomerase.

Enhancement of expression of these genes may be achieved by incorporating a DNA fragment containing such a gene into an appropriate plasmid which is able to autonomously replicate in coryneform bacterium, and transforming bacterial cells with the resultant plasmid; integrating such a gene into a chromosome by homologous recombination, conjugation, transposition, etc.; or introducing a mutation into a promoter region of such a gene (WO/0018935).

When the above-mentioned genes are introduced by a plasmid or integrated on a chromosome, a promoter for expression of the genes may be any promoter so long as it is able to function in coryneform bacteria. Examples of such promoters include lac promoter, trp promoter, trc promoter, PS2 promoter, and pL promoter. A native promoter of the gene may also be used.

Examples of microorganisms modified so that expression of citrate synthetase gene, phosphoenolpyruvate carboxylase gene, and/or glutamate dehydrogenase gene is enhanced include those microorganisms disclosed in JP2001-333769A (EP1078989A), JP2000-106869A (EP955368A), JP2000-189169A (EP952221A), and JP2001-333769A (EP1078989A).

The modification for imparting the L-glutamic acid-producing ability includes decreasing or eliminating an activity of an enzyme that catalyzes a reaction for synthesizing a compound other than L-glutamic acid, and branching from an L-glutamic acid biosynthesis pathway. Examples of such enzymes include isocitrate lyase, acetyl phosphate transferase, acetate kinase, acetohydroxy acid synthase, acetolactate synthase, acetyl formate transferase, lactate dehydrogenase, glutamate decarboxylase, and 1-pyrophosphate dehydrogenase.

To decrease or eliminate the activity of the enzymes as described above, a mutation or deletion which causes a decrease or loss of the activity of the enzymes may be introduced into the genes of the enzymes on the chromosome. This may be achieved by, for example, disrupting the gene encoding the enzyme on the chromosome, or by modifying an expression control sequence such as a promoter and/or Shine Dargarno (SD) sequence of the gene. In addition, the activities of such enzymes may be decreased or eliminated by introducing a missense mutation which causes an amino acid substitution, a nonsense mutation which generates a stop codon, or a frame shift mutation which adds or deletes one or two nucleotides into a coding region, or by deleting a portion of the gene (Journal of biological Chemistry 272:8611-8617 (1997)). Furthermore, the activities of such enzymes may be decreased or eliminated by constructing a gene encoding a mutant enzyme in which its coding region is deleted and replacing a chromosomal gene with the resulting gene by homologous recombination.

The L-glutamic acid-producing ability may also be imparted by screening a strain resistant to organic acid analogues or respiratory inhibitors, or by screening a strain sensitive to inhibitors of cell wall synthesis. Examples of such methods include imparting resistance to benzopirone or naphtoquinone (JP56-1889A), imparting resistance to HOQNO (JP56-140895A), imparting resistance to α-ketomalonic acid (JP57-2689A), imparting resistance to guanidine (JP56-35981A), and imparting sensitivity to penicillin (JP04-88994A).

Specific examples of such bacteria include the following strains.

Brevibacterium flavum AJ11355 (FERM P-5007; JP56-1889A)

Corynebacterium glutamicum AJ11355 (FERM P-5020; JP56-1889A)
Brevibacterium flavum AJ11217 (FERM P-4318; JP57-2689A)
Corynebacterium glutamicum AJ11218 (FERM P-4319; JP57-2689A)
Brevibacterium flavum AJ11564 (FERM P-5472; JP56-140895A)
Brevibacterium flavum AJ11439 (FERM P-5136; JP56-35981A)
Corynebacterium glutamicum H7684 (FERM BP-3004; JP04-88994A)

The coryneform bacterium of the present invention can be obtained from coryneform bacterium having the L-glutamic acid-producing ability as described above by introducing a mutation into a chromosomal odhA gene which encodes the E1o subunit of the α-KGDH complex, and selecting those strains that grow almost at the same growth rate as a non-mutated strain or a wild-type strain, and exhibits α-KGDH activity less than half that of the non-mutated strain or wild-type strain. Alternatively, such a mutation may be introduced into the odhA gene first, followed by imparting an L-amino acid-producing ability.

In the present invention, α-KDGH activity means an activity catalyzing a reaction of oxidative decarboxylation of α-ketoglutarate (2-oxoglutarate) to generate succinyl-CoA. The above-mentioned reaction is catalyzed by the α-KDGH complex, which includes three kinds of subunits, i.e., α-ketoglutarate dehydrogenase (E1o, EC1.2.4.2), dihydrolipoamide-S-succinyltransferase (E2o, EC:2.3.1.61), and dihydrolipoamide dehydrogenase (E3, EC:1.8.1.4). That is, these three subunits catalyze each of the following reactions:

E1o subunit:

2-oxoglutarate + [dihydrolipoyllysine-residue succinyltransferase]lipoyllysine = [dihydrolipoyllysine-residue succinyltransferase]S-succinyldihydrolipoyllysine + CO_2

E2o subunit:

CoA + enzymeN6-(S-succinyldihydrolipoyl)lysine=succinyl-CoA + enzyme N6-(dihydrolipoyl)lysine

E3 subunit:

protein N6-(dihydrolipoyl)lysine + NAD^+ = protein N6-(lipoyl)lysine+ NADH + H^+

The activity of the "α-KDGH complex" means an activity catalyzing the total reaction of the above three reactions.

In *Escherichia coli*, these three subunits form a complex.

In the case of coryneform bacterium, the E1o subunit is encoded by the odhA gene and the E3 subunit is encoded by the lpd gene (GenBank Accession NO. Y16642; SEQ ID NO: 17). It is controversial whether the E2o subunit is encoded by the odhA gene as a bifunctional protein together with the E1o subunit (Usuda et al., Microbiology 1996 142, 3347-3354), or encoded by a separate gene registered as an accession No. NCg12126 of NC_003450 (SEQ ID NO: 27) in the GenBank database. Thus, the odhA gene may encode the E2o subunit in addition to the E1o subunit.

The coryneform bacteria of the present invention have a mutation in the chromosomal odhA gene. The odhA gene includes, for example, a gene having a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO: 10. The odhA gene also includes a gene having a nucleotide sequence encoding the amino acid sequence shown in SEQ ID NO: 51. In addition, it is possible that the "gtg" at positions 551 to 553 in the nucleotide sequence of SEQ ID NO: 9 may be translated as Met and translation may be initiated at this codon, even though it is a codon for Val. Therefore, the odhA gene also includes a gene having a nucleotide sequence encoding the amino acid sequence of amino acids 37 to 1257 of SEQ ID NO: 10. Furthermore, the odhA gene may also be a gene encoding a protein that has an amino acid sequence shown in SEQ ID NO: 10 or 51, or amino acid sequence of amino acids 37 to 1257 of SEQ ID NO: 10, including substitution, deletion, insertion or addition of one or several amino acids so long as it exhibits an activity of the E1o subunit of the α-KGDH complex. The activity of the E1o subunit itself can be determined by the method of Massey et al. (Biochim. Biophys. Acta 38,447-460). "Several" as used herein is preferably 2 to 20, more preferably 2 to 10, and particularly preferably 2 to 5.

More specifically, the odhA gene preferably has a nucleotide sequence of nucleotides 443 to 4213 of SEQ ID NO: 9, or a nucleotide sequence of nucleotides 551 to 4213 of SEQ ID NO: 9. The odhA gene may have a nucleotide sequence shown in SEQ ID NO: 50. Furthermore, since the nucleotide sequences of the odhA genes may differ between the species or strains of the coryneform bacteria, the odhA gene may be a gene that hybridizes with a polynucleotide having a nucleotide sequence of nucleotides 443 to 4213 of SEQ ID NO: 9, a polynucleotide having a nucleotide sequence shown in SEQ ID NO: 50, or a nucleotide sequence of nucleotides 551 to 4213 of SEQ ID NO: 9, or a probe prepared from the nucleotide sequences under stringent conditions so long as the gene encodes a protein that exhibits the activity of the E1o subunit of the α-KGDH complex. The “stringent conditions” as used herein are conditions under which a so-called specific hybrid is formed, and a non-specific hybrid is not formed. It is difficult to clearly express this condition by using any numerical value. However, examples of stringent conditions include those under which DNAs hybridize to each other at a salt concentration with washing typical of Southern hybridization, i.e., washing once or preferably 2-3 times under 1 x SSC, 0.1% SDS at 60°C, preferably 0.1 x SSC, 0.1% SDS at 60°C, more preferably 0.1 x SSC, 0.1% SDS at 68°C.

In the present invention, "a mutation is introduced into a chromosomal odhA gene" includes the case where the odhA gene on a chromosome is replaced by a mutant odhA gene to generate substantially the same condition in which a mutation is directly introduced into the chromosomal odhA gene.

The above-mentioned mutation may be introduced not only in the coding region but also in the expression controlling region of the odhA gene. The expression controlling region includes, for example, a promoter, SD sequence, and operator. The expression controlling region of the odhA gene includes a nucleotide sequence of nucleotides 1 to 442 of SEQ ID NO: 9. Expression controlling sequence of the odhA gene may also be identified by genetic analysis software such as GENETYX or by the method disclosed in Goldstein *et al.* (Prokaryotic promoters in biotechnology. Biotechnol. Annu. Rev., 1995, 1, 105-128).

The "α-KGDH activity less than half that of a non-mutated or wild-type strain" preferably means that the α-KGDH activity per unit cell (per unit weight of protein) of the coryneform bacterium of the present invention cultured for 4 hours is less than half the activity of a non-mutated or wild-type strain of coryneform bacteria cultured under the same conditions. Examples of coryneform bacterium having such decreased α-KGDH activity include a bacterium in which the number of α-KGDH molecules per cell is decreased and a bacterium in which the activity per α-KGDH molecule is decreased. Examples of a wild-type coryneform bacterium used as a control include *Brevibacterium lactofermentum* ATCC13869 strain. The intracellular α-KGDH activity of the coryneform bacterium of the present invention is preferably less than 40%, more preferably less than 30% that of the activity of a non-mutated or wild-type strain. Although α-KGDH activity may be decreased to an undetectable level, it is preferable that the activity is not completely eliminated. The α-KGDH activity (activity of α-KGDH complex) can be measured by the method of Shiio et al. (Isamu Shiio and Kyoko Ujigawa-Takeda, Agric. Biol. Chem., 44(8), 1897-1904, 1980).

As a result of the decrease of intracellular α-KGDH activity, the L-glutamic acid-producing ability of the coryneform bacterium is improved. In the present invention, "L-glutamic acid-producing ability is improved" preferably means that when the strain of coryneform bacterium into which a mutation has been introduced into odhA gene is cultured in a medium, the amount of L-glutamic acid which accumulates in the medium by the mutant coryneform bacterium is larger than that which accumulates by the wild-type or non-mutated strain, or the rate of L-glutamic acid production by the mutant coryneform bacterium is higher than that of the wild-type or non-mutated strain.

The phrase “the bacterium grows almost at the same growth rate compared to a wild-type strain or non-mutated strain” preferably means the bacterium of the present invention grows almost at the same growth rate as a wild-type strain such as *Brevibacterium lactofermentum* ATCC13869. Here, "almost at the same growth rate" means 80% or more, more preferably 90%, or more preferably 95% or more of the growth rate of a wild-type or non-mutated strain. It is not necessary that the coryneform bacterium of the present invention grows almost at the same growth rate as a wild-type or non-mutated strain at any culture temperature. That is, coryneform bacterium which exhibits a sufficient growth rate at low temperatures but exhibits a decreased growth rate at high temperatures such as GN-2-2 strain as shown in the Examples is also included in the coryneform bacterium of the present invention.

The growth rates of the strain of the present invention and the wild-type or non-mutated strain can be compared, for example, by inoculating the same number of cells of each strain in a medium and comparing viable cell numbers after a predetermined time. When a liquid medium is used, the viable cell number can be calculated based on, for example, optical density (OD) at a wavelength of 600 nm or weight of bacterial cells after a predetermined time. When a solid medium such as a plate medium is used, the viable cell numbers can be calculated based on the number of colonies that appeared after a predetermined time.

Examples of the method of introducing a mutation into the odhA gene on the chromosome include using X-rays or ultraviolet rays to irradiate the coryneform bacterium, and treating the coryneform bacterium with a mutagen such as N-methyl-N'-nitro-N-nitrosoguanidine. Mutation may also be introduced into the odhA gene on the chromosome by preparing a mutant odhA gene, and replacing the chromosomal odhA gene with such a mutant odhA gene by homologous recombination technique. Such a mutant odhA gene may be prepared by error-prone PCR, DNA shuffling, or StEP-PCR （Firth AE, Patrick WM; Bioinformatics. 2005 Jun 2; Statistics of protein library construction.）, or overlap-extension PCR （Urban, A., Neukirchen, S. and Jaeger, K. E., A rapid and efficient method for site-directed mutagenesis using one-step overlap extension PCR. Nucleic Acids Res, 25, 2227-8. (1997)）.

Homologous recombination may be performed by a method called “Red-driven integration” in which a linear DNA is used (Datsenko, K.A., PNAS, 97(12), 6640-6645, 2000) or by a method using a plasmid having temperature-sensitive replication origin (USP6303383, and JP05-007491A). Introduction of a mutation into a chromosomal odhA gene may also be performed by using a plasmid which is not replicable in cells of coryneform bacteria or a plasmid capable of transferring to coryneform bacteria by conjugation.

Examples of such a temperature-sensitive plasmid for Coryneform bacteria include p48K and pSFKT2 (JP2000-262288A), pHSC4 (France Patent Laid-open Publication No. 2667875, 1992 and JP5-7491A), pBS5Tand so forth. These plasmids can autonomously replicate at least at a temperature of 25°C, but cannot autonomously replicate at a temperature of 37°C in Coryneform bacteria. The AJ12571 strain harboring pHSC4 was deposited at National Institute of Bioscience and Human Technology, Agency of Industrial Science and Technology, Ministry of International Trade and Industry (currently International Patent Organism Depositary, National Institute of Advanced Industrial Science and Technology at Tsukuba Central 6, 1-1, Higashi 1-chome, Tsukuba-shi, Ibaraki-ken 305-5466, Japan) on August 26, 1991 under the provisions of the Budapest Treaty and given an accession number of FERM BP-3524.

A plasmid which is not replicable in cells of coryneform bacteria is preferably one replicable in cells of *Escherichia* bacteria, and examples thereof include pHSG299 (Takara Bio) and pHSG399 (Takara Bio). Examples of a plasmid capable of transferring to coryneform bacteria by conjugation include pK19mobsacB (J. Bacteriology 174:5462-65(1992)).

Mutant odhA gene is inserted into a temperature-sensitive plasmid or a plasmid which is not replicable in coryneform bacteria, and the obtained recombinant plasmids are used to transform coryneform bacteria. Transformation can be performed by conventional methods. For example, a method of treating recipient cells with calcium chloride so as to increase the permeability of DNA, which has been reported for *Escherichia coli* (Mandel, M. and Higa, A., J. Mol. Biol., 53, 159 (1970)), and a method of using competent cells prepared from growing cells to introduce a DNA, which has been reported for *Bacillus subtilis* (Duncan, C.H., Wilson, G.A. and Young, F.E., Gene, 1, 153 (1977)) can be employed. In addition to these methods, a method of introducing a recombinant DNA into protoplast- or spheroplast-like recipient cells, which have been reported to be applicable to *Bacillus subtilis*, actinomycetes, and yeasts (Chang, S. and Choen, S.N., Molec. Gen. Genet., 168, 111 (1979); Bibb, M.J., Ward, J.M. and Hopwood, O.A., Nature, 274, 398 (1978); Hinnen, A., Hicks, J.B. and Fink, G.R., Proc. Natl. Sci., USA, 75, 1929 (1978)), can be employed. In addition, transformation of *Coryneform* bacteria can also be performed by the electric pulse method (Sugimoto et al., JP2-207791A).

In the case of using a plasmid which is not capable in cells of coryneform bacteria, a wild-type odhA gene on a chromosome is replaced with the mutant odhA gene on the plasmid.

In the case of using a temperature-sensitive plasmid, the transformant strain is cultured at a temperature at which the temperature sensitive replication origin does not function (e.g. 25°C) to obtain a strain into which the plasmid is introduced. Then,. the transformant is cultured at a high temperature to eliminate the temperature-sensitive plasmid, and spread over a plate medium containing an antibiotic drug such as kanamycin. Although strains from which the plasmid is eliminated cannot grow on a plate containing such an antibiotic drug, a few strains in which the chromosomal odhA gene is replaced with the mutant odhA gene can grow and appear as colonies.

In such a strain in which the recombinant DNA containing the mutant odhA gene is integrated into the chromosomal DNA as described above, the recombinant DNA causes recombination with the odhA gene that originally exists on the chromosome, and the fusion genes of the chromosomal odhA gene and the mutant odhA gene are inserted into the chromosome so that the other portions of the recombinant DNA (vector segment, temperature sensitive replication origin and drug resistance marker) is present between the fusion genes. Then, in order to leave only the mutant odhA gene on the chromosomal DNA, one copy of the odhA gene is eliminated together with the vector segment (including the temperature sensitive replication origin and the drug resistance marker) from the chromosomal DNA. In this case, the normal odhA gene is left on the chromosomal DNA and the mutant odhA gene is excised from the chromosomal DNA, or to the contrary, the mutant odhA gene is left on the chromosomal DNA and the normal odhA gene is excised from the chromosome DNA. Then, a strain in which only the mutant odhA gene is left on the chromosome can be selected using PCR, Southern hybridization or the like.

Homologous recombination may be performed using a sacB gene encoding levan sucrase as a marker for recombination. The sacB gene encoding levan sucrase is used to efficiently select strains in which a chromosomal odhA gene is replaced by the mutant odhA gene and a vector portion is cured from a chromosome (Schafer, A. et al., Gene 145 (1994) 69-73). That is, in the case of the coryneform bacteria, when levan sucrase is expressed, levan generated by assimilation of sucrose becomes lethal for the bacteria and hence the bacteria cannot grow. Therefore, by culturing on a sucrose-containing plate, strains in which substitution occurs between the mutant odhA gene in the vector and a chromosomal odhA gene and from which the other portions of the vector are cured can be selected.

Examples of the sacB gene include the followings.

Bacillus subillus : sacB GenBank Accession Number X02730 (SEQ ID NO: 19)
Bacillus amyloliqufaciens : sacB GenBank Accession Number X52988
Zymomonas mobilis : sacB GenBank Accession Number L33402
Bacillus stearothermophilus : surB GenBank Accession Number U34874
Lactobacillus sanfranciscensis : frfA GenBank Accession Number AJ508391
Acetobacter xylinus : lsxA GenBank Accession Number AB034152

Gluconacetobacter diazotrophicus : lsdA GenBank Accession Number L41732

<2> The mutant odhA gene of the present invention

The mutation to be introduced into the chromosomal odhA gene is not particularly limited so long as it is a mutation which decreases the α-KGDH activity to be less than half of the α-KGDH activity of a non-mutated strain or wild-type strain, but does not cause retardation of the growth of the bacterium. Specific examples of the mutation include the followings.

(1) Mutation in the thiamine pyrophosphate binding region

This mutation is introduced into the binding region of thiamine pyrophosphate, which is a coenzyme. Thiamine pyrophosphate binding region means a region corresponding to that encoded by nucleotides 2498 to 2584 of the odhA gene (SEQ ID NO: 9). The amino acid sequence of the region is shown as amino acids 686 to 714 in SEQ ID NO: 10. Examples of a mutation in this region include one that causes a deletion of one or more amino acid residues selected from Gly at position 686, Leu at position 687, Gly at position 688, Asn at position 713, and Asn at position 714.

The mutation in the thiamine pyrophosphate binding region may also be introduced in the region of nucleotides 2534 to 2548 of the odhA gene (SEQ ID NO: 9). This mutation is named a GN type mutation. The GN type mutation is preferably a mutation that causes deletion and/or substitution of one or more amino acid residues selected from Lys at position 698, Leu at position 699, Arg at position 700, Gly at position 701, and Tyr at position 702 in SEQ ID NO: 10. An example of such a mutation is that which deletes Gly at position 701 in SEQ ID NO: 10. Examples of the mutant odhA gene having this mutation include a gene having nucleotide sequence of nucleotides 443 to 4213 of SEQ ID NO: 13, and genes having nucleotide sequence of nucleotides 443 to 4210 of SEQ ID NOS: 44, 46 or 48, and the mutant α-KGDH proteins encoded by these genes are shown in SEQ ID NOS: 14, 45, 47, and 49. Examples of the mutant odhA gene having this mutation also include a gene having nucleotide sequence of nucleotides 551 to 4213 of SEQ ID NO: 13 and genes having nucleotide sequence of nucleotides 551 to 4210 of SEQ ID NOS: 44, 46, or 48, and the mutant α-KGDH proteins encoded by these genes are shown in amino acids 37 to 1255 of SEQ ID NO: 14, and amino acids 37 to 1256 of

SEQ ID NOS: 45, 47, and 49. In the nucleotide sequence of SEQ ID NO: 13, a mutation which deletes "t" at position 2538 and "ggcta" at positions 2543 to 2547 of SEQ ID NO: 9 is introduced.

Furthermore, mutant odhA genes having a mutation which results in replacement of one or more amino acid residues selected from Lys at position 698, Leu at position 699, Arg at position 700, and Tyr at position 702 with another amino acid in SEQ ID NO: 10 are also preferable. The "another amino acid" is not particularly limited so long as it is different from the original amino acid, and selected from natural amino acids such as Lys, Glu, Thr, Val, Leu, Ile, Ser, Asp, Asn, Gln, Arg, Cys, Met, Phe, Trp, Tyr, Gly, Ala, Pro, and His. However, it is preferable that Lys at position 698 is replaced by amino acids other than basic amino acids such as Arg and His, Leu at position 699 is replaced by amino acids other than hydrophobic aliphatic amino acids such as Ile and Val, Arg at position 700 is replaced by amino acids other than basic amino acids such as Lys and His, Tyr at position 702 is replaced by amino acids other than hydroxy amino acids such as Ser and Thr. It is particularly preferable that Lys at position 698 is replaced by hydrophobic aliphatic amino acid such as Ile, Leu, or Val, Leu at position 699 is replaced by hydroxyl amino acid such as Ser, Thr or Tyr, Arg at position 700 is replaced by sulfur-containing amino acid such as Cys or Met, Tyr at position 702 is replaced by hydrophobic aliphatic amino acid such as Ile, Leu, or Val.

A GN-type mutation may cause both the deletion of Gly at position 701 and replacement of one or more amino acid residues selected from Lys at position 698, Leu at position 699, Arg at position 700, and Tyr at position 702 in SEQ ID NO: 10. Examples of such mutant odhA gene include genes having the nucleotide sequence of nucleotides 443 to 4210 of SEQ ID NOS: 44, 46, and 48. Amino acid sequences of mutant α-KGDH proteins encoded by these mutant odhA genes are shown in SEQ ID NOS: 45, 47, and 49. Examples of such a mutant odhA gene also include genes having nucleotide sequence of nucleotides 551 to 4210 of SEQ ID NOS: 44, 46, and 48. Amino acid sequences of mutant α-KGDH proteins encoded by these mutant odhA genes are shown in amino acids 37 to 1256 of SEQ ID NOS: 45, 47, and 49. However, the mutant odhA gene having a mutation in the thiamine pyrophosphate binding region is not limited to these examples.

(2) 2-2 type mutation

This type of mutation is preferably a mutation introduced into the region of nucleotides 1094 to 1111 of the odhA gene (SEQ ID NO: 9) which causes deletion and/or substitution of one or more amino acid residues selected from Asp at position 218, Val at position 219, Ile at position 220, Asp at position 221, Gly at position 222, Lys at position 223, and Pro at position 224 in SEQ ID NO: 10. The 2-2 type mutation is preferably a mutation which deletes Asp at position 221 in SEQ ID NO: 10. Examples of the odhA gene having this mutation include an odhA gene having a nucleotide sequence of nucleotides 443 to 4213 of SEQ ID NO: 11, or an odhA gene having a nucleotide sequence of nucleotides 551 to 4213 of SEQ ID NO: 11. The amino acid sequences of the mutant α-KGDH encoded by these genes are shown in SEQ ID NO: 12 or amino acid numbers 37 to 1256 of SEQ ID NO: 12, respectively. The nucleotide sequence of SEQ ID NO: 11 has the mutations to delete “gacgt” at 1094 to 1098 and replace “ag” at 1110 to 1111 with “ggcc” in the nucleotide sequence shown in SEQ ID NO: 9.

The 2-2 type mutation is also preferably a mutation which replaces one or more amino acids selected from Val at position 219, Ile at position 220, Asp at position 221, Gly at position 222, and Lys at position 223. Although amino acid which replaces these amino acids are not particularly limited, Val at position 219 is preferably replaced with an amino acid other than an aliphatic hydrophobic amino acid such as Ile and Leu, Ile at position 220 is preferably replaced with an amino acid other than an aliphatic hydrophobic amino acid such as Leu, Asp at position 221 is preferably replaced with an amino acid other than an acidic amino acid such as Glu, and Gly at position 222 is preferably replaced with an amino acid other than a simple amino acid such as Ala. More preferably, Val at position 219, Ile at position 220, and Asp at position 221 are replaced with basic amino acids such as His, Arg and Lys, Gly at 222 is replaced with an amino acid having amide-containing side chain such as Asp and Gln, and Lys at position 223 is replaced with an amino acid such as Gly and Ala.

However, mutant odhA gene having 2-2 type mutation is not limited to these examples.

(3) GN2-2 Type mutation

This mutation includes both the GN type mutation and the 2-2 type mutation. Examples of the odhA gene having this mutation include an odhA gene having a nucleotide sequence of nucleotides 443 to 4213 of SEQ ID NO: 15, or an odhA gene having a nucleotide sequence of nucleotides 551 to 4213 of SEQ ID NO: 15. The amino acid sequences of the mutant α-KGDH encoded by these genes are shown in SEQ ID NO: 16 or amino acids 37 to 1254 of SEQ ID NO: 16, respectively. However, the mutant odhA gene having a GN2-2 type mutation is not limited to these examples.

Other kinds of mutant odhA gene used in the present invention may be screened by using a ygg mutant strain, such as ATCC13869-L as described in Example 5 shown below. That is, a random mutation is introduced into the odhA gene and used to transform the ygg mutant strain. A strain which grows almost at the same growth rate as a wild-type strain or a non-mutated strain and exhibits α-KGDH activity which is less than half that of the wild-type strain or non-mutated strain is selected from the transformants, followed by sequence determination. Thereby, mutant odhA genes can be obtained.

A mutant E1o subunit of α-KGDH complex encoded by the above-described mutant odhA gene is a protein which has α-KGDH activity which is less than half that of a wild-type or non-mutated strain by forming a complex with E2o and E3 subunits of α-KGDH complex, and does not cause severe growth retardation of a coryneform bacterium when it is expressed in the coryneform bacterium.

Such properties of the mutant E1o subunit are considered to be maintained even if one or several amino acids other than the specific amino acids replaced in the above-described GN type or 2-2 type mutants, for example, amino acids that do not influence the enzymatic activity, are replaced by other amino acids. Therefore, in the above-mentioned amino acid sequences of the mutant E1o subunit protein (e.g., SEQ ID NOS: 12, 14, 16, 45, 47 and 49, amino acids 37 to 1256 of SEQ ID NOS: 12, 45, 47 and 49, amino acids 37 to 1255 of SEQ ID NO: 14, or amino acids 37 to 1254 of SEQ ID NO: 16), one or several amino acids other than the specific amino acids substituted in the GN type or 2-2 type mutants may be replaced, so long as the encoded protein exhibits α-KGDH activity less than half of a wild-type α-KGDH complex by forming a complex together with α-KGDH E2o subunit and E3 subunit proteins. Here, "several" means preferably 2 to 20, more preferably 2 to 10, and particularly preferably 2 to 5. Such amino acid substitution may be one caused by a naturally occurring mutation arising from individual difference and difference in species of bacterium from which odhA gene is derived. For example, mutant odhA gene having a nucleotide sequence encoding amino acid sequence of SEQ ID NO: 51 whereby amino acids corresponding to the above-mentioned GN-type mutation or 2-2 type mutation are deleted and/or substituted can also be used in the present invention. Such amino acids corresponding to the GN-type mutation or 2-2 type mutation in the amino acid sequence of SEQ ID NO: 51 can be easily identified by aligning the amino acid sequences of SEQ ID NOS: 10 and 51.The above-mentioned substitution is preferably a conservative substitution. In the case of aromatic amino acids, conservative substitutions are referred to substitutions between phe, trp, and tyr for each other. In the case of hydrophobic amino acids, conservative substitutions are referred to substitutions between leu, ile, and val for each other. In the case of polar amino acids, conservative substitutions are referred to substitutions between gln and asn for each other. In the case of basic amino acids, conservative substitutions are referred to substitutions between arg, lys, and his for each other. In the case of acidic amino acids, conservative substitutions are substitutions between asp and glu for each other. In the case of hydroxyl group-containig amino acids, conservative substitutions are referred to substitutions between ser and thr for each other. The conservative substitutions also include: substitution of ser or thr for ala, substitution of gln, his, or lys for arg; substitution of glu, gln, lys, his, or asp for asn; substitution of asn, glu, or gln for asp; substitution of ser or ala for cys; substitution of asn, glu, lys, his, asp, or arg for gln; substitution of asn, gln, lys, or asp for glu; substitution of vfor gly; substitution of asn, lys, gln, arg, or tyr for his; substitution of leu, met, val, or phe for ile; substitution of ile, met, val, or phe for leu; substitution of asn, glu, gln, his, or arg for lys; substitution of ile, leu, val or phe for met; substitution of trp, tyr, met, ile, or leu for phe; substitution of thr or ala for ser; substitution of ser or ala for thr; substitution of phe or tyr for trp; substitution of his, phe, or trp for tyr; and substitution of met, ile, or leu for val.

When the E1o subunit and E2o subunit are encoded by a single odhA gene, the α-KGDH complex may include the protein of SEQ ID NO: 10 (or amino acids 37 to 1257 of SEQ ID NO: 10) and the protein of SEQ ID NO: 18. When the E1o subunit is encoded by the odhA gene and the E2o subunit is encoded by the gene of SEQ ID NO: 27, the α-KGDH complex may include the protein of SEQ ID NO: 10, the protein of SEQ ID NO: 18, and the protein of SEQ ID NO: 28.

A mutant odhA gene of the present invention is a gene encoding the above-mentioned mutant α-KGDH E1o subunit. The mutant odhA gene of the present invention may be genes that hybridize with a polynucleotide each having the nucleotide sequence of nucleotides 443 to 4213 of SEQ ID NO: 11, 13, or 15, with a polynucleotide each having the nucleotide sequence of nucleotides 443 to 4210 of SEQ ID NO: 44, 46 or 48, with the nucleotide sequence of nucleotide numbers of 551 to 4213 of SEQ ID NO: 11, 13, or 15, or with the nucleotide sequence of nucleotide numbers 443 to 4210 of SEQ ID NO: 44, 46, or 48, or with a probe prepared from the sequences under stringent conditions so long as the gene encodes a protein that exhibits α-KGDH activity less than half that of a wild-type α-KGDH complex by forming a complex together with the E2o subunit and E3 subunit proteins. Examples of stringent conditions include those under which DNAs hybridize to each other at a salt concentration with washing typical of Southern hybridization, i.e., washing once or preferably 2-3 times under 1 x SSC, 0.1% SDS at 60°C, preferably 0.1 x SSC, 0.1% SDS at 60°C, more preferably 0.1 x SSC, 0.1% SDS at 68°C.

<3> Method of producing L-glutamic acid

L-glutamic acid can be produced by culturing the coryneform bacterium of the present invention in a medium to cause accumulation of L-glutamic acid in the medium and/or in the bacterial cells, and collecting the L-glutamic acid from the medium and/or the bacterial cells. In the production method of the present invention, L-glutamic acid is produced preferably by culturing the coryneform bacterium of the present invention, for example, at 25 to 40°C for 8 to 120 hours. If a strain which exhibits a sufficient growth rate at low temperatures but exhibits decreased growth rate at high temperatures such as the GN-2-2 strain shown in the

Examples is used for L-glutamic acid production, it is preferable to culture such a strain at a low temperature such as 25 to 30 °C for 8 to 30 hours so that the strain can grow; and then incubate the obtained bacterial cells at high temperature such as 34 to 40°C for 16 to 48 hours so that the strain can produce L-glutamic acid.

The culture medium may be an ordinary medium that contains a carbon source, a nitrogen source, an inorganic salt, and optionally organic micronutrients such as amino acids and vitamins. Either a synthetic medium or a natural medium may be used. Any kinds of the carbon source and nitrogen source may be used so long as they can be utilized by the strain to be cultured.

Saccharides such as glucose, glycerol, fructose, sucrose, maltose, mannose, galactose, starch hydrolysate, and molasses may be used as the carbon source. In addition, organic acids such as acetic acid and citric acid, and alcohols such as ethanol may also be used alone or in combination as a carbon source. Ammonia, ammonium salts such as ammonium sulfate, ammonium carbonate, ammonium chloride, ammonium phosphate, and ammonium acetate, nitrates, and the like may be used as the nitrogen source. Amino acids, vitamins, fatty acids, nucleic acids, substances containing peptone, casamino acid, yeast extract, and soybean protein decomposition products may be used in a slight amount as the organic nutrients. When an auxotrophic mutant strain that requires an amino acid etc. for growth is used, such a required nutrient is preferably added. Phosphates, magnesium salts, calcium salts, iron salts, manganese salts, and the like can be used as inorganic salts.

Preferably, aerobic culturing is performed by controlling the fermentation temperature and adjusting the pH of the culture medium to 3 to 9. When the pH decreases during the culture, the medium is neutralized by adding alkali such as calcium carbonate or ammonia gas. Culture for about 10 to about 120 hours results in accumulation of a considerable amount of L-glutamic acid in the medium.

Furthermore, the culture may be performed by using a liquid medium adjusted to conditions under which the produced L-glutamic acid crystallizes and precipitates. The conditions under which L-glutamic acid crystallizes include pH 5.0 to 4.0, preferably pH 4.5 to 4.0, more preferably pH 4.3 to 4.0, particularly preferably pH 4.0 (EP1233069, EP1233070).

Collection of L-glutamic acid from the medium after completion of the culture may be performed by conventional methods. L-glutamic acid may be collected, for example, by removing bacterial cells from the medium and concentrating L-glutamic acid or by using ion exchange chromatography. When the culture is performed under conditions under which L-glutamic acid crystallizes and precipitates, the crystallized L-glutamic acid can be collected, for example, by centrifugation or filtration. In this case, L-glutamic acid dissolved in the medium may also be collected after crystallization of the dissolved L-glutamic acid.

EXAMPLES

Hereinafter, the present invention will be more specifically explained by referring to the following non-limiting examples.

Example 1

<1> Construction of a vector carrying the sacB gene

(A) Construction of pBS3

A sacB gene (SEQ ID NO: 19) was obtained by PCR using a chromosomal DNA of *Bacillus subtilis* as a template and the oligonucleotides of SEQ ID NOS: 21 and 22 as primers. The PCR was performed using LAtaq (available from TaKaRa) according to the program of one cycle of pre-denaturation at 94°C for 5 minutes; and 25 cycles of denaturation at 94°C for 30 seconds, annealing at 49°C for 30 seconds, and elongation at 72°C for 2 minutes. The obtained PCR product was purified by a conventional method, and then digested with Bg1II and BamHI and blunt-ended. The fragment was inserted into pHSG299 which had been digested with AvaII and blunt-ended. The resulting DNA was used to transform competent cells of *Escherichia coli* JM109 (available from Takara Bio). Then, the transformed bacterial cells were applied onto an LB agar plate containing 25 μg/ml of kanamycin (hereinafter, abbreviated as "Km"), and incubated for one night. Thereafter, colonies that appeared were selected as transformants. Plasmids were isolated from the obtained transformants and the plasmid having an insert of the object PCR product was named pBS3. Fig. 1 shows the procedure for constructing pBS3.

(B) Construction of pBS4S

The SmaI recognition site in the kanamycin-resistant gene on pBS3 was destroyed by nucleotide substitution using cross-over PCR without causing amino acid substitution. First, PCR was performed using pBS3 as a template and synthetic DNAs of SEQ ID NOS: 23 and 24 as primers to obtain an N-terminal fragment of the kanamycin-resistant gene. On the other hand, to obtain a C-terminal fragment of kanamycin-resistant gene, PCR was performed using pBS3 as a template and synthetic DNAs of SEQ ID NOS: 25 and 26 as primers. The PCR was performed using Pyrobest DNA Polymerase (available from Takara Bio) according to the program of pre-denaturation at 98°C for 5 minutes; and 25 cycles of denaturation at 98°C for 10 seconds, annealing at 57°C for 30 seconds, and elongation at 72°C for 1 minute. SEQ ID NOS: 24 and 25 are partially complementary to each other and do not contain the SmaI recognition site. Then, to obtain a full-length fragment of the mutant kanamycin-resistant gene without the SmaI recognition site, the above-mentioned N-terminal and C-terminal gene products were mixed with each other in substantially equimolar amounts. PCR was performed using the gene products as a template and synthetic DNAs of SEQ ID NOS: 23 and 26 as primers to obtain a mutation-introduced Km resistant gene. The PCR was performed using Pyrobest DNA Polymerase (available from Takara Bio) according to the program of pre-denaturation at 98°C for 5 minutes; and 25 cycles of denaturation at 98°C for 10 seconds, annealing at 57°C for 30 seconds, and elongation at 72°C for 1.5 minutes.

The PCR product was purified by a conventional method, and then digested with BanII and then inserted into the above-described BanII recognition site of pBS3. The resulting plasmid was used to transform competent cells of *Escherichia coli* JM109 (available from Takara Bio). That is, the transformed bacterial cells were applied onto LB agar medium containing 25 μg/ml of kanamycin, and incubated for one night. Thereafter, colonies that appeared were selected as transformants. Plasmids were isolated from the obtained transformants and the plasmid having an insert of the object PCR product was named pBS4S. Fig. 2 shows the procedure for constructing pBS4S.

<2> Introduction of odhA mutation (GN-type) into *C. glutamicum* ATCC13969 strain

The sequence of odhA that encodes α-ketoglutarate dehydrogenase of coryneform bacteria has already been reported (Microbiology 142, 3347-3354 (1996), GenBank accession No. D84102).

Analysis of the nucleotide sequence of the L-glutamic acid-producing bacterium strain GN which the inventors of the present invention had succeeded in breeding revealed that this strain has deletions of the nucleotides 2538 and 2543 to 2547 in the nucleotide sequence of the odhA gene (SEQ ID NO: 9) as shown in Table 1. In Table 1, amino acid sequence of mutant E1o subunit encoded by the mutant odhA gene is also shown.

Table 1

Strain	Nucleotide sequence of odhA gene
ATCC13869	GCT AAG CTG CGT GGC TAC GAC GTC GGA GGC ACC ATC
OAGN	GCT AAG C-G CGT --- --C GAC GTC GGA GGC ACC ATC
Strain	Amino acid sequence of E1o subunit
ATCC13869	Ala Lys Leu Arg Gly Tyr Asp Val Gly Gly Thr Ile
OAGN	Ala Lys Arg Val --- --- Asp Val Gly Gly Thr Ile

Then, this mutant odhA gene was introduced into *C. glutamicum* 2256 strain (ATCC13869) and evaluated. At first, a plasmid for introducing these mutations into *C. glutamicum* 2256 strain (ATCC13869) was prepared. A chromosomal DNA was extracted from the above-mentioned GN strain using Bacterial Genomic DNA Purif. Kit (manufactured by MS Technosystems Co., Ltd.) and PCR was performed using the obtained chromosomal DNA as a template and oligonucleotides of SEQ ID NOS: 1 and 2 as primers. PCR was performed using Pyrobest polymerase (available from Takara Bio) according to the program of 30 cycles of denaturation at 98°C for 10 seconds, annealing at 50°C for 30 seconds, and elongation at 72°C for 3 minutes to amplify a fragment of about 2.75 kb. The primers contain a BamHI recognition sequence at the 5'-end and are designed to amplify the region of nucleotide numbers 1521 to 4270 of the sequence of GenBank accession No. D84102. The amplified fragment was digested with BamHI and ligated to pBS4S vector digested with BamHI (Ligation kit Ver. 2, using a product available from Takara Bio), and thereby plasmid pBSOAGN was obtained (Fig. 3 shows the construction procedure).

pBSOAGN was introduced into *C. glutamicum* ATCC13869 strain by an electric pulse method (JP02-207791A) and the obtained bacterial cells were applied to CM-Dex agar medium (5g/l glucose, 10g/l polypeptone, 10g/l yeast extract, 1 g/l

KH_2PO_4, 0.4 g/l $MgSO_4{\cdot}7H_2O$, 0.01 g/l $FeSO_4{\cdot}7H_2O$, 0.01 g/l $MnSO_4{\cdot}4\text{-}5H_2O$, 3 g/l urea, 1.2 g/l soybean protein hydrolysate, and 20 g/l agar, pH adjusted to 7.5) containing 25 μg/ml of kanamycin. After culturing at 25°C, it was confirmed by using PCR that the colonies which appeared were once recombinant strains in which pBSOAGN was incorporated by homologous recombination on the chromosome. The PCR was performed using the chromosomal DNA of a candidate strain as template and an oligonucleotide having a nucleotide sequence specific to the sequence of pBS4S (SEQ ID NO: 3) and an oligonucleotide having a nucleotide sequence specific to the sequence on the chromosome (SEQ ID NO: 4) as primers. That is, since the sequence of pBS4S is absent on the chromosome of a non-recombinant strain, no fragment is amplified by PCR if the candidate strain is not a recombinant strain. The obtained once recombinant strains were cultured at 25°C for one day in CM-Dex liquid medium containing 25 μg/ml kanamycin and the obtained culture was diluted appropriately and applied onto S10 plate which has a composition of the above-mentioned CM-Dex medium whereby 5g/l glucose is replaced by 10 g/l of sucrose. Several strains that grew on the S10 plate and showed kanamycin sensitivity were selected, and then the nucleotide sequence of the odhA sequence was confirmed by the method of Sanger (J. Mol. Biol., 143, 161 (1980)). The nucleotide sequence was analyzed by genetic Analyzer ABI310 (manufactured by Applied Biosystems) using BigDye terminator sequencing kit (manufactured by Applied Biyosystems). The thus obtained strain carrying the GN-type mutant odhA gene was named ATCC13869 OAGN.

<3> Introduction of the 2-2 type mutant odhA gene into *C. glutamicum* ATCC13869 strain

Analysis of the nucleotide sequence of the L-glutamic acid-producing “2-2” strain which the inventors of the present invention had succeeded in breeding revealed that the strain contains deletions of the nucleotides 1094 to 1098 and replacement of “ag” at 1110 to 1111 with “ggcc” in the odhA gene (SEQ ID NO: 9) as shown in Table 2. In Table 2, amino acid sequence of mutant E1o subunit encoded by the mutant odhA gene is also shown.

Table 2

Strain	Nucleotide sequence of odhA gene
ATCC13869	AAC TCC TAC GAC GTC ATC GAC GGC AAG CCA ACC CTG
OA2-2	AAC TCC TAC --- CAT CGA CGG CAG GCC CCA ACC CTG
Strain	**Amino acid sequence of E1o subunit**
ATCC13869	Asn Ser Tyr Asp Val Ile Asp Gly Lys Pro Thr Leu
OA2-2	Asn Ser Tyr --- His Arg Arg Gln Ala Pro Thr Leu

Then, this mutant odhA gene was introduced into *C. glutamicum* 2256 strain (ATCC13869) and evaluated. At first, a plasmid for introducing these mutations into *C. glutamicum* 2256 was prepared. A chromosomal DNA was isolated from the 2-2 strain using Bacterial Genomic DNA Purif. Kit (manufactured by MS Technosystems Co., Ltd.) and PCR was performed using this chromosomal DNA as a template and oligonucleotides of SEQ ID NOS: 5 and 6 as primers. PCR was performed using TaKaRa Ex Taq (available from Takara Bio) according to the program of 25 cycles of denaturation at 94°C for 30 seconds, annealing at 55°C for 10 seconds, and elongation at 72°C for 2 minutes to amplify a fragment of about 2.0 kb. The primers contain a BamHI recognition sequence at the 5'-end and designed to amplify the region of nucleotides 51 to 2150 of the nucleotide sequence of GenBank accession No. D84102. The amplified fragment was digested with BamHI and ligated to pBS4S vector digested with BamHI using Ligation kit Ver. 2 of Takara Bio, and thereby the plasmid pBSOA2-2 was obtained (Fig. 4 shows the construction diagram). The same procedure described in Example 1<2> was performed to obtain a strain carrying the 2-2 type mutant odhA gene (ATCC13869 OA2-2 strain).

<4> Introduction of 2-2 type mutation into GN type odhA gene of ATCC13869 OAGN strain

According to the same procedures as described in Example 1<2>, the plasmid pBSOA2-2 constructed in Example 1<3> was introduced into ATCC13869 OAGN strain prepared in Example 1<2> to obtain ATCC13869 strain carrying both the GN type and 2-2 type mutations in odhA gene. Hereinafter, a double mutation consisting of 2-2 type mutation and GN type mutation is also called GN2-2 mutation.

Although the mutant strains were prepared using mutant odhA genes amplified by PCR using a chromosomal DNA from the GN strain or 2-2 strain as a template in Example 1<2> to <4>, they can also be prepared by using mutant odhA genes obtained by site-directed mutagenesis technique such as those using Mutan-Super Express Km kit (Takara Bio). For example, a plasmid having a similar structure to pBSOAGN prepared in Example 1<2> can be obtained as follows. That is, an odhA gene fragment is prepared by PCR using synthetic DNAs of SEQ ID NOS: 2 and 5 as primers and a chromosomal DNA of a wild-type odhA gene as a template, and the resultant PCR fragment is cloned into the BamHI recognition site of plasmid pKF19k attached to Mutan-Super Express Km kit. Next, another PCR is performed using a template of the obtained plasmid and primers of a synthetic DNA of SEQ ID NO: 7 having phosphorylated 5'-end and the selection primer attached to Mutan-Super Express Km kit. Transformation of sup^0 *E. coli*, for example, MV1184 strain (available from Takara Bio) with the obtained PCR product results in construction of a plasmid containing the mutant odhA gene fragment. Finally, the fragment is digested with BamHI and inserted into the pBS4S vector, and thereby a plasmid similar to pBSOAGN can be constructed.

Similarly, to obtain odhA gene containing the 2-2 type mutation, a plasmid similar to pBSOA2-2 can be constructed by using the synthetic DNA of SEQ ID NO: 8 having phosphorylated 5'-end instead of the synthetic DNA of SEQ ID NO: 7 having phosphorylated 5'-end in the procedure as described above.

Furthermore, to obtain odhA gene containing GN2-2 double mutations, a fragment containing the GN-type mutation is excised or PCR-amplified from the above-described plasmid similar to pBSOAGN and used to replace the corresponding fragment on the above-described plasmid similar to pBSOA2-2.

Example 2

Comparison of the ability of strains ATCC13869 OAGN, OA2-2, and OAGN2-2 to degrade glutamic acid

While strains carrying a wild-type odhA gene can assimilate L-glutamic acid in a medium, the strains in which the activity of α-KGDH is weakened or eliminated due to the odhA mutation is presumed to also have a decreased ability to degrade glutamic acid. Then, the ability to degrade glutamic acid was determined using each of the odhA mutant strains ATCC13869 OAGN, OA2-2, and OAGN2-2 prepared in Example 1<2> to <4>. Each strain was cultured on a CM-Dex plate for one day at 25°C and then inoculated into a liquid medium composed of 20 g/l sodium glutamate, 2.64 g/l $(NH_4)_2SO_4$, 0.5 g/l KH_2PO_4, 0.5 g/l K_2HPO_4, 0.25 g/l $MgSO_4 \cdot 7H_2O$, 0.01 g/l $FeSO_4 \cdot 7H_2O$, 0.01 g/l $MnSO_4 \cdot 4\text{-}5H_2O$, 0.01 g/l $CaCl_2$, 0.02 mg/l $CuSO_4$, 40g/l MOPS, 0.03 g/l protocatechinic acid, 200 μg/l vitamin B1, and 300 μg/l biotin (adjusted to pH 6.7 with NaOH), followed by culturing at 25°C and 34°C for 50 hours. The amounts of glutamic acid at the starting point, and after 25 hours and 50 hours of the culture were measured, respectively and the amounts of degraded glutamic acid were compared between the strains cultured at 25°C and 34°C. Table 3 shows the results. In particular, the GN2-2 mutant strain exhibited a significant decrease in the amount of degraded glutamic acid, especially when the culture temperature was 34°C. These results suggest that introduction of the GN2-2 mutation can efficiently reduce the α-KGDH activity and a strain having this mutation is preferably used in L-glutamic acid production.

Table 3: Amount of degraded glutamic acid

Strains	25 Hours		50 Hours	
	25°C	34°C	25°C	34°C
ATCC13869	15	15	15.4	15.4
OAGN	3.8	5.8	9.4	10.0
OA2-2	11.7	15.1	15.4	15.4
OAGN2-2	0.7	0.5	4.9	1.0

(Unit: g/l)

Example 3

Comparison of the α-KGDH activity of ATCC13869 OAGN, OA2-2, and OAGN2-2 strains

The α-KGDH activity of the strains ATCC13869 OAGN, OA2-2, and OAGN2-2 was measured using the culture broth collected after 4 hours from the start of the culture in Example 4 as described below. The activity was measured according to the method described in Agric. Biol. Chem., 44(8), p1897 (1980). Specifically, after bacterial cells were washed with 0.2% sodium chloride, they were suspended in a buffer solution of 100 mM TES-NaOH (pH 7.5) containing 30% glycerol. The bacterial cells were sonicated using Bioruptor (Olympus) and then centrifuged to remove non-ruptured bacterial cells, followed by gel filtration with the same buffer using Sephadex-G25 (Amersham Pharmacia). The thus obtained preparation was used as a crude enzyme solution. The crude enzyme solution was added to a reaction system containing 100 mM TES-NaOH (pH 7.7), 5 mM $MgCl_2$, 0.2 mM CoA, 0.3 mM cocarboxylase; 1 mM α-ketoglutaric acid, 3 mM L-cysteine, and 1 mM acetylpyridine-adenine-dinucleotide and absorption at 365 nm at 31.5°C was measured using Hitachi spectrophotometer U-2001. In the measurement of the protein concentration in the crude enzyme solution, protein Assay (Bio-Rad) was used. Bovine serum albumin was used as a standard protein.

Table 4 shows the results of the measurement of the α-KGDH activity. Introduction of the GN type mutation, 2-2 type mutation, and GN2-2 type mutation leads to a decrease in the α-KGDH as compared to ATCC13869. In particular, in the case of GN2-2 type mutation-introduced strain, a considerable decrease in the activity was observed. This indicates that the GN type mutation, 2-2 type mutation, and GN2-2 type mutation are mutations that reduce the α-KGDH activity.

Table 4: α-KGDH activity

strains	Culture temperature 25°C	Culture temperature 34°C
ATCC13869	0.036	0.021
OAGN	0.001	0.002
OA2-2	0.007	0.009
OAGN2-2	0.001>	0.001>

(Unit: ΔAbs/min/mg protein)

Example 4

Comparison of L-glutamic acid-producing ability of the strains ATCC13869 OAGN, OA2-2, and OAGN2-2

The L-glutamic acid-producing ability of the strains ATCC13869 OAGN, OA2-2, and OAGN2-2 were examined in a jar fermenter culture. First, the above-mentioned four strains were cultured on a CM-Dex agar medium at 25°C for one day and the obtained bacterial cells were inoculated in 300 ml of a sterilized seed medium containing 60 g/l glucose, 1.54 g/l H_3PO_4, 1.45 g/l KOH, 0.9 g/l

$MgSO_4 \cdot 7H_2O$, 0.01 g/l $FeSO_4 \cdot 7H_2O$, 670 μg/l vitamin B1, 3,200 μg/l biotin, 0.28 g/l DL-Met, 1.54 g/l soybean protein hydrolysate, and 0.1 ml/l defoaming agent AZ-20R, and cultured until the sugar was completely consumed. During the culture, the medium was stirred with aeration of 1/1 VVM so that the concentration of dissolved oxygen was maintained not less than 5%. The pH during the culture was controlled to pH 7.2 with ammonia gas. Then, 30 ml of the obtained seed culture was inoculated in 270 ml of a main culture medium containing 80 g/l glucose, 3.46 g/l KH_2PO_4, 1.0 g/l $MgSO_4 \cdot 7H_2O$, 0.01 g/l $FeSO_4 \cdot 7H_2O$, 0.01 g/l $MnSO_4 \cdot 4\text{-}5H_2O$, 230 μg/l vitamin B1, 525 μg/l biotin, 0.35 g/l soybean protein hydrolysate, and 0.2 ml/l defoaming agent AZ-20R, and cultured at 25°C or 34°C. During the culture, aeration was performed as described above. The pH during the culturing was controlled at pH 7.3 with ammonia gas.

Table 5 shows amount of accumulated L-glutamic acid after about 7.5 hours from the start of the culture. Figures 5, 6, and 7 show time courses of L-glutamic acid accumulation, bacterial cell amount, and residual sugar, respectively. ATCC13869 strain did not accumulate L-glutamic acid, whereas OAGN and OAGN2-2 mutant strains accumulated L-glutamic acid. In particular, when these strains were cultured at 34°C, the amounts of accumulated L-glutamic acid significantly increased. Each mutation-introduced strain showed almost the same growth rate as the wild-type strain.

From these results, it was confirmed that the GN type mutation, 2-2 type mutation, and GN2-2 type mutation are effective to increase L-glutamic acid production. Among these mutations, GN2-2 type mutation was found to have the most significant effect on the L-glutamic acid production.

Table 5: Amount of produced L-glutamic acid (Glu) of odhA mutation-introduced strains

Strains	25°C Glu (g/L)	34°C Glu (g/L)
ATCC13869	0.24	0.13
OAGN	0.18	1.88
OA2-2	0.59	4.70
OAGN2-2	0.38	5.13

Example 5

Screening of odhA mutant strains using a yggB mutant strain

<Construction of L30 type yggB mutant strain>

At first, a mutant strain having a mutation in yggB gene was constructed from ATCC13869 strain. The L30 type mutation is a mutation which replaces “C” at position 1768 with “T” in the yggB gene (SEQ ID NO: 29). The mutant yggB gene having the L30 type mutation is shown in SEQ ID NO: 31 and the amino acid sequence encoded by the gene is shown in SEQ ID NO: 32. The mutant yggB gene was constructed by the same method as in Example 1. That is, a fragment encoding the N-terminus portion of the ygg gene was prepared by PCR using primers of SEQ ID NOS: 33 and 34 and a template of chromosomal DNA of the ATCC13869 strain. In a similar way, a fragment encoding the C-terminus portion of the ygg gene was prepared by PCR using primers of SEQ ID NOS: 35 and 36 and a template of chromosomal DNA of the ATCC13869 strain. Subsequently, a fragment of the yggB gene including the L30 type mutation was obtained by PCR using primers of SEQ ID NOS: 37 and 35 and a template of a mixture of equal amounts of the N-terminus fragment and C-terminus fragment. The obtained PCR product is digested by SacI and ligated to SacI-digested pBS4S, and thereby the plasmid for introducing the mutation is obtained (pBS4 yggB-L). The obtained pBS4 yggB-L was integrated into the chromosome of the ATCC13869 strain and then cured from the strain according to a similar method as in Example 1. The nucleotide sequence of yggB gene of the obtained kanamycin-resistant strain is determined and the strain in which yggB gene is replaced with L30 type was selected. The strain having yggB gene of SEQ ID NO: 31 was named ATCC13869-L strain. This strain can be used in the screening of odhA mutant genes.

<Construction of the ygg, odhA double mutant strain>

Then, each of the mutations shown in Table 6 was introduced into the chromosomal odhA gene of ATCC13869-L strain. In Table 6, nucleotide sequences of the region corresponding to nucleotides 2528 to 2562 of SEQ ID NO: 9 of each strain are shown. In Table 7, amino acid sequences of the region corresponding to amino acids 696 to 707 of SEQ ID NO: 10 of each strain are shown.

The L30sucA8 strain in which odhA gene having nucleotide sequence of

SEQ ID NO: 42 is introduced can be obtained as follows. The mutant odhA gene fragment is prepared by PCR using primers of SEQ ID NOS: 2 and 5. The obtained fragment is digested with BamHI and ligated to the BamHI site of plasmid pKF19m which is attached to Mutan-Super Express Km (Takara Bio). Then, PCR is performed using a primer of SEQ ID NO: 38 having a phosphorylated 5'-end and the selection primer of Mutan-Super Express Km, and the obtained PCR product is used to transform sup0-*E. coli* strain such as MV1184 strain to obtain a plasmid containing the mutant odhA fragment. This fragment is inserted into the pBS4S plasmid and the obtained plasmid is used to transform ATCC13869-L strain according to a similar method as in Example 1 to thereby obtain a strain in which the plasmid is integrated into its chromosome. Then, a strain which is resistant to sucrose and sensitive to kanamycin is selected from these strains. The nucleotide sequence of odhA gene of the selected strains is determined and the strain in which function of α-KGDH is deficient by frameshift mutation in odhA gene is selected as ATCC13869-L30sucA8 (odhA8) strain. The other odhA mutant strains can be obtained by the similar procedures using the yggB mutant strain.

sucA801 strain in which a mutant odhA gene having a nucleotide sequence of SEQ ID NO: 44 is introduced can be obtained by a similar method as described above in which a primer of SEQ ID NO: 39 having a phosphorylated 5'-end is used instead of a primer of SEQ ID NO: 38.

sucA805 strain in which a mutant odhA gene having a nucleotide sequence of SEQ ID NO: 46 is introduced can be obtained by a similar method as described above in which a primer of SEQ ID NO: 40 having a phosphorylated 5'-end is used instead of a primer of SEQ ID NO: 38.

sucA77 strain in which a mutant odhA gene having a nucleotide sequence of SEQ ID NO: 48 is introduced can be obtained by a similar method as described above in which a primer of SEQ ID NO: 41 having a phosphorylated 5'-end is used instead of a primer of SEQ ID NO: 38.

The L30sucA8 strain does not have intracellular α-KGDH because the sucA8 mutation is a frame-shift mutation which causes immature truncation of α-KGDH protein. On the other hand, sucA801 strain, sucA805 strain, and sucA77 strain have decreased but some α-KGDH activity because these mutations are not frame-shift mutations and do not cause immature truncation of α-KGDH protein.

Table 6: partial nucleotide acid sequence of odhA mutant genes

Strains	Nucleotide sequence of odhA gene
ATCC13869-L	CTG GCT AAG CTG CGT GGC TAC GAC GTC GGA GGC ACC
L30sucA8	CTG GCT AAG CTG CGT C GAC GTC GGA GGC ACC
L30sucA801	CTG GCT AAG CTG CGT CTC GAC GTC GGA GGC ACC
L30sucA805	CTG GCT AAA AGC TGC GTC GAC GTC GGA GGC ACC
L30sucA77	CTG GCT ATA AGC TGC GTC GAC GTC GGA GGC ACC

Table 7: amino acid sequence of odhA mutants

Strains	Amino acid sequence of E1o subunit
wild	Leu Ala Lys Leu Arg Gly Tyr Asp Val Gly Gly Thr
L30sucA8 (⊿sucA)	Leu Ala Lys Leu Arg Arg Arg Arg Arg His
L30sucA801	Leu Ala Lys Leu Arg --- Leu Asp Val Gly Gly Thr
L30sucA805	Leu Ala Lys Ser Cys --- Val Asp Val Gly Gly Thr
L30sucA77	Leu Ala Ile Ser Cys --- Val Asp Val Gly Gly Thr

<L-glutamic acid production using strains carrying each of the mutant odhA genes>

L-glutamic acid productivity of the obtained odhA mutant strains was evaluated by culturing these strains in Sakaguchi flask. Each of the strains listed in Table 6 was cultured at 31.5°C overnight on CM-Dex agar medium, and then 1/6 of the culture was transferred to 20 ml of a medium containing 60 g/l glucose, 22.5 g/l $(NH_4)_2SO_4$, 1 g/l KH_2PO_4, 0.4 g/l $MgSO_4 \cdot 7H_2O$, 0.01 g/l $FeSO_4 \cdot 7H_2O$, 0.01 g/l $MnSO_4 \cdot 4\text{-}5H_2O$, 200 μg/l vitamin B1, 0.48 g/l soybean protein hydrolysate, and 300 μg/l biotin (adjusted to pH 8.0 with KOH), added with $CaCO_3$ and cultured with stirring at 115rpm at 31.5°C. The amount of accumulated L-glutamic acid after 19 hours of culture was shown in Table 8. The sucA801, sucA805, and sucA77 strains exhibited higher L-glutamic acid productivity than the ATCC13869-L strain carrying a wild-type odhA gene and the sucA8 strain carrying odhA gene with a frame-shift mutation. These results showed that L-glutamic acid is efficiently produced by regulating α-KGDH activity by introducing mutations into the proximate of thiamine pyrophosphate binding region of the odhA gene.

Table 8: L-glutamic acid production by odhA mutant strains

Strain	L-glutamic acid (g/L)
ATCC13869-L	4.9
L30sucA8	19.8
L30sucA801	22.1
L30sucA805	23.8
L30sucA77	21.6

CLAIMS

1. An L-glutamic acid-producing coryneform bacterium comprising

a) intracellular α-ketoglutarate dehydrogenase activity which is less than half that of a non-mutated or wild-type strain, and

b) a mutation in a coding region or an expression control region of a chromosomal odhA gene encoding the E1o subunit of the α-ketoglutarate dehydrogenase complex,

wherein said bacterium grows almost at the same growth rate as a non-mutated or wild-type strain.

2. The coryneform bacterium according to claim 1, wherein said odhA gene encodes a protein selected from the group consisting of:

(A) a protein comprising an amino acid sequence of SEQ ID NO: 10,

(B) a protein comprising an amino acid sequence of SEQ ID NO: 10, whereby one or several amino acids in said protein are substituted, deleted, inserted, or added, and wherein said protein has an activity of the E1o subunit of the α-ketoglutarate dehydrogenase complex,

(C) a protein comprising amino acids 37 to 1257 of SEQ ID NO: 10, and

(D) a protein comprising amino acids 37 to 1257 of SEQ ID NO: 10, whereby one or several amino acids in said protein are substituted, deleted, inserted, or added, and wherein said protein has an activity of the E1o subunit of the α-ketoglutarate dehydrogenase complex.

3. The coryneform bacterium according to claim 2, wherein said several amino acids are 2 to 20 amino acids.

4. The coryneform bacterium according to claim 1, wherein said odhA gene is selected from the group consisting of:

(a) a gene comprising nucleotides 443 to 4213 of SEQ ID NO: 9,

(b) a gene that is able to hybridize under stringent conditions to a polynucleotide comprising nucleotides 443 to 4213 of SEQ ID NO: 9 or a probe prepared from a polynucleotide comprising nucleotides 443 to 4213 of SEQ ID NO: 9, and wherein said gene encodes a protein which has the activity of the E1o subunit of the α-ketoglutarate dehydrogenase complex,

(c) a gene comprising nucleotides 551 to 4213 of SEQ ID NO: 9, and

(d) a gene that is able to hybridize under stringent conditions to a polynucleotide comprising nucleotides 551 to 4213 of SEQ ID NO: 9 or a probe prepared from a polynucleotide comprising nucleotides 551 to 4213 of SEQ ID NO: 9, and wherein said gene encodes a protein which has the activity of the E1o subunit of the α-ketoglutarate dehydrogenase complex.

5. The coryneform bacterium according to any one of claims 1 to 4, wherein said mutation is introduced into a region encoding a thiamine pyrophosphate binding region.

6. The coryneform bacterium according to claim 5, wherein said mutation is introduced into the region comprising nucleotides 2534 to 2548 of SEQ ID NO: 9.

7. The coryneform bacterium according to claim 5, wherein said mutation comprises deletion of one or more amino acids in the region comprising amino acids 698 to 702 of SEQ ID NO: 10.

8. The coryneform bacterium according to claim 5, wherein said mutation comprises replacement of an amino acid selected from the group consisting of Lys at position 698, Leu at position 699, Arg at position 700, Tyr at position 702, and combinations thereof in the amino acid sequence shown in SEQ ID NO: 10.

9. The coryneform bacterium according to any one of claims 1 to 4, wherein said mutation is introduced into the region comprising nucleotides 1094 to 1111 of SEQ ID NO: 9.

10. The coryneform bacterium according to claim 9, wherein said mutation comprises deletion of one or more amino acids in the region comprising amino acids 218 to 224 of SEQ ID NO: 10.

11. A method for producing L-glutamic acid comprising:

a) culturing the coryneform bacterium according to any one of claims 1 to 10 in a culture medium, and

b) collecting L-glutamic acid from the culture medium and/or the bacterium.

12. A gene encoding mutant α-ketoglutarate dehydrogenase selected from the group consisting of:

(a) a gene comprising nucleotides 443 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, or a gene comprising nucleotides 443 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48,

(b) a gene that is able to hybridize under stringent conditions to a polynucleotide comprising nucleotides 443 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, a polynucleotide comprising nucleotides 443 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48, a probe prepared from nucleotides 443 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, or a probe prepared from nucleotides 443 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48, and wherein said gene encodes a protein which has α-ketoglutarate dehydrogenase activity which is less than half that of a wild-type or non-mutated strain by forming a complex with E2o and E3 subunits,

(c) a gene comprising nucleotides 551 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, or a gene comprising nucleotides 551 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48,

(d) a gene that is able to hybridize under stringent conditions to a polynucleotide comprising nucleotides 551 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, a polynucleotide comprising nucleotides 551 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48, or a probe prepared from nucleotides 551 to 4213 of a polynucleotide selected from the group consisting of SEQ ID NO: 11, 13, and 15, or a probe prepared from nucleotides 551 to 4210 of a polynucleotide selected from the group consisting of SEQ ID NO: 44, 46, and 48, and wherein said gene encodes a protein which has α-ketoglutarate dehydrogenase activity which is less than half that of a wild-type or non-mutated strain by forming a complex with E2o and E3 subunits.

13. A mutant α-ketoglutarate dehydrogenase selected from the group consisting of:

(a) a protein selected from the group consisting of SEQ ID NO: 12, 14, 16, 45, 47, and 49,

(b) a protein selected from the group consisting of SEQ ID NO: 12, 14, 16, 45, 47, and 49, whereby one or several amino acids in said protein are substituted, deleted, or added, and wherein said protein exhibits α-ketoglutarate dehydrogenase activity which is less than half that of a wild-type or non-mutated strain by forming a complex with E2o and E3 subunits,

(c) a protein comprising amino acids 37 to 1256 of an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 45, 47, and 49, a protein comprising amino acids 37 to 1255 of an amino acid sequence of SEQ ID NO: 14, or a protein comprising amino acids 37 to 1254 of an amino acid sequence of SEQ ID NO: 16, and

(d) a protein comprising amino acids 37 to 1256 of an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 45, 47, and 49, a protein comprising amino acids 37 to 1255 of an amino acid sequence of SEQ ID NO: 14, or a protein comprising amino acids 37 to 1254 of an amino acid sequence of SEQ ID NO: 16, whereby one or several amino acids in said protein are substituted, deleted, or added, and wherein said protein exhibits α-ketoglutarate dehydrogenase activity which is less than half that of a wild-type or non-mutated strain by forming a complex with E2o and E3 subunits.

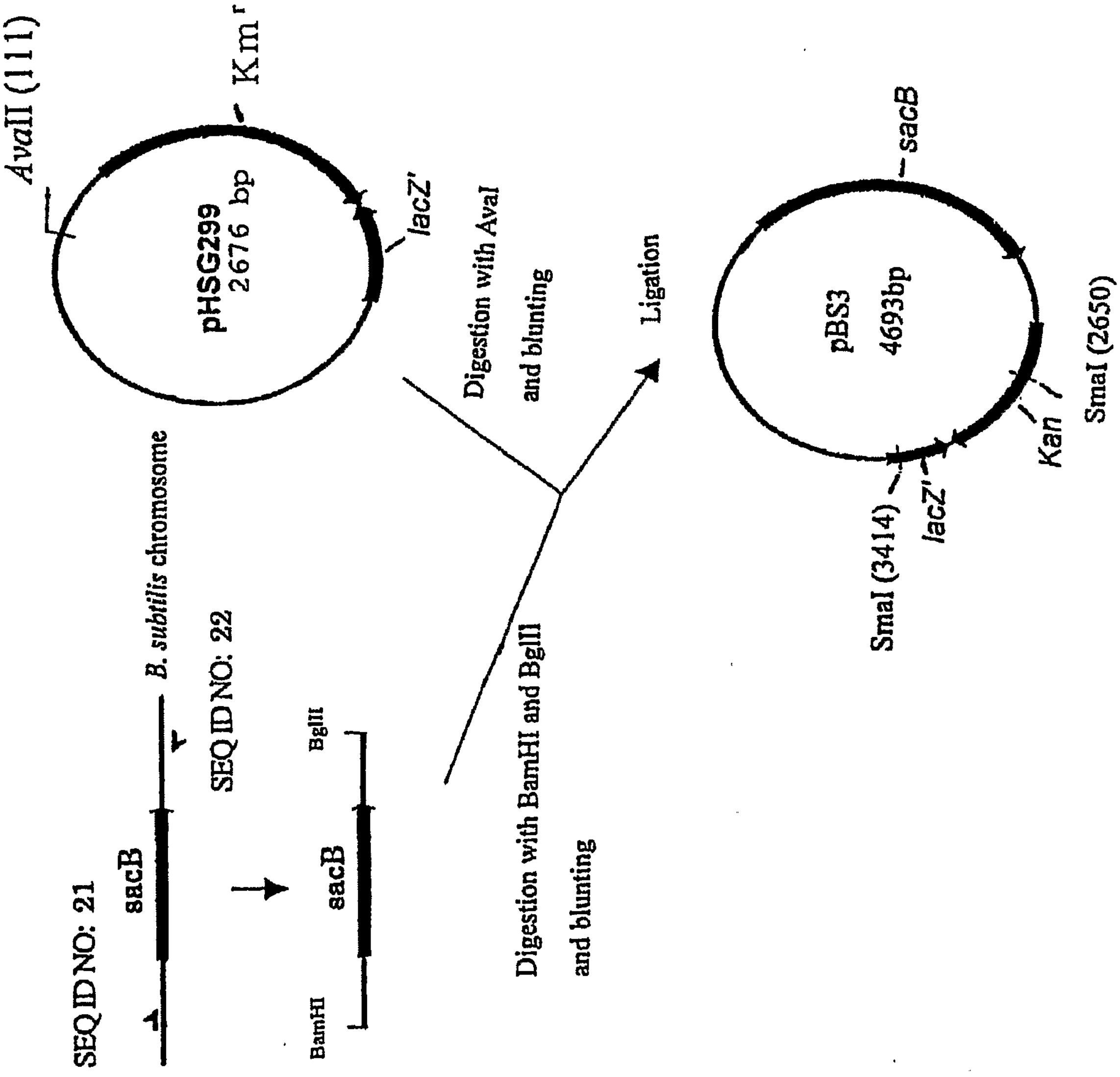

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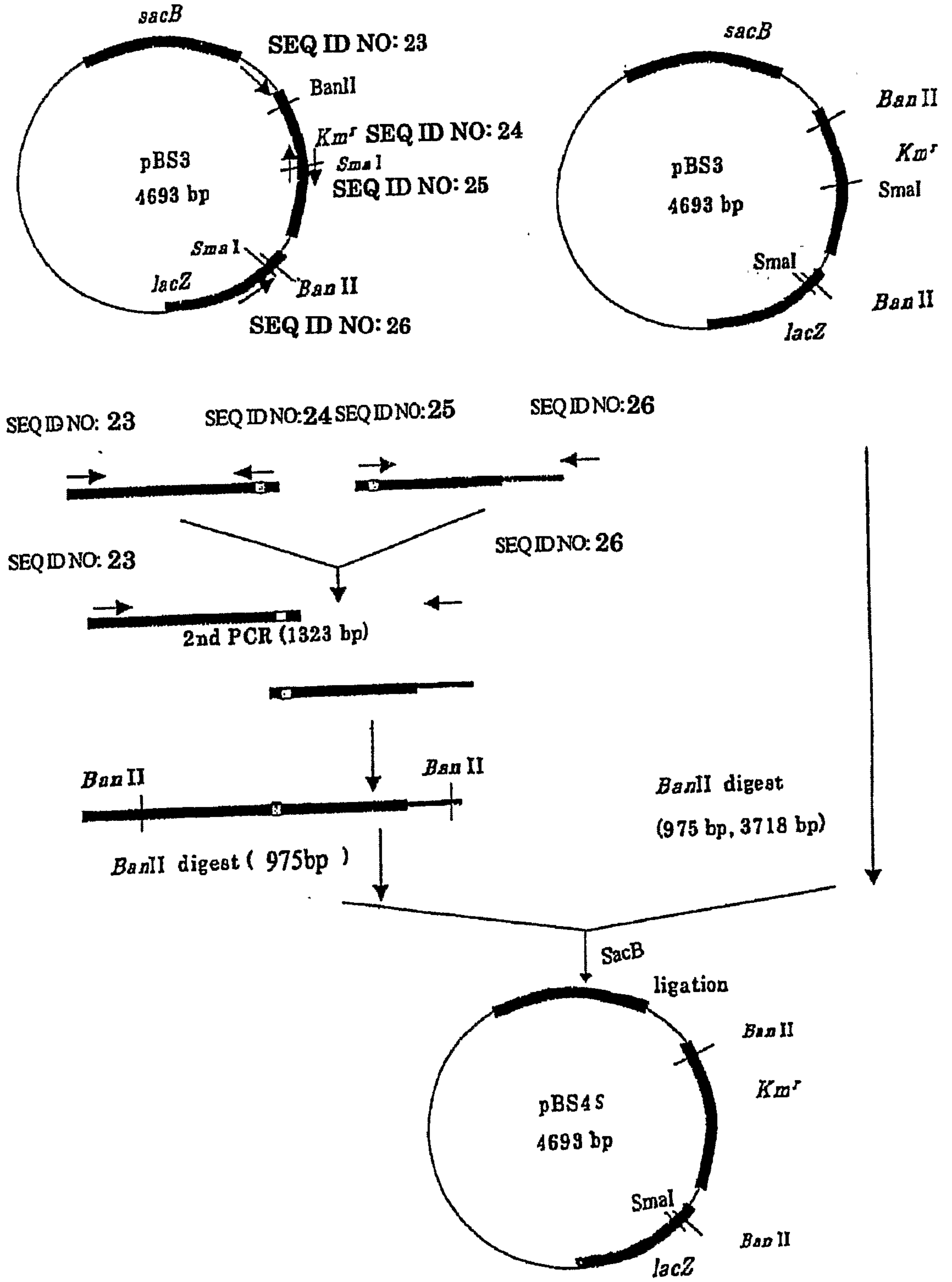
Figure 1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lacZ
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BanII
BanII digest (975bp)
BanII digest
(975 bp, 3718 bp)
SacB
ligation
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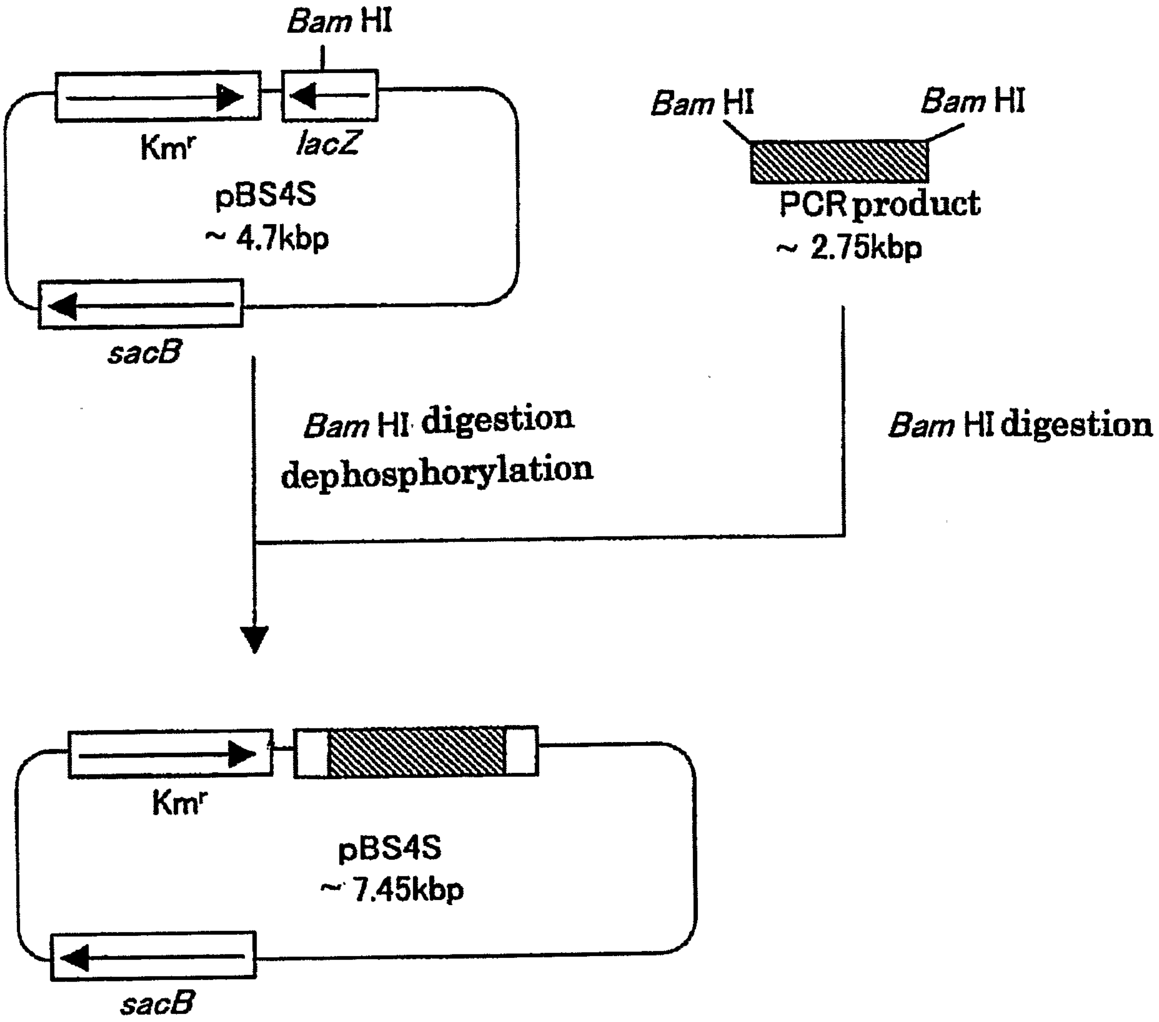
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sacB
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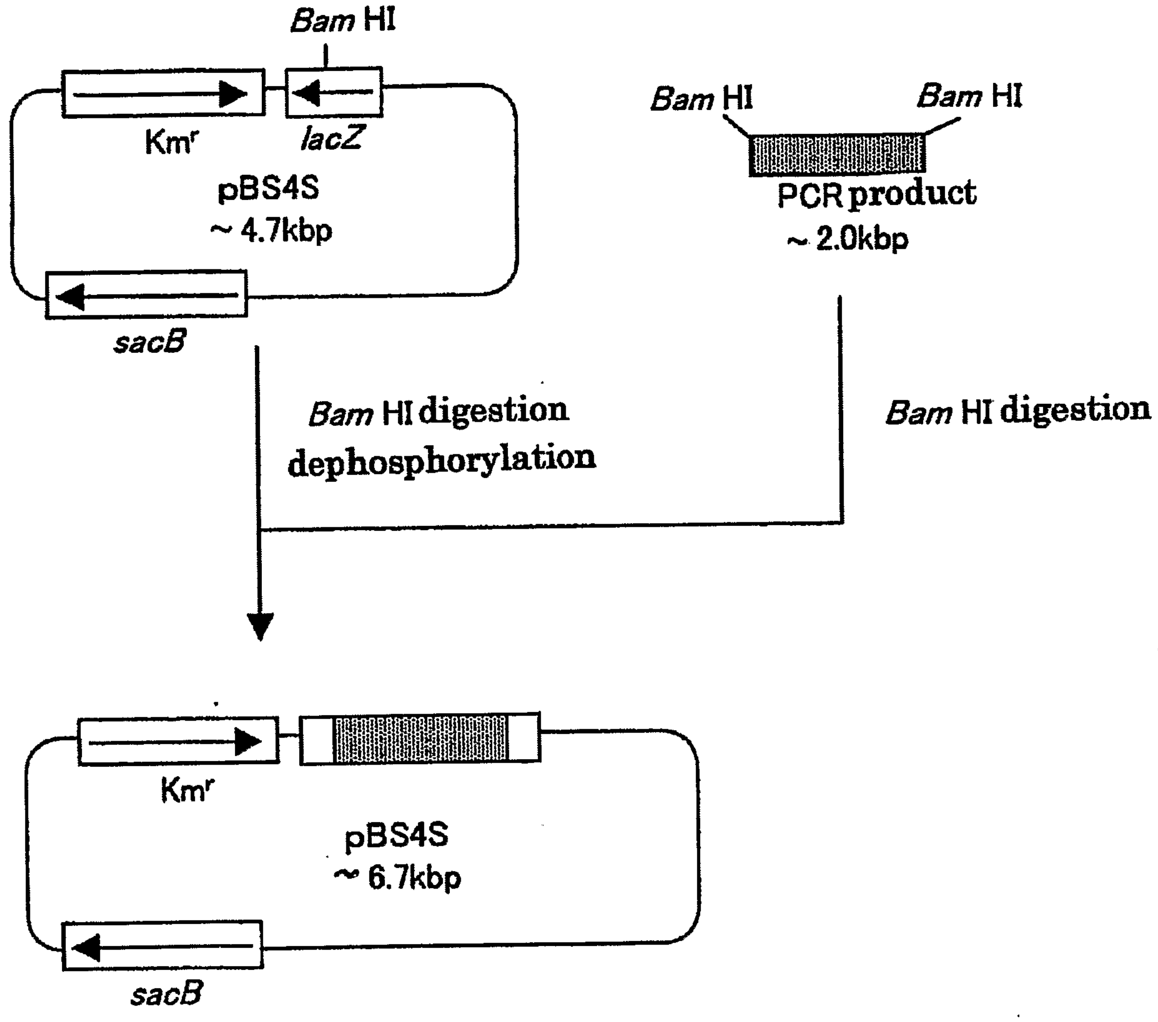
Figure 3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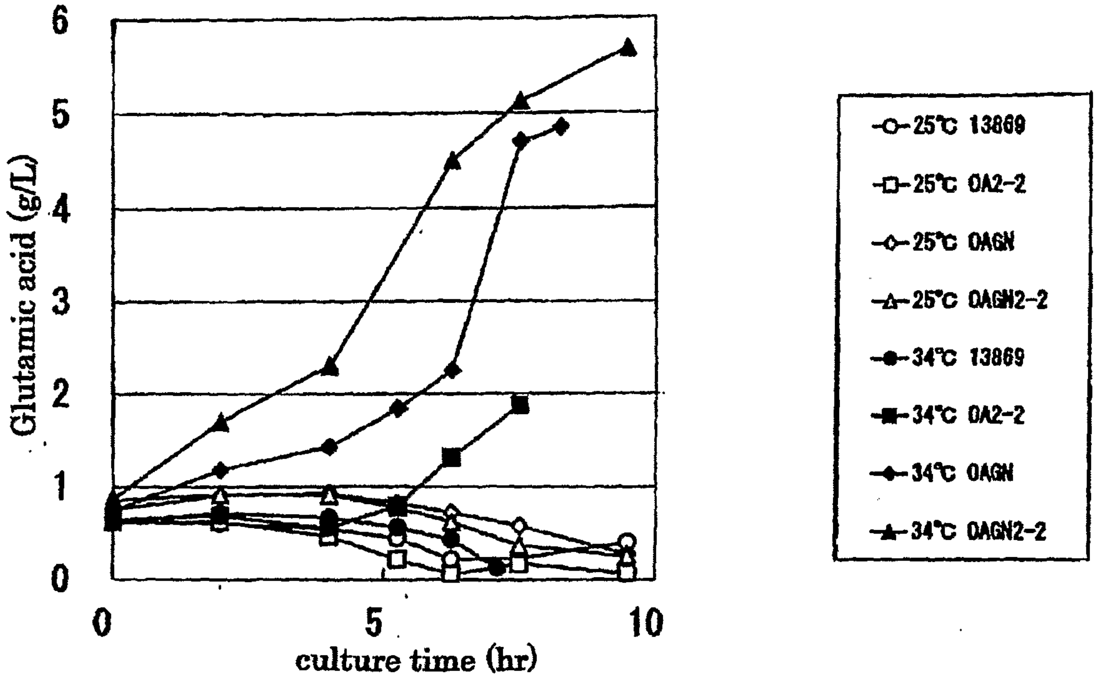

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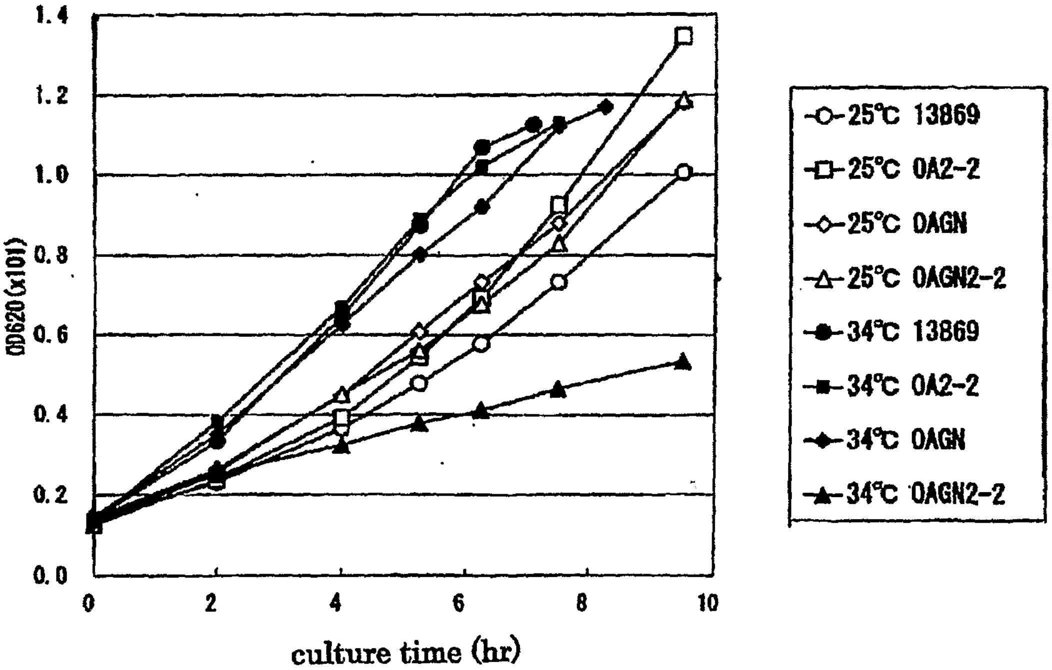
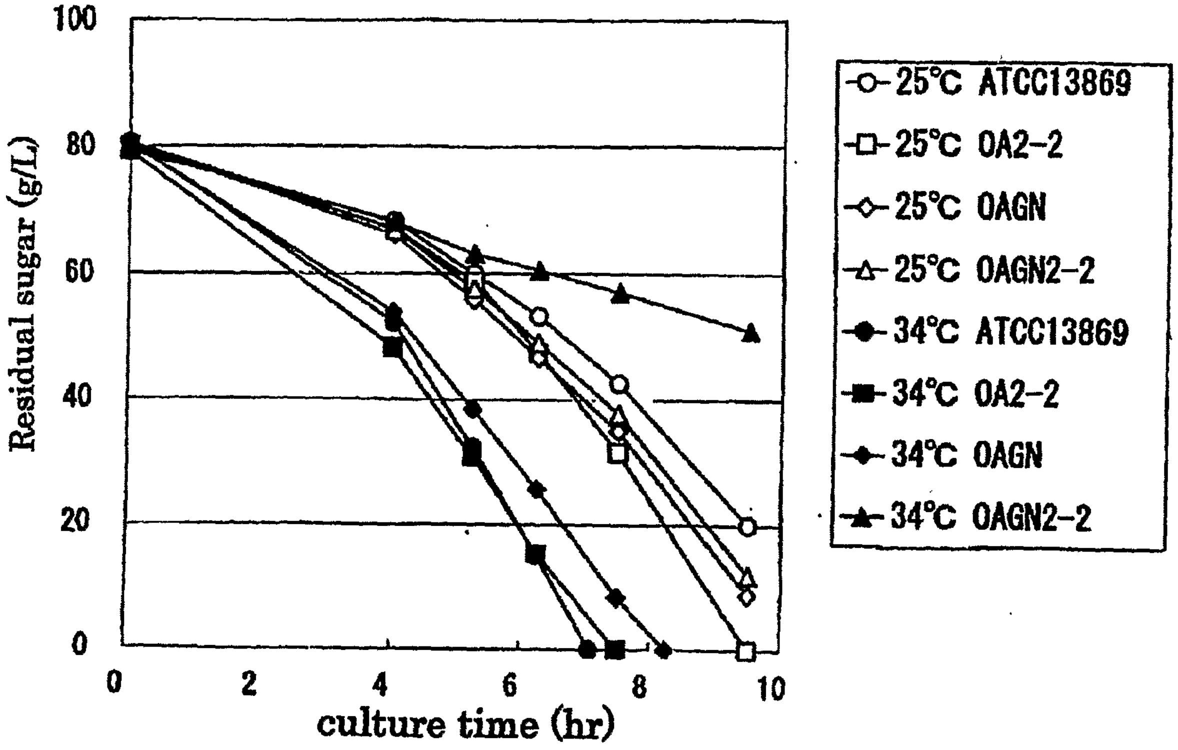


Figure 6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6
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10
culture time (hr)
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-□- 25°C OA2-2
-◇- 25°C OAGN
-△- 25°C OAGN2-2
-●- 34°C ATCC13869
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Figure 7

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Ile Gly Gly Ser Gly Asp Val Lys Tyr His Leu Gly Ser Glu Gly Gln
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His Leu Gln Met Phe Gly Asp Gly Glu Ile Lys Val Ser Leu Thr Ala
625                 630                 635                 640
Asn Pro Ser His Leu Glu Ala Val Asn Pro Val Met Glu Gly Ile Val
                645                 650                 655
Arg Ala Lys Gln Asp Tyr Leu Asp Lys Gly Val Asp Gly Lys Thr Val
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Val Pro Leu Leu Leu His Gly Asp Ala Ala Phe Ala Gly Leu Gly Ile
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Val Pro Glu Thr Ile Asn Leu Ala Lys Leu Arg Gly Tyr Asp Val Gly
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Gly Thr Ile His Ile Val Val Asn Asn Gln Ile Gly Phe Thr Thr Thr
705                 710                 715                 720
Pro Asp Ser Ser Arg Ser Met His Tyr Ala Thr Asp Tyr Ala Lys Ala
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Phe Gly Cys Pro Val Phe His Val Asn Gly Asp Asp Pro Glu Ala Val
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Val Trp Val Gly Gln Leu Ala Thr Glu Tyr Arg Arg Arg Phe Gly Lys
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Asp Val Phe Ile Asp Leu Val Cys Tyr Arg Leu Arg Gly His Asn Glu
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Gln Ala Glu Ala Gln Thr Gly Ile Thr Gly Ser Gln Lys Leu Pro His
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Pro Val Ala Lys Lys Arg Val Ser Ser Val Thr Glu Gly Gly Ile Asp
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Trp Ala Trp Gly Glu Leu Leu Ala Phe Gly Ser Leu Ala Asn Ser Gly
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Gln Arg His Ala Val Ala Ile Asp Pro Ala Thr Ala Glu Glu Phe Asn
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980 985 990
Gly Tyr Ser Val Gly Asn Glu Asp Ser Val Val Ala Trp Glu Ala Gln
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Phe Gly Asp Phe Ala Asn Gly Ala Gln Thr Ile Ile Asp Glu Tyr
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Pro Glu Asp Phe Thr Glu Val Thr Lys Phe Gln Ser Val Ile Asp
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Asp Pro Asn Val Ala Asp Ala Ala Lys Val Lys Lys Val Met Leu
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Val Ser Gly Lys Leu Tyr Tyr Glu Leu Ala Lys Arg Lys Glu Lys
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Asp Gly Arg Asp Asp Ile Ala Ile Val Arg Ile Glu Met Leu His

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gttgtctgct aacggcacct acgccccgcat gtggcattta atggcctgac acgttatttt 420
taggagaact gtcaacaaat ta atg cta caa ctg ggg ctt agg cat aat cag 472
Met Leu Gln Leu Gly Leu Arg His Asn Gln
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Pro Thr Thr Asn Val Thr Val Asp Lys Ile Lys Leu Asn Lys Pro Ser
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Arg Ser Lys Glu Lys Arg Arg Val Pro Ala Val Ser Ser Ala Ser Thr
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Phe Gly Gln Asn Ala Trp Leu Val Asp Glu Met Phe Gln Gln Phe Gln
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Lys Asp Pro Lys Ser Val Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala
60 65 70

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Gln Gly Gly Pro Asn Ala Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser
75                  80                  85                  90
gcg ccc aag gag tct gcg aaa cca gca cca aag gct gcc cct gca gcc      760
Ala Pro Lys Glu Ser Ala Lys Pro Ala Pro Lys Ala Ala Pro Ala Ala
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aag gca gca ccg cgc gta gaa acc aag ccg gcc gcc aag acc gcc cct      808
Lys Ala Ala Pro Arg Val Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro
            110                 115                 120
aag gcc aag gag tcc tca gtg cca cag caa cct aag ctt ccg gag cca      856
Lys Ala Lys Glu Ser Ser Val Pro Gln Gln Pro Lys Leu Pro Glu Pro
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gga caa acc cca atc agg ggt att ttc aag tcc atc gcg aag aac atg      904
Gly Gln Thr Pro Ile Arg Gly Ile Phe Lys Ser Ile Ala Lys Asn Met
    140                 145                 150
gat atc tcc ctg gaa atc cca acc gca acc tcg gtt cgc gat atg cca      952
Asp Ile Ser Leu Glu Ile Pro Thr Ala Thr Ser Val Arg Asp Met Pro
155                 160                 165                 170
gct cgc ctc atg ttc gaa aac cgc gcg atg gtc aac gat cag ctc aag      1000
Ala Arg Leu Met Phe Glu Asn Arg Ala Met Val Asn Asp Gln Leu Lys
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cgc acc cgc ggt ggc aag atc tcc ttc acc cac atc att ggc tac gcc      1048
Arg Thr Arg Gly Gly Lys Ile Ser Phe Thr His Ile Ile Gly Tyr Ala
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atg gtg aag gca gtc atg gct cac ccg gac atg aac aac tcc tac gac      1096
Met Val Lys Ala Val Met Ala His Pro Asp Met Asn Asn Ser Tyr Asp
        205                 210                 215
gtc atc gac ggc aag cca acc ctg atc gtg cct gag cac atc aac ctg      1144
Val Ile Asp Gly Lys Pro Thr Leu Ile Val Pro Glu His Ile Asn Leu
    220                 225                 230
ggc ctt gcc atc gac ctt cct cag aag gac ggc tcc cgc gca ctt gtc      1192
Gly Leu Ala Ile Asp Leu Pro Gln Lys Asp Gly Ser Arg Ala Leu Val
235                 240                 245                 250
gta gca gcc atc aag gaa acc gag aag atg aac ttc tcc gag ttc ctc      1240
Val Ala Ala Ile Lys Glu Thr Glu Lys Met Asn Phe Ser Glu Phe Leu
                255                 260                 265
gca gca tac gaa gac atc gtg aca cgc tcc cgc aag ggc aag ctc acc      1288
Ala Ala Tyr Glu Asp Ile Val Thr Arg Ser Arg Lys Gly Lys Leu Thr
            270                 275                 280
atg gat gac tac cag ggc gtt acc gtt tcc ttg acc aac cca ggt ggc      1336
Met Asp Asp Tyr Gln Gly Val Thr Val Ser Leu Thr Asn Pro Gly Gly
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atc ggt acc cgc cac tct gtc cca cgt ctg acc aag ggc cag ggc acc      1384
Ile Gly Thr Arg His Ser Val Pro Arg Leu Thr Lys Gly Gln Gly Thr
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atc atc ggt gtc ggt tcc atg gat tac cca gca gag ttc cag ggc gct      1432
Ile Ile Gly Val Gly Ser Met Asp Tyr Pro Ala Glu Phe Gln Gly Ala
315                 320                 325                 330
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Ser Glu Asp Arg Leu Ala Glu Leu Gly Val Gly Lys Leu Val Thr Ile
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cc tcc acc tac gat cac cgc gtg atc cag ggt gct gtg tcc ggt gaa 1528
Thr Ser Thr Tyr Asp His Arg Val Ile Gln Gly Ala Val Ser Gly Glu
350 355 360

ttc ctg cgt acc atg tct cgc ctg ctc acc gat gat tcc ttc tgg gat 1576
Phe Leu Arg Thr Met Ser Arg Leu Leu Thr Asp Asp Ser Phe Trp Asp
365 370 375

gag atc ttc gac gca atg aac gtt cct tac acc cca atg cgt tgg gca 1624
Glu Ile Phe Asp Ala Met Asn Val Pro Tyr Thr Pro Met Arg Trp Ala
380 385 390

cag gac gtt cca aac acc ggt gtt gat aag aac acc cgc gtc atg cag 1672
Gln Asp Val Pro Asn Thr Gly Val Asp Lys Asn Thr Arg Val Met Gln
395 400 405 410

ctc att gag gca tac cgc tcc cgt gga cac ctc atc gct gac acc aac 1720
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415 420 425

cca ctt tca tgg gtt cag cct ggc atg cca gtt cca gac cac cgc gac 1768
Pro Leu Ser Trp Val Gln Pro Gly Met Pro Val Pro Asp His Arg Asp
430 435 440

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Leu Asp Ile Glu Thr His Ser Leu Thr Ile Trp Asp Leu Asp Arg Thr
445 450 455

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Phe Ser Val Gly Gly Phe Gly Gly Lys Glu Thr Met Thr Leu Arg Glu
460 465 470

gta ctg tcc cgc ctg cgc gct gcc tac acc ttg aag gtc ggc tcc gaa 1912
Val Leu Ser Arg Leu Arg Ala Ala Tyr Thr Leu Lys Val Gly Ser Glu
475 480 485 490

tac acc cac atc ctg gac cgc gac gag cgc acc tgg ctg cag gac cgc 1960
Tyr Thr His Ile Leu Asp Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg
495 500 505

ctc gaa gcc gga atg cca aag cca acc cag gca gag cag aag tac atc 2008
Leu Glu Ala Gly Met Pro Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile
510 515 520

ctg cag aag ctg aac gcc gca gag gct ttc gag aac ttc ctg cag acc 2056
Leu Gln Lys Leu Asn Ala Ala Glu Ala Phe Glu Asn Phe Leu Gln Thr
525 530 535

aag tac gtc ggc cag aag cgc ttc tcc ctc gaa ggt gca gaa gct ctc 2104
Lys Tyr Val Gly Gln Lys Arg Phe Ser Leu Glu Gly Ala Glu Ala Leu
540 545 550

atc cca ctg atg gac tcc gcc atc gac acc gcc gca ggc cag ggc ctc 2152
Ile Pro Leu Met Asp Ser Ala Ile Asp Thr Ala Ala Gly Gln Gly Leu
555 560 565 570

gac gaa gtt gtc atc ggt atg cca cac cgt ggt cgc ctc aac gtg ctg 2200
Asp Glu Val Val Ile Gly Met Pro His Arg Gly Arg Leu Asn Val Leu
575 580 585

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Phe Asn Ile Val Gly Lys Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu
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ggc caa atg gag cag ggc cag atc ggt ggc tcc ggt gac gtg aag tac     2296
Gly Gln Met Glu Gln Gly Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr
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cac ctc ggt tcc gaa ggc cag cac ctg cag atg ttc ggc gac ggc gag     2344
His Leu Gly Ser Glu Gly Gln His Leu Gln Met Phe Gly Asp Gly Glu
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atc aag gtc tcc ctg act gct aac ccg tcc cac ctg gaa gct gtt aac     2392
Ile Lys Val Ser Leu Thr Ala Asn Pro Ser His Leu Glu Ala Val Asn
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cca gtg atg gaa ggt atc gtc cgc gca aag cag gac tac ctg gac aag     2440
Pro Val Met Glu Gly Ile Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys
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ggc gta gac ggc aag act gtt gtg cca ctg ctg ctc cac ggt gac gct     2488
Gly Val Asp Gly Lys Thr Val Val Pro Leu Leu Leu His Gly Asp Ala
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gca ttc gca ggc ctg ggc atc gtg cca gaa acc atc aac ctg gct aag     2536
Ala Phe Ala Gly Leu Gly Ile Val Pro Glu Thr Ile Asn Leu Ala Lys
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cgc gtc gac gtc gga ggc acc atc cac atc gtg gtg aac aac cag atc     2584
Arg Val Asp Val Gly Gly Thr Ile His Ile Val Val Asn Asn Gln Ile
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ggc ttc acc acc acc cca gac tcc agc cgc tcc atg cac tac gca acc     2632
Gly Phe Thr Thr Thr Pro Asp Ser Ser Arg Ser Met His Tyr Ala Thr
715                 720                 725                 730
gac tac gcc aag gca ttc ggc tgc cca gtc ttc cac gtc aat ggt gat     2680
Asp Tyr Ala Lys Ala Phe Gly Cys Pro Val Phe His Val Asn Gly Asp
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Asp Pro Glu Ala Val Val Trp Val Gly Gln Leu Ala Thr Glu Tyr Arg
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cgt cgc ttc ggc aag gac gtc ttc atc gac ctc gtt tgc tac cgc ctc     2776
Arg Arg Phe Gly Lys Asp Val Phe Ile Asp Leu Val Cys Tyr Arg Leu
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cgc ggc cac aac gaa gct gat gat cct tcc atg acc cag cca aag atg     2824
Arg Gly His Asn Glu Ala Asp Asp Pro Ser Met Thr Gln Pro Lys Met
    780                 785                 790
tat gag ctc atc acc ggc cgc gag acc gtt cgt gct cag tac acc gaa     2872
Tyr Glu Leu Ile Thr Gly Arg Glu Thr Val Arg Ala Gln Tyr Thr Glu
795                 800                 805                 810
gac ctg ctc gga cgt gga gac ctc tcc aac gaa gat gca gaa gca gtc     2920
Asp Leu Leu Gly Arg Gly Asp Leu Ser Asn Glu Asp Ala Glu Ala Val
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gtc cgc gac ttc cac gac cag atg gaa tct gtg ttc aac gaa gtc aag     2968
Val Arg Asp Phe His Asp Gln Met Glu Ser Val Phe Asn Glu Val Lys
            830                 835                 840
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gaa ggc ggc aag aag cag gct gag gca cag acc ggc atc acc ggc tcc 3016
Glu Gly Gly Lys Lys Gln Ala Glu Ala Gln Thr Gly Ile Thr Gly Ser
845 850 855

cag aag ctt cca cac ggc ctt gag acc aac atc tcc cgt gaa gag ctc 3064
Gln Lys Leu Pro His Gly Leu Glu Thr Asn Ile Ser Arg Glu Glu Leu
860 865 870

ctg gaa ctg gga cag gct ttc gcc aac acc cca gaa ggc ttc aac tac 3112
Leu Glu Leu Gly Gln Ala Phe Ala Asn Thr Pro Glu Gly Phe Asn Tyr
875 880 885 890

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His Pro Arg Val Ala Pro Val Ala Lys Lys Arg Val Ser Ser Val Thr
895 900 905

gaa ggt ggc atc gac tgg gca tgg ggc gag ctc ctc gcc ttc ggt tcc 3208
Glu Gly Gly Ile Asp Trp Ala Trp Gly Glu Leu Leu Ala Phe Gly Ser
910 915 920

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Leu Ala Asn Ser Gly Arg Leu Val Arg Leu Ala Gly Glu Asp Ser Arg
925 930 935

cgc ggt acc ttc acc cag cgc cac gca gtt gcc atc gac cca gcg acc 3304
Arg Gly Thr Phe Thr Gln Arg His Ala Val Ala Ile Asp Pro Ala Thr
940 945 950

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Met Gly Phe Glu Tyr Gly Tyr Ser Val Gly Asn Glu Asp Ser Val Val
990 995 1000

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Cys Ala Glu Gly Ser Met Thr Val Ala Gln Pro Ser Thr Pro Ala
1065 1070 1075

aac cac ttc cac ctg ctg cgt cgt cac gct ctg tcc gac ctg aag 3718
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1080 1085 1090

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Ala Ala Ala  Ser Ala Pro Glu Asp  Phe Thr Glu Val Thr  Lys Phe
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Gln Ser Val  Ile Asp Asp Pro Asn  Val Ala Asp Ala Ala  Lys Val
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Lys Lys Val  Met Leu Val Ser Gly  Lys Leu Tyr Tyr Glu  Leu Ala
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Lys Arg Lys  Glu Lys Asp Gly Arg  Asp Asp Ile Ala Ile  Val Arg
        1155                 1160                 1165
atc gaa atg  ctc cac cca att ccg  ttc aac cgc atc tcc  gag gct      3988
Ile Glu Met  Leu His Pro Ile Pro  Phe Asn Arg Ile Ser  Glu Ala
        1170                 1175                 1180
ctt gcc ggc  tac cct aac gct gag  gaa gtc ctc ttc gtt  cag gat      4033
Leu Ala Gly  Tyr Pro Asn Ala Glu  Glu Val Leu Phe Val  Gln Asp
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Glu Pro Ala  Asn Gln Gly Pro Trp  Pro Phe Tyr Gln Glu  His Leu
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cca gag ctg  atc ccg aac atg cca  aag atg cgc cgc gtt  tcc cgc      4123
Pro Glu Leu  Ile Pro Asn Met Pro  Lys Met Arg Arg Val  Ser Arg
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cgc gct cag  tcc tcc acc gca act  ggt gtt gct aag gtg  cac cag      4168
Arg Ala Gln  Ser Ser Thr Ala Thr  Gly Val Ala Lys Val  His Gln
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Leu Glu Glu  Lys Gln Leu Ile Asp  Glu Ala Phe Glu Ala      Val
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Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala Gln Gly Gly Pro Asn Ala
65                  70                  75                  80
Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser Ala Pro Lys Glu Ser Ala
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Lys Pro Ala Pro Lys Ala Ala Pro Ala Ala Lys Ala Ala Pro Arg Val
            100                 105                 110
Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro Lys Ala Lys Glu Ser Ser
        115                 120                 125
Val Pro Gln Gln Pro Lys Leu Pro Glu Pro Gly Gln Thr Pro Ile Arg
    130                 135                 140
Gly Ile Phe Lys Ser Ile Ala Lys Asn Met Asp Ile Ser Leu Glu Ile
145                 150                 155                 160
Pro Thr Ala Thr Ser Val Arg Asp Met Pro Ala Arg Leu Met Phe Glu
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Asn Arg Ala Met Val Asn Asp Gln Leu Lys Arg Thr Arg Gly Gly Lys
            180                 185                 190
Ile Ser Phe Thr His Ile Ile Gly Tyr Ala Met Val Lys Ala Val Met
        195                 200                 205
Ala His Pro Asp Met Asn Asn Ser Tyr Asp Val Ile Asp Gly Lys Pro
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Thr Leu Ile Val Pro Glu His Ile Asn Leu Gly Leu Ala Ile Asp Leu
225                 230                 235                 240
Pro Gln Lys Asp Gly Ser Arg Ala Leu Val Val Ala Ala Ile Lys Glu
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Val Thr Arg Ser Arg Lys Gly Lys Leu Thr Met Asp Asp Tyr Gln Gly
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Val Pro Arg Leu Thr Lys Gly Gln Gly Thr Ile Ile Gly Val Gly Ser
305                 310                 315                 320
Met Asp Tyr Pro Ala Glu Phe Gln Gly Ala Ser Glu Asp Arg Leu Ala
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Glu Leu Gly Val Gly Lys Leu Val Thr Ile Thr Ser Thr Tyr Asp His
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Arg Val Ile Gln Gly Ala Val Ser Gly Glu Phe Leu Arg Thr Met Ser
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Arg Leu Leu Thr Asp Asp Ser Phe Trp Asp Glu Ile Phe Asp Ala Met
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Ser Leu Thr Ile Trp Asp Leu Asp Arg Thr Phe Ser Val Gly Gly Phe
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Gly Gly Lys Glu Thr Met Thr Leu Arg Glu Val Leu Ser Arg Leu Arg
465                 470                 475                 480
Ala Ala Tyr Thr Leu Lys Val Gly Ser Glu Tyr Thr His Ile Leu Asp
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Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg Leu Glu Ala Gly Met Pro
            500                 505                 510
Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile Leu Gln Lys Leu Asn Ala
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Ala Glu Ala Phe Glu Asn Phe Leu Gln Thr Lys Tyr Val Gly Gln Lys
    530                 535                 540
Arg Phe Ser Leu Glu Gly Ala Glu Ala Leu Ile Pro Leu Met Asp Ser
545                 550                 555                 560
Ala Ile Asp Thr Ala Ala Gly Gln Gly Leu Asp Glu Val Val Ile Gly
                565                 570                 575
Met Pro His Arg Gly Arg Leu Asn Val Leu Phe Asn Ile Val Gly Lys
            580                 585                 590
Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu Gly Gln Met Glu Gln Gly
        595                 600                 605
Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr His Leu Gly Ser Glu Gly
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Gln His Leu Gln Met Phe Gly Asp Gly Glu Ile Lys Val Ser Leu Thr
625                 630                 635                 640
Ala Asn Pro Ser His Leu Glu Ala Val Asn Pro Val Met Glu Gly Ile
                645                 650                 655
Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys Gly Val Asp Gly Lys Thr
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Val Val Pro Leu Leu Leu His Gly Asp Ala Ala Phe Ala Gly Leu Gly
        675                 680                 685
Ile Val Pro Glu Thr Ile Asn Leu Ala Lys Arg Val Asp Val Gly Gly
    690                 695                 700
Thr Ile His Ile Val Val Asn Asn Gln Ile Gly Phe Thr Thr Thr Pro
705                 710                 715                 720
Asp Ser Ser Arg Ser Met His Tyr Ala Thr Asp Tyr Ala Lys Ala Phe
                725                 730                 735
Gly Cys Pro Val Phe His Val Asn Gly Asp Asp Pro Glu Ala Val Val
            740                 745                 750
Trp Val Gly Gln Leu Ala Thr Glu Tyr Arg Arg Arg Phe Gly Lys Asp
        755                 760                 765
Val Phe Ile Asp Leu Val Cys Tyr Arg Leu Arg Gly His Asn Glu Ala
    770                 775                 780
Asp Asp Pro Ser Met Thr Gln Pro Lys Met Tyr Glu Leu Ile Thr Gly
785                 790                 795                 800
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Asp Leu Ser Asn Glu Asp Ala Glu Ala Val Val Arg Asp Phe His Asp
820 825 830
Gln Met Glu Ser Val Phe Asn Glu Val Lys Glu Gly Gly Lys Lys Gln
835 840 845
Ala Glu Ala Gln Thr Gly Ile Thr Gly Ser Gln Lys Leu Pro His Gly
850 855 860
Leu Glu Thr Asn Ile Ser Arg Glu Glu Leu Leu Glu Leu Gly Gln Ala
865 870 875 880
Phe Ala Asn Thr Pro Glu Gly Phe Asn Tyr His Pro Arg Val Ala Pro
885 890 895
Val Ala Lys Lys Arg Val Ser Ser Val Thr Glu Gly Gly Ile Asp Trp
900 905 910
Ala Trp Gly Glu Leu Leu Ala Phe Gly Ser Leu Ala Asn Ser Gly Arg
915 920 925
Leu Val Arg Leu Ala Gly Glu Asp Ser Arg Arg Gly Thr Phe Thr Gln
930 935 940
Arg His Ala Val Ala Ile Asp Pro Ala Thr Ala Glu Glu Phe Asn Pro
945 950 955 960
Leu His Glu Leu Ala Gln Ser Lys Gly Asn Asn Gly Lys Phe Leu Val
965 970 975
Tyr Asn Ser Ala Leu Thr Glu Tyr Ala Gly Met Gly Phe Glu Tyr Gly
980 985 990
Tyr Ser Val Gly Asn Glu Asp Ser Val Val Ala Trp Glu Ala Gln Phe
995 1000 1005
Gly Asp Phe Ala Asn Gly Ala Gln Thr Ile Ile Asp Glu Tyr Val
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Ser Ser Gly Glu Ala Lys Trp Gly Gln Thr Ser Lys Leu Ile Leu
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Ala Arg Ile Glu Arg Phe Leu Gln Leu Cys Ala Glu Gly Ser Met
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Glu Asp Phe Thr Glu Val Thr Lys Phe Gln Ser Val Ile Asp Asp
1115 1120 1125
Pro Asn Val Ala Asp Ala Ala Lys Val Lys Lys Val Met Leu Val
1130 1135 1140
Ser Gly Lys Leu Tyr Tyr Glu Leu Ala Lys Arg Lys Glu Lys Asp
1145 1150 1155
Gly Arg Asp Asp Ile Ala Ile Val Arg Ile Glu Met Leu His Pro
1160 1165 1170

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Ile Pro Phe Asn Arg Ile Ser Glu Ala Leu Ala Gly Tyr Pro Asn
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Ala Glu Glu Val Leu Phe Val Gln Asp Glu Pro Ala Asn Gln Gly
    1190                1195                1200
Pro Trp Pro Phe Tyr Gln Glu His Leu Pro Glu Leu Ile Pro Asn
    1205                1210                1215
Met Pro Lys Met Arg Arg Val Ser Arg Arg Ala Gln Ser Ser Thr
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Ile Asp Glu Ala Phe Glu Ala
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gcgccaactg atcgcgctgg cgcgcgccga actcatcgag ccttccatca tgcttctcga     180
cgaagccacc tccaccctcg accccgccac cgaagccgtt atcctcaacg cctccgatcg     240
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cgaccgtatt cttgttgttg aacaaggacg tatcattgag gacggatctc acgacgcgtt     360
gttgtctgct aacggcacct acgccccgcat gtggcattta atggcctgac acgttatttt     420
taggagaact gtcaacaaat ta atg cta caa ctg ggg ctt agg cat aat cag      472
                         Met Leu Gln Leu Gly Leu Arg His Asn Gln
                         1               5                   10

cca acg acc aac gtt aca gtg gat aaa ata aag ctc aat aaa ccc tca      520
Pro Thr Thr Asn Val Thr Val Asp Lys Ile Lys Leu Asn Lys Pro Ser
                15                  20                  25

aga agc aag gaa aag agg cga gta cct gcc gtg agc agc gct agt act      568
Arg Ser Lys Glu Lys Arg Arg Val Pro Ala Val Ser Ser Ala Ser Thr
            30                  35                  40

ttc ggc cag aat gcg tgg ctg gta gac gag atg ttc cag cag ttc cag      616
Phe Gly Gln Asn Ala Trp Leu Val Asp Glu Met Phe Gln Gln Phe Gln
        45                  50                  55

aag gac ccc aag tcc gtg gac aag gaa tgg aga gaa ctc ttt gag gcg      664
Lys Asp Pro Lys Ser Val Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala
    60                  65                  70

cag ggg gga cca aat gct acc ccc gct aca aca gaa gca cag cct tca      712
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Gln Gly Gly Pro Asn Ala Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser
75 80 85 90

gcg ccc aag gag tct gcg aaa cca gca cca aag gct gcc cct gca gcc 760
Ala Pro Lys Glu Ser Ala Lys Pro Ala Pro Lys Ala Ala Pro Ala Ala
95 100 105

aag gca gca ccg cgc gta gaa acc aag ccg gcc gcc aag acc gcc cct 808
Lys Ala Ala Pro Arg Val Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro
110 115 120

aag gcc aag gag tcc tca gtg cca cag caa cct aag ctt ccg gag cca 856
Lys Ala Lys Glu Ser Ser Val Pro Gln Gln Pro Lys Leu Pro Glu Pro
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gga caa acc cca atc agg ggt att ttc aag tcc atc gcg aag aac atg 904
Gly Gln Thr Pro Ile Arg Gly Ile Phe Lys Ser Ile Ala Lys Asn Met
140 145 150

gat atc tcc ctg gaa atc cca acc gca acc tcg gtt cgc gat atg cca 952
Asp Ile Ser Leu Glu Ile Pro Thr Ala Thr Ser Val Arg Asp Met Pro
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175 180 185

cgc acc cgc ggt ggc aag atc tcc ttc acc cac atc att ggc tac gcc 1048
Arg Thr Arg Gly Gly Lys Ile Ser Phe Thr His Ile Ile Gly Tyr Ala
190 195 200

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Met Val Lys Ala Val Met Ala His Pro Asp Met Asn Asn Ser Tyr His
205 210 215

cga cgg cag gcc cca acc ctg atc gtg cct gag cac atc aac ctg ggc 1144
Arg Arg Gln Ala Pro Thr Leu Ile Val Pro Glu His Ile Asn Leu Gly
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ctt gcc atc gac ctt cct cag aag gac ggc tcc cgc gca ctt gtc gta 1192
Leu Ala Ile Asp Leu Pro Gln Lys Asp Gly Ser Arg Ala Leu Val Val
235 240 245 250

gca gcc atc aag gaa acc gag aag atg aac ttc tcc gag ttc ctc gca 1240
Ala Ala Ile Lys Glu Thr Glu Lys Met Asn Phe Ser Glu Phe Leu Ala
255 260 265

gca tac gaa gac atc gtg aca cgc tcc cgc aag ggc aag ctc acc atg 1288
Ala Tyr Glu Asp Ile Val Thr Arg Ser Arg Lys Gly Lys Leu Thr Met
270 275 280

gat gac tac cag ggc gtt acc gtt tcc ttg acc aac cca ggt ggc atc 1336
Asp Asp Tyr Gln Gly Val Thr Val Ser Leu Thr Asn Pro Gly Gly Ile
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ggt acc cgc cac tct gtc cca cgt ctg acc aag ggc cag ggc acc atc 1384
Gly Thr Arg His Ser Val Pro Arg Leu Thr Lys Gly Gln Gly Thr Ile
300 305 310

atc ggt gtc ggt tcc atg gat tac cca gca gag ttc cag ggc gct tcc 1432
Ile Gly Val Gly Ser Met Asp Tyr Pro Ala Glu Phe Gln Gly Ala Ser
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gaa gac cgc ctt gca gag ctc ggc gtt gga aag ctt gtc acc atc acc 1480

Glu Asp Arg Leu Ala Glu Leu Gly Val Gly Lys Leu Val Thr Ile Thr
335 340 345

tcc acc tac gat cac cgc gtg atc cag ggt gct gtg tcc ggt gaa ttc 1528
Ser Thr Tyr Asp His Arg Val Ile Gln Gly Ala Val Ser Gly Glu Phe
350 355 360

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Leu Arg Thr Met Ser Arg Leu Leu Thr Asp Asp Ser Phe Trp Asp Glu
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Ile Phe Asp Ala Met Asn Val Pro Tyr Thr Pro Met Arg Trp Ala Gln
380 385 390

gac gtt cca aac acc ggt gtt gat aag aac acc cgc gtc atg cag ctc 1672
Asp Val Pro Asn Thr Gly Val Asp Lys Asn Thr Arg Val Met Gln Leu
395 400 405 410

att gag gca tac cgc tcc cgt gga cac ctc atc gct gac acc aac cca 1720
Ile Glu Ala Tyr Arg Ser Arg Gly His Leu Ile Ala Asp Thr Asn Pro
415 420 425

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Leu Ser Trp Val Gln Pro Gly Met Pro Val Pro Asp His Arg Asp Leu
430 435 440

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Asp Ile Glu Thr His Ser Leu Thr Ile Trp Asp Leu Asp Arg Thr Phe
445 450 455

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Ser Val Gly Gly Phe Gly Gly Lys Glu Thr Met Thr Leu Arg Glu Val
460 465 470

ctg tcc cgc ctg cgc gct gcc tac acc ttg aag gtc ggc tcc gaa tac 1912
Leu Ser Arg Leu Arg Ala Ala Tyr Thr Leu Lys Val Gly Ser Glu Tyr
475 480 485 490

acc cac atc ctg gac cgc gac gag cgc acc tgg ctg cag gac cgc ctc 1960
Thr His Ile Leu Asp Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg Leu
495 500 505

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Glu Ala Gly Met Pro Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile Leu
510 515 520

cag aag ctg aac gcc gca gag gct ttc gag aac ttc ctg cag acc aag 2056
Gln Lys Leu Asn Ala Ala Glu Ala Phe Glu Asn Phe Leu Gln Thr Lys
525 530 535

tac gtc ggc cag aag cgc ttc tcc ctc gaa ggt gca gaa gct ctc atc 2104
Tyr Val Gly Gln Lys Arg Phe Ser Leu Glu Gly Ala Glu Ala Leu Ile
540 545 550

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Pro Leu Met Asp Ser Ala Ile Asp Thr Ala Ala Gly Gln Gly Leu Asp
555 560 565 570

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Glu Val Val Ile Gly Met Pro His Arg Gly Arg Leu Asn Val Leu Phe
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aac atc gtg ggc aag cca ctg gca tcc atc ttc aac gag ttt gaa ggc 2248

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Asn Ile Val Gly Lys Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu Gly
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caa atg gag cag ggc cag atc ggt ggc tcc ggt gac gtg aag tac cac      2296
Gln Met Glu Gln Gly Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr His
    605                 610                 615
ctc ggt tcc gaa ggc cag cac ctg cag atg ttc ggc gac ggc gag atc      2344
Leu Gly Ser Glu Gly Gln His Leu Gln Met Phe Gly Asp Gly Glu Ile
620                 625                 630
aag gtc tcc ctg act gct aac ccg tcc cac ctg gaa gct gtt aac cca      2392
Lys Val Ser Leu Thr Ala Asn Pro Ser His Leu Glu Ala Val Asn Pro
635                 640                 645                 650
gtg atg gaa ggt atc gtc cgc gca aag cag gac tac ctg gac aag ggc      2440
Val Met Glu Gly Ile Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys Gly
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gta gac ggc aag act gtt gtg cca ctg ctg ctc cac ggt gac gct gca      2488
Val Asp Gly Lys Thr Val Val Pro Leu Leu Leu His Gly Asp Ala Ala
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ttc gca ggc ctg ggc atc gtg cca gaa acc atc aac ctg gct aag cgc      2536
Phe Ala Gly Leu Gly Ile Val Pro Glu Thr Ile Asn Leu Ala Lys Arg
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Val Asp Val Gly Gly Thr Ile His Ile Val Val Asn Asn Gln Ile Gly
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Phe Thr Thr Thr Pro Asp Ser Ser Arg Ser Met His Tyr Ala Thr Asp
715                 720                 725                 730
tac gcc aag gca ttc ggc tgc cca gtc ttc cac gtc aat ggt gat gac      2680
Tyr Ala Lys Ala Phe Gly Cys Pro Val Phe His Val Asn Gly Asp Asp
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cca gag gca gtt gtc tgg gtt ggc cag ctg gca acc gag tac cgt cgt      2728
Pro Glu Ala Val Val Trp Val Gly Gln Leu Ala Thr Glu Tyr Arg Arg
            750                 755                 760
cgc ttc ggc aag gac gtc ttc atc gac ctc gtt tgc tac cgc ctc cgc      2776
Arg Phe Gly Lys Asp Val Phe Ile Asp Leu Val Cys Tyr Arg Leu Arg
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ggc cac aac gaa gct gat gat cct tcc atg acc cag cca aag atg tat      2824
Gly His Asn Glu Ala Asp Asp Pro Ser Met Thr Gln Pro Lys Met Tyr
780                 785                 790
gag ctc atc acc ggc cgc gag acc gtt cgt gct cag tac acc gaa gac      2872
Glu Leu Ile Thr Gly Arg Glu Thr Val Arg Ala Gln Tyr Thr Glu Asp
795                 800                 805                 810
ctg ctc gga cgt gga gac ctc tcc aac gaa gat gca gaa gca gtc gtc      2920
Leu Leu Gly Arg Gly Asp Leu Ser Asn Glu Asp Ala Glu Ala Val Val
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cgc gac ttc cac gac cag atg gaa tct gtg ttc aac gaa gtc aag gaa      2968
Arg Asp Phe His Asp Gln Met Glu Ser Val Phe Asn Glu Val Lys Glu
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ggc ggc aag aag cag gct gag gca cag acc ggc atc acc ggc tcc cag      3016
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860 865 870

gaa ctg gga cag gct ttc gcc aac acc cca gaa ggc ttc aac tac cac 3112
Glu Leu Gly Gln Ala Phe Ala Asn Thr Pro Glu Gly Phe Asn Tyr His
875 880 885 890

cca cgt gtg gct cca gtt gct aag aag cgc gtc tcc tct gtc acc gaa 3160
Pro Arg Val Ala Pro Val Ala Lys Lys Arg Val Ser Ser Val Thr Glu
895 900 905

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Gly Gly Ile Asp Trp Ala Trp Gly Glu Leu Leu Ala Phe Gly Ser Leu
910 915 920

gct aac tcc ggc cgc ttg gtt cgc ctt gca ggt gaa gat tcc cgc cgc 3256
Ala Asn Ser Gly Arg Leu Val Arg Leu Ala Gly Glu Asp Ser Arg Arg
925 930 935

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Gly Thr Phe Thr Gln Arg His Ala Val Ala Ile Asp Pro Ala Thr Ala
940 945 950

gaa gag ttc aac cca ctc cac gag ctt gca cag tcc aag ggc aac aac 3352
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955 960 965 970

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Ser Lys Leu Ile Leu Leu Leu Pro His Gly Tyr Glu Gly Gln Gly
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Ala Glu Gly Ser Met Thr Val Ala Gln Pro Ser Thr Pro Ala Asn
1065 1070 1075

cac ttc cac ctg ctg cgt cgt cac gct ctg tcc gac ctg aag cgt 3718
His Phe His Leu Leu Arg Arg His Ala Leu Ser Asp Leu Lys Arg
1080 1085 1090

cca ctg gtt atc ttc acc ccg aag tcc atg ctg cgt aac aag gct 3763

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tcc gtg atc gac gat cca aac gtt gca gat gca gcc aag gtg aag      3853
Ser Val Ile Asp Asp Pro Asn Val Ala Asp Ala Ala Lys Val Lys
        1125                1130                1135
aag gtc atg ctg gtc tcc ggc aag ctg tac tac gaa ttg gca aag      3898
Lys Val Met Leu Val Ser Gly Lys Leu Tyr Tyr Glu Leu Ala Lys
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cgc aag gag aag gac gga cgc gac gac atc gcg atc gtt cgt atc      3943
Arg Lys Glu Lys Asp Gly Arg Asp Asp Ile Ala Ile Val Arg Ile
        1155                1160                1165
gaa atg ctc cac cca att ccg ttc aac cgc atc tcc gag gct ctt      3988
Glu Met Leu His Pro Ile Pro Phe Asn Arg Ile Ser Glu Ala Leu
        1170                1175                1180
gcc ggc tac cct aac gct gag gaa gtc ctc ttc gtt cag gat gag      4033
Ala Gly Tyr Pro Asn Ala Glu Glu Val Leu Phe Val Gln Asp Glu
        1185                1190                1195
cca gca aac cag ggc cca tgg ccg ttc tac cag gag cac ctc cca      4078
Pro Ala Asn Gln Gly Pro Trp Pro Phe Tyr Gln Glu His Leu Pro
        1200                1205                1210
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Glu Leu Ile Pro Asn Met Pro Lys Met Arg Arg Val Ser Arg Arg
        1215                1220                1225
gct cag tcc tcc acc gca act ggt gtt gct aag gtg cac cag ctg      4168
Ala Gln Ser Ser Thr Ala Thr Gly Val Ala Lys Val His Gln Leu
        1230                1235                1240
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Glu Glu Lys Gln Leu Ile Asp Glu Ala Phe Glu Ala     Val Phe
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Arg Val Pro Ala Val Ser Ser Ala Ser Thr Phe Gly Gln Asn Ala Trp
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Leu Val Asp Glu Met Phe Gln Gln Phe Gln Lys Asp Pro Lys Ser Val

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Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala Gln Gly Gly Pro Asn Ala

65 70 75 80

Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser Ala Pro Lys Glu Ser Ala

85 90 95

Lys Pro Ala Pro Lys Ala Ala Pro Ala Ala Lys Ala Ala Pro Arg Val

100 105 110

Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro Lys Ala Lys Glu Ser Ser

115 120 125

Val Pro Gln Gln Pro Lys Leu Pro Glu Pro Gly Gln Thr Pro Ile Arg

130 135 140

Gly Ile Phe Lys Ser Ile Ala Lys Asn Met Asp Ile Ser Leu Glu Ile

145 150 155 160

Pro Thr Ala Thr Ser Val Arg Asp Met Pro Ala Arg Leu Met Phe Glu

165 170 175

Asn Arg Ala Met Val Asn Asp Gln Leu Lys Arg Thr Arg Gly Gly Lys

180 185 190

Ile Ser Phe Thr His Ile Ile Gly Tyr Ala Met Val Lys Ala Val Met

195 200 205

Ala His Pro Asp Met Asn Asn Ser Tyr His Arg Arg Gln Ala Pro Thr

210 215 220

Leu Ile Val Pro Glu His Ile Asn Leu Gly Leu Ala Ile Asp Leu Pro

225 230 235 240

Gln Lys Asp Gly Ser Arg Ala Leu Val Val Ala Ala Ile Lys Glu Thr

245 250 255

Glu Lys Met Asn Phe Ser Glu Phe Leu Ala Ala Tyr Glu Asp Ile Val

260 265 270

Thr Arg Ser Arg Lys Gly Lys Leu Thr Met Asp Asp Tyr Gln Gly Val

275 280 285

Thr Val Ser Leu Thr Asn Pro Gly Gly Ile Gly Thr Arg His Ser Val

290 295 300

Pro Arg Leu Thr Lys Gly Gln Gly Thr Ile Ile Gly Val Gly Ser Met

305 310 315 320

Asp Tyr Pro Ala Glu Phe Gln Gly Ala Ser Glu Asp Arg Leu Ala Glu

325 330 335

Leu Gly Val Gly Lys Leu Val Thr Ile Thr Ser Thr Tyr Asp His Arg

340 345 350

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

355 360 365

Leu Leu Thr Asp Asp Ser Phe Trp Asp Glu Ile Phe Asp Ala Met Asn

370 375 380

Val Pro Tyr Thr Pro Met Arg Trp Ala Gln Asp Val Pro Asn Thr Gly

385 390 395 400

Val Asp Lys Asn Thr Arg Val Met Gln Leu Ile Glu Ala Tyr Arg Ser

405 410 415

Arg Gly His Leu Ile Ala Asp Thr Asn Pro Leu Ser Trp Val Gln Pro

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Gly Met Pro Val Pro Asp His Arg Asp Leu Asp Ile Glu Thr His Ser
435 440 445
Leu Thr Ile Trp Asp Leu Asp Arg Thr Phe Ser Val Gly Gly Phe Gly
450 455 460
Gly Lys Glu Thr Met Thr Leu Arg Glu Val Leu Ser Arg Leu Arg Ala
465 470 475 480
Ala Tyr Thr Leu Lys Val Gly Ser Glu Tyr Thr His Ile Leu Asp Arg
485 490 495
Asp Glu Arg Thr Trp Leu Gln Asp Arg Leu Glu Ala Gly Met Pro Lys
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Pro Thr Gln Ala Glu Gln Lys Tyr Ile Leu Gln Lys Leu Asn Ala Ala
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Glu Ala Phe Glu Asn Phe Leu Gln Thr Lys Tyr Val Gly Gln Lys Arg
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Phe Ser Leu Glu Gly Ala Glu Ala Leu Ile Pro Leu Met Asp Ser Ala
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Ile Asp Thr Ala Ala Gly Gln Gly Leu Asp Glu Val Val Ile Gly Met
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Pro His Arg Gly Arg Leu Asn Val Leu Phe Asn Ile Val Gly Lys Pro
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Leu Ala Ser Ile Phe Asn Glu Phe Glu Gly Gln Met Glu Gln Gly Gln
595 600 605
Ile Gly Gly Ser Gly Asp Val Lys Tyr His Leu Gly Ser Glu Gly Gln
610 615 620
His Leu Gln Met Phe Gly Asp Gly Glu Ile Lys Val Ser Leu Thr Ala
625 630 635 640
Asn Pro Ser His Leu Glu Ala Val Asn Pro Val Met Glu Gly Ile Val
645 650 655
Arg Ala Lys Gln Asp Tyr Leu Asp Lys Gly Val Asp Gly Lys Thr Val
660 665 670
Val Pro Leu Leu Leu His Gly Asp Ala Ala Phe Ala Gly Leu Gly Ile
675 680 685
Val Pro Glu Thr Ile Asn Leu Ala Lys Arg Val Asp Val Gly Gly Thr
690 695 700
Ile His Ile Val Val Asn Asn Gln Ile Gly Phe Thr Thr Thr Pro Asp
705 710 715 720
Ser Ser Arg Ser Met His Tyr Ala Thr Asp Tyr Ala Lys Ala Phe Gly
725 730 735
Cys Pro Val Phe His Val Asn Gly Asp Asp Pro Glu Ala Val Val Trp
740 745 750
Val Gly Gln Leu Ala Thr Glu Tyr Arg Arg Arg Phe Gly Lys Asp Val
755 760 765
Phe Ile Asp Leu Val Cys Tyr Arg Leu Arg Gly His Asn Glu Ala Asp
770 775 780
Asp Pro Ser Met Thr Gln Pro Lys Met Tyr Glu Leu Ile Thr Gly Arg
785 790 795 800
Glu Thr Val Arg Ala Gln Tyr Thr Glu Asp Leu Leu Gly Arg Gly Asp

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Leu Ser Asn Glu Asp Ala Glu Ala Val Val Arg Asp Phe His Asp Gln
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Met Glu Ser Val Phe Asn Glu Val Lys Glu Gly Gly Lys Lys Gln Ala
        835                 840                 845
Glu Ala Gln Thr Gly Ile Thr Gly Ser Gln Lys Leu Pro His Gly Leu
    850                 855                 860
Glu Thr Asn Ile Ser Arg Glu Glu Leu Leu Glu Leu Gly Gln Ala Phe
865                 870                 875                 880
Ala Asn Thr Pro Glu Gly Phe Asn Tyr His Pro Arg Val Ala Pro Val
                885                 890                 895
Ala Lys Lys Arg Val Ser Ser Val Thr Glu Gly Gly Ile Asp Trp Ala
            900                 905                 910
Trp Gly Glu Leu Leu Ala Phe Gly Ser Leu Ala Asn Ser Gly Arg Leu
        915                 920                 925
Val Arg Leu Ala Gly Glu Asp Ser Arg Arg Gly Thr Phe Thr Gln Arg
    930                 935                 940
His Ala Val Ala Ile Asp Pro Ala Thr Ala Glu Glu Phe Asn Pro Leu
945                 950                 955                 960
His Glu Leu Ala Gln Ser Lys Gly Asn Asn Gly Lys Phe Leu Val Tyr
                965                 970                 975
Asn Ser Ala Leu Thr Glu Tyr Ala Gly Met Gly Phe Glu Tyr Gly Tyr
            980                 985                 990
Ser Val Gly Asn Glu Asp Ser Val  Val Ala Trp Glu Ala  Gln Phe Gly
        995                 1000                1005
Asp Phe  Ala Asn Gly Ala Gln  Thr Ile Ile Asp Glu  Tyr Val Ser
    1010                1015                1020
Ser Gly  Glu Ala Lys Trp Gly  Gln Thr Ser Lys Leu  Ile Leu Leu
    1025                1030                1035
Leu Pro  His Gly Tyr Glu Gly  Gln Gly Pro Asp His  Ser Ser Ala
    1040                1045                1050
Arg Ile  Glu Arg Phe Leu Gln  Leu Cys Ala Glu Gly  Ser Met Thr
    1055                1060                1065
Val Ala  Gln Pro Ser Thr Pro  Ala Asn His Phe His  Leu Leu Arg
    1070                1075                1080
Arg His  Ala Leu Ser Asp Leu  Lys Arg Pro Leu Val  Ile Phe Thr
    1085                1090                1095
Pro Lys  Ser Met Leu Arg Asn  Lys Ala Ala Ala Ser  Ala Pro Glu
    1100                1105                1110
Asp Phe  Thr Glu Val Thr Lys  Phe Gln Ser Val Ile  Asp Asp Pro
    1115                1120                1125
Asn Val  Ala Asp Ala Ala Lys  Val Lys Lys Val Met  Leu Val Ser
    1130                1135                1140
Gly Lys  Leu Tyr Tyr Glu Leu  Ala Lys Arg Lys Glu  Lys Asp Gly
    1145                1150                1155
Arg Asp  Asp Ile Ala Ile Val  Arg Ile Glu Met Leu  His Pro Ile
    1160                1165                1170
Pro Phe  Asn Arg Ile Ser Glu  Ala Leu Ala Gly Tyr  Pro Asn Ala
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    1175                1180                1185
Glu Glu Val Leu Phe Val Gln Asp Glu Pro Ala Asn Gln Gly Pro
    1190                1195                1200
Trp Pro Phe Tyr Gln Glu His Leu Pro Glu Leu Ile Pro Asn Met
    1205                1210                1215
Pro Lys Met Arg Arg Val Ser Arg Arg Ala Gln Ser Ser Thr Ala
    1220                1225                1230
Thr Gly Val Ala Lys Val His Gln Leu Glu Glu Lys Gln Leu Ile
    1235                1240                1245
Asp Glu Ala Phe Glu Ala
    1250

<210>  17
<211>  1800
<212>  DNA
<213>  Corynebacterium glutamicum

<220>
<221>  CDS
<222>  (211)..(1620)
<223>

<400>  17
gatcctccgc attcagtaat ctttcccaca gcatcggctt gttctaaaac agcacggtgc      60
ttagaccgta cataaaacac ctgcatttct gtgcccattt gggcccggat gtgggtgttt     120
ttcattttct tccactctaa aattaagtat ggaaaaccaa ccgcacccgg atgcacgaca     180
atgacccact aaacacgtat ccttgaatgc gtg act gaa cat tat gac gta gta     234
                                 Met Thr Glu His Tyr Asp Val Val
                                 1               5

gta ctc gga gcc ggc ccc ggt ggc tat gtc tcc gcc atc cgt gca gcg      282
Val Leu Gly Ala Gly Pro Gly Gly Tyr Val Ser Ala Ile Arg Ala Ala
    10                  15                  20

cag ctt ggc aag aag gtt gct gta att gag aag cag tac tgg ggt ggt      330
Gln Leu Gly Lys Lys Val Ala Val Ile Glu Lys Gln Tyr Trp Gly Gly
25                  30                  35                  40

gtt tgc cta aac gtg ggc tgc att cct tcc aag tct ctg atc aaa aac      378
Val Cys Leu Asn Val Gly Cys Ile Pro Ser Lys Ser Leu Ile Lys Asn
                45                  50                  55

gct gaa gtt gcc cat acc ttt acc cat gag aag aag acc ttc ggc atc      426
Ala Glu Val Ala His Thr Phe Thr His Glu Lys Lys Thr Phe Gly Ile
            60                  65                  70

aat ggc gaa gtg acc ttc aac tat gag gat gct cac aag cgt tcc cgt      474
Asn Gly Glu Val Thr Phe Asn Tyr Glu Asp Ala His Lys Arg Ser Arg
        75                  80                  85

ggc gtt tcc gac aag atc gtt gga ggc gtt cat tac ttg atg aag aag      522
Gly Val Ser Asp Lys Ile Val Gly Gly Val His Tyr Leu Met Lys Lys
    90                  95                  100

aac aag atc atc gaa att cat ggt ctt gga aac ttc aag gat gct aag      570
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Asn Lys Ile Ile Glu Ile His Gly Leu Gly Asn Phe Lys Asp Ala Lys
105                 110                 115                 120
act ctt gag gtc acc gac ggt aag gat gct ggc aag acc atc acc ttt      618
Thr Leu Glu Val Thr Asp Gly Lys Asp Ala Gly Lys Thr Ile Thr Phe
                125                 130                 135
gat gac tgc atc atc gca acc ggt tcg gta gtc aac acc ctc cgt ggc      666
Asp Asp Cys Ile Ile Ala Thr Gly Ser Val Val Asn Thr Leu Arg Gly
            140                 145                 150
gtt gac ttc tca gag aac gtt gtg tct ttt gaa gag cag att ctt aac      714
Val Asp Phe Ser Glu Asn Val Val Ser Phe Glu Glu Gln Ile Leu Asn
        155                 160                 165
cct gtt gcg cca aag aag atg gtc att gtt ggt gca ggc gca att gga      762
Pro Val Ala Pro Lys Lys Met Val Ile Val Gly Ala Gly Ala Ile Gly
    170                 175                 180
atg gaa ttc gcc tac gtt ctt ggt aac tac ggt gta gat gta acc gtc      810
Met Glu Phe Ala Tyr Val Leu Gly Asn Tyr Gly Val Asp Val Thr Val
185                 190                 195                 200
atc gag ttc atg gat cgt gtg ctt cca aat gaa gat gct gaa gtc tcc      858
Ile Glu Phe Met Asp Arg Val Leu Pro Asn Glu Asp Ala Glu Val Ser
                205                 210                 215
aag gtt att gca aag gcc tac aag aag atg ggc gtt aag ctt ctt cct      906
Lys Val Ile Ala Lys Ala Tyr Lys Lys Met Gly Val Lys Leu Leu Pro
            220                 225                 230
ggc cat gca acc act gct gtt cgg gac aac ggt gac ttt gtc gag gtt      954
Gly His Ala Thr Thr Ala Val Arg Asp Asn Gly Asp Phe Val Glu Val
        235                 240                 245
gat tac cag aag aag ggc tct gac aag aca gag act ctt act gtt gat     1002
Asp Tyr Gln Lys Lys Gly Ser Asp Lys Thr Glu Thr Leu Thr Val Asp
    250                 255                 260
cga gtc atg gtt tcc gtt ggt ttc cgt cca cgc gtt gag gga ttt ggt     1050
Arg Val Met Val Ser Val Gly Phe Arg Pro Arg Val Glu Gly Phe Gly
265                 270                 275                 280
ctt gaa aac act ggc gtt aag ctc acc gag cgt ggc gca atc gag atc     1098
Leu Glu Asn Thr Gly Val Lys Leu Thr Glu Arg Gly Ala Ile Glu Ile
                285                 290                 295
gat gat tac atg cgt acc aac gtc gat ggc att tac gcc atc ggt gac     1146
Asp Asp Tyr Met Arg Thr Asn Val Asp Gly Ile Tyr Ala Ile Gly Asp
            300                 305                 310
gtg acc gcc aag ctt cag ctt gct cac gtc gca gaa gca cag ggc att     1194
Val Thr Ala Lys Leu Gln Leu Ala His Val Ala Glu Ala Gln Gly Ile
        315                 320                 325
gtt gcc gca gag act att gct ggt gca gaa act cag act ctt ggt gat     1242
Val Ala Ala Glu Thr Ile Ala Gly Ala Glu Thr Gln Thr Leu Gly Asp
    330                 335                 340
tac atg atg atg cca cgt gca acc ttc tgc aac cca cag gtt tct tcc     1290
Tyr Met Met Met Pro Arg Ala Thr Phe Cys Asn Pro Gln Val Ser Ser
345                 350                 355                 360
ttt ggt tac acc gaa gag cag gcc aag gag aag tgg cca gat cgt gag     1338
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Phe Gly Tyr Thr Glu Glu Gln Ala Lys Glu Lys Trp Pro Asp Arg Glu
365 370 375
atc aag gtt gct tcc ctc cca ttc tct gca aac ggt aaa gca gtt ggc 1386
Ile Lys Val Ala Ser Leu Pro Phe Ser Ala Asn Gly Lys Ala Val Gly
380 385 390
ctg gca gaa act gat ggt ttc gca aag atc gtt gct gat gca gaa ttc 1434
Leu Ala Glu Thr Asp Gly Phe Ala Lys Ile Val Ala Asp Ala Glu Phe
395 400 405
ggt gag ctg ctc ggt gca cac ctg gtt gga gca aat gca tca gag ctc 1482
Gly Glu Leu Leu Gly Ala His Leu Val Gly Ala Asn Ala Ser Glu Leu
410 415 420
atc aat gaa ttg gtg ctt gct cag aac tgg gat ctc acc act gaa gag 1530
Ile Asn Glu Leu Val Leu Ala Gln Asn Trp Asp Leu Thr Thr Glu Glu
425 430 435 440
atc tct cgt agc gtc cat att cac cca acg cta tct gag gca gtt aag 1578
Ile Ser Arg Ser Val His Ile His Pro Thr Leu Ser Glu Ala Val Lys
445 450 455
gaa gct gca cac ggt atc tct gga cac atg atc aac ttc tag 1620
Glu Ala Ala His Gly Ile Ser Gly His Met Ile Asn Phe
460 465
aatccacctc gttggccctg tttctgtatg gaaacagggc caaaaccgat tttcaatcca 1680
aaccgagtgc tggttagtgc tcatactcac acaaactttt cgattatcaa agagaattat 1740
ttctaaaatt cggtatcgtc taagaaatga gtttgccaat agctcagcat caaaatgctg 1800

<210> 18
<211> 469
<212> PRT
<213> Corynebacterium glutamicum

<400> 18
Met Thr Glu His Tyr Asp Val Val Val Leu Gly Ala Gly Pro Gly Gly
1 5 10 15
Tyr Val Ser Ala Ile Arg Ala Ala Gln Leu Gly Lys Lys Val Ala Val
20 25 30
Ile Glu Lys Gln Tyr Trp Gly Gly Val Cys Leu Asn Val Gly Cys Ile
35 40 45
Pro Ser Lys Ser Leu Ile Lys Asn Ala Glu Val Ala His Thr Phe Thr
50 55 60
His Glu Lys Lys Thr Phe Gly Ile Asn Gly Glu Val Thr Phe Asn Tyr
65 70 75 80
Glu Asp Ala His Lys Arg Ser Arg Gly Val Ser Asp Lys Ile Val Gly
85 90 95
Gly Val His Tyr Leu Met Lys Lys Asn Lys Ile Ile Glu Ile His Gly
100 105 110
Leu Gly Asn Phe Lys Asp Ala Lys Thr Leu Glu Val Thr Asp Gly Lys
115 120 125
Asp Ala Gly Lys Thr Ile Thr Phe Asp Asp Cys Ile Ile Ala Thr Gly

130 135 140
Ser Val Val Asn Thr Leu Arg Gly Val Asp Phe Ser Glu Asn Val Val
145 150 155 160
Ser Phe Glu Glu Gln Ile Leu Asn Pro Val Ala Pro Lys Lys Met Val
165 170 175
Ile Val Gly Ala Gly Ala Ile Gly Met Glu Phe Ala Tyr Val Leu Gly
180 185 190
Asn Tyr Gly Val Asp Val Thr Val Ile Glu Phe Met Asp Arg Val Leu
195 200 205
Pro Asn Glu Asp Ala Glu Val Ser Lys Val Ile Ala Lys Ala Tyr Lys
210 215 220
Lys Met Gly Val Lys Leu Leu Pro Gly His Ala Thr Thr Ala Val Arg
225 230 235 240
Asp Asn Gly Asp Phe Val Glu Val Asp Tyr Gln Lys Lys Gly Ser Asp
245 250 255
Lys Thr Glu Thr Leu Thr Val Asp Arg Val Met Val Ser Val Gly Phe
260 265 270
Arg Pro Arg Val Glu Gly Phe Gly Leu Glu Asn Thr Gly Val Lys Leu
275 280 285
Thr Glu Arg Gly Ala Ile Glu Ile Asp Asp Tyr Met Arg Thr Asn Val
290 295 300
Asp Gly Ile Tyr Ala Ile Gly Asp Val Thr Ala Lys Leu Gln Leu Ala
305 310 315 320
His Val Ala Glu Ala Gln Gly Ile Val Ala Ala Glu Thr Ile Ala Gly
325 330 335
Ala Glu Thr Gln Thr Leu Gly Asp Tyr Met Met Met Pro Arg Ala Thr
340 345 350
Phe Cys Asn Pro Gln Val Ser Ser Phe Gly Tyr Thr Glu Glu Gln Ala
355 360 365
Lys Glu Lys Trp Pro Asp Arg Glu Ile Lys Val Ala Ser Leu Pro Phe
370 375 380
Ser Ala Asn Gly Lys Ala Val Gly Leu Ala Glu Thr Asp Gly Phe Ala
385 390 395 400
Lys Ile Val Ala Asp Ala Glu Phe Gly Glu Leu Leu Gly Ala His Leu
405 410 415
Val Gly Ala Asn Ala Ser Glu Leu Ile Asn Glu Leu Val Leu Ala Gln
420 425 430
Asn Trp Asp Leu Thr Thr Glu Glu Ile Ser Arg Ser Val His Ile His
435 440 445
Pro Thr Leu Ser Glu Ala Val Lys Glu Ala Ala His Gly Ile Ser Gly
450 455 460
His Met Ile Asn Phe
465

<210> 19
<211> 2014
<212> DNA
<213> Bacillus subtilis

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<220>
<221>  CDS
<222>  (464)..(1885)
<223>

<400>  19
gatccttttt aacccatcac atatacctgc cgttcactat tatttagtga aatgagatat      60
tatgatattt tctgaattgt gattaaaaag gcaactttat gcccatgcaa cagaaactat     120
aaaaaataca gagaatgaaa agaaacagat agattttttta gttctttagg cccgtagtct    180
gcaaatcctt ttatgatttt ctatcaaaca aaagaggaaa atagaccagt tgcaatccaa     240
acgagagtct aatagaatga ggtcgaaaag taaatcgcgc gggtttgtta ctgataaagc     300
aggcaagacc taaaatgtgt aaagggcaaa gtgtatactt tggcgtcacc ccttacatat     360
tttaggtctt tttttattgt gcgtaactaa cttgccatct tcaaacagga gggctggaag     420
aagcagaccg ctaacacagt acataaaaaa ggagacatga acg atg aac atc aaa       475
                                                Met Asn Ile Lys
                                                1

aag ttt gca aaa caa gca aca gta tta acc ttt act acc gca ctg ctg       523
Lys Phe Ala Lys Gln Ala Thr Val Leu Thr Phe Thr Thr Ala Leu Leu
5                   10                  15                  20

gca gga ggc gca act caa gcg ttt gcg aaa gaa acg aac caa aag cca       571
Ala Gly Gly Ala Thr Gln Ala Phe Ala Lys Glu Thr Asn Gln Lys Pro
                25                  30                  35

tat aag gaa aca tac ggc att tcc cat att aca cgc cat gat atg ctg       619
Tyr Lys Glu Thr Tyr Gly Ile Ser His Ile Thr Arg His Asp Met Leu
            40                  45                  50

caa atc cct gaa cag caa aaa aat gaa aaa tat caa gtt cct gaa ttc       667
Gln Ile Pro Glu Gln Gln Lys Asn Glu Lys Tyr Gln Val Pro Glu Phe
        55                  60                  65

gat tcg tcc aca att aaa aat atc tct tct gca aaa ggc ctg gac gtt       715
Asp Ser Ser Thr Ile Lys Asn Ile Ser Ser Ala Lys Gly Leu Asp Val
    70                  75                  80

tgg gac agc tgg cca tta caa aac gct gac ggc act gtc gca aac tat       763
Trp Asp Ser Trp Pro Leu Gln Asn Ala Asp Gly Thr Val Ala Asn Tyr
85                  90                  95                  100

cac ggc tac cac atc gtc ttt gca tta gcc gga gat cct aaa aat gcg       811
His Gly Tyr His Ile Val Phe Ala Leu Ala Gly Asp Pro Lys Asn Ala
                105                 110                 115

gat gac aca tcg att tac atg ttc tat caa aaa gtc ggc gaa act tct       859
Asp Asp Thr Ser Ile Tyr Met Phe Tyr Gln Lys Val Gly Glu Thr Ser
            120                 125                 130

att gac agc tgg aaa aac gct ggc cgc gtc ttt aaa gac agc gac aaa       907
Ile Asp Ser Trp Lys Asn Ala Gly Arg Val Phe Lys Asp Ser Asp Lys
        135                 140                 145

ttc gat gca aat gat tct atc cta aaa gac caa aca caa gaa tgg tca       955
Phe Asp Ala Asn Asp Ser Ile Leu Lys Asp Gln Thr Gln Glu Trp Ser
    150                 155                 160

ggt tca gcc aca ttt aca tct gac gga aaa atc cgt tta ttc tac act      1003
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Gly Ser Ala Thr Phe Thr Ser Asp Gly Lys Ile Arg Leu Phe Tyr Thr
165                 170                 175                 180
gat ttc tcc ggt aaa cat tac ggc aaa caa aca ctg aca act gca caa       1051
Asp Phe Ser Gly Lys His Tyr Gly Lys Gln Thr Leu Thr Thr Ala Gln
                185                 190                 195
gtt aac gta tca gca tca gac agc tct ttg aac atc aac ggt gta gag       1099
Val Asn Val Ser Ala Ser Asp Ser Ser Leu Asn Ile Asn Gly Val Glu
            200                 205                 210
gat tat aaa tca atc ttt gac ggt gac gga aaa acg tat caa aat gta       1147
Asp Tyr Lys Ser Ile Phe Asp Gly Asp Gly Lys Thr Tyr Gln Asn Val
        215                 220                 225
cag cag ttc atc gat gaa ggc aac tac agc tca ggc gac aac cat acg       1195
Gln Gln Phe Ile Asp Glu Gly Asn Tyr Ser Ser Gly Asp Asn His Thr
    230                 235                 240
ctg aga gat cct cac tac gta gaa gat aaa ggc cac aaa tac tta gta       1243
Leu Arg Asp Pro His Tyr Val Glu Asp Lys Gly His Lys Tyr Leu Val
245                 250                 255                 260
ttt gaa gca aac act gga act gaa gat ggc tac caa ggc gaa gaa tct       1291
Phe Glu Ala Asn Thr Gly Thr Glu Asp Gly Tyr Gln Gly Glu Glu Ser
                265                 270                 275
tta ttt aac aaa gca tac tat ggc aaa agc aca tca ttc ttc cgt caa       1339
Leu Phe Asn Lys Ala Tyr Tyr Gly Lys Ser Thr Ser Phe Phe Arg Gln
            280                 285                 290
gaa agt caa aaa ctt ctg caa agc gat aaa aaa cgc acg gct gag tta       1387
Glu Ser Gln Lys Leu Leu Gln Ser Asp Lys Lys Arg Thr Ala Glu Leu
        295                 300                 305
gca aac ggc gct ctc ggt atg att gag cta aac gat gat tac aca ctg       1435
Ala Asn Gly Ala Leu Gly Met Ile Glu Leu Asn Asp Asp Tyr Thr Leu
    310                 315                 320
aaa aaa gtg atg aaa ccg ctg att gca tct aac aca gta aca gat gaa       1483
Lys Lys Val Met Lys Pro Leu Ile Ala Ser Asn Thr Val Thr Asp Glu
325                 330                 335                 340
att gaa cgc gcg aac gtc ttt aaa atg aac ggc aaa tgg tac ctg ttc       1531
Ile Glu Arg Ala Asn Val Phe Lys Met Asn Gly Lys Trp Tyr Leu Phe
                345                 350                 355
act gac tcc cgc gga tca aaa atg acg att gac ggc att acg tct aac       1579
Thr Asp Ser Arg Gly Ser Lys Met Thr Ile Asp Gly Ile Thr Ser Asn
            360                 365                 370
gat att tac atg ctt ggt tat gtt tct aat tct tta act ggc cca tac       1627
Asp Ile Tyr Met Leu Gly Tyr Val Ser Asn Ser Leu Thr Gly Pro Tyr
        375                 380                 385
aag ccg ctg aac aaa act ggc ctt gtg tta aaa atg gat ctt gat cct       1675
Lys Pro Leu Asn Lys Thr Gly Leu Val Leu Lys Met Asp Leu Asp Pro
    390                 395                 400
aac gat gta acc ttt act tac tca cac ttc gct gta cct caa gcg aaa       1723
Asn Asp Val Thr Phe Thr Tyr Ser His Phe Ala Val Pro Gln Ala Lys
405                 410                 415                 420
gga aac aat gtc gtg att aca agc tat atg aca aac aga gga ttc tac       1771
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Gly Asn Asn Val Val Ile Thr Ser Tyr Met Thr Asn Arg Gly Phe Tyr
                425                 430                 435

gca gac aaa caa tca acg ttt gcg cca agc ttc ctg ctg aac atc aaa      1819
Ala Asp Lys Gln Ser Thr Phe Ala Pro Ser Phe Leu Leu Asn Ile Lys
            440                 445                 450

ggc aag aaa aca tct gtt gtc aaa gac agc atc ctt gaa caa gga caa      1867
Gly Lys Lys Thr Ser Val Val Lys Asp Ser Ile Leu Glu Gln Gly Gln
        455                 460                 465

tta aca gtt aac aaa taa aaacgcaaaa gaaaatgccg atatcctatt             1915
Leu Thr Val Asn Lys
    470

ggcattttct tttatttctt atcaacataa aggtgaatcc catatgaact atataaaagc    1975

aggcaaatgg ctaaccgtat tcctaacctt ttgaagatc                           2014



<210>  20
<211>  473
<212>  PRT
<213>  Bacillus subtilis

<400>  20

Met Asn Ile Lys Lys Phe Ala Lys Gln Ala Thr Val Leu Thr Phe Thr
1               5                   10                  15

Thr Ala Leu Leu Ala Gly Gly Ala Thr Gln Ala Phe Ala Lys Glu Thr
            20                  25                  30

Asn Gln Lys Pro Tyr Lys Glu Thr Tyr Gly Ile Ser His Ile Thr Arg
        35                  40                  45

His Asp Met Leu Gln Ile Pro Glu Gln Gln Lys Asn Glu Lys Tyr Gln
    50                  55                  60

Val Pro Glu Phe Asp Ser Ser Thr Ile Lys Asn Ile Ser Ser Ala Lys
65                  70                  75                  80

Gly Leu Asp Val Trp Asp Ser Trp Pro Leu Gln Asn Ala Asp Gly Thr
                85                  90                  95

Val Ala Asn Tyr His Gly Tyr His Ile Val Phe Ala Leu Ala Gly Asp
            100                 105                 110

Pro Lys Asn Ala Asp Asp Thr Ser Ile Tyr Met Phe Tyr Gln Lys Val
        115                 120                 125

Gly Glu Thr Ser Ile Asp Ser Trp Lys Asn Ala Gly Arg Val Phe Lys
    130                 135                 140

Asp Ser Asp Lys Phe Asp Ala Asn Asp Ser Ile Leu Lys Asp Gln Thr
145                 150                 155                 160

Gln Glu Trp Ser Gly Ser Ala Thr Phe Thr Ser Asp Gly Lys Ile Arg
                165                 170                 175

Leu Phe Tyr Thr Asp Phe Ser Gly Lys His Tyr Gly Lys Gln Thr Leu
            180                 185                 190

Thr Thr Ala Gln Val Asn Val Ser Ala Ser Asp Ser Ser Leu Asn Ile
        195                 200                 205

Asn Gly Val Glu Asp Tyr Lys Ser Ile Phe Asp Gly Asp Gly Lys Thr
```

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    210                 215                 220
Tyr Gln Asn Val Gln Gln Phe Ile Asp Glu Gly Asn Tyr Ser Ser Gly
225                 230                 235                 240
Asp Asn His Thr Leu Arg Asp Pro His Tyr Val Glu Asp Lys Gly His
                245                 250                 255
Lys Tyr Leu Val Phe Glu Ala Asn Thr Gly Thr Glu Asp Gly Tyr Gln
            260                 265                 270
Gly Glu Glu Ser Leu Phe Asn Lys Ala Tyr Tyr Gly Lys Ser Thr Ser
        275                 280                 285
Phe Phe Arg Gln Glu Ser Gln Lys Leu Leu Gln Ser Asp Lys Lys Arg
    290                 295                 300
Thr Ala Glu Leu Ala Asn Gly Ala Leu Gly Met Ile Glu Leu Asn Asp
305                 310                 315                 320
Asp Tyr Thr Leu Lys Lys Val Met Lys Pro Leu Ile Ala Ser Asn Thr
                325                 330                 335
Val Thr Asp Glu Ile Glu Arg Ala Asn Val Phe Lys Met Asn Gly Lys
            340                 345                 350
Trp Tyr Leu Phe Thr Asp Ser Arg Gly Ser Lys Met Thr Ile Asp Gly
        355                 360                 365
Ile Thr Ser Asn Asp Ile Tyr Met Leu Gly Tyr Val Ser Asn Ser Leu
    370                 375                 380
Thr Gly Pro Tyr Lys Pro Leu Asn Lys Thr Gly Leu Val Leu Lys Met
385                 390                 395                 400
Asp Leu Asp Pro Asn Asp Val Thr Phe Thr Tyr Ser His Phe Ala Val
                405                 410                 415
Pro Gln Ala Lys Gly Asn Asn Val Val Ile Thr Ser Tyr Met Thr Asn
            420                 425                 430
Arg Gly Phe Tyr Ala Asp Lys Gln Ser Thr Phe Ala Pro Ser Phe Leu
        435                 440                 445
Leu Asn Ile Lys Gly Lys Lys Thr Ser Val Val Lys Asp Ser Ile Leu
    450                 455                 460
Glu Gln Gly Gln Leu Thr Val Asn Lys
465                 470
```

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<210>  21
<211>  24
<212>  DNA
<213>  Artificial

<220>
<223>  primer

<400>  21
cgggatcctt tttaacccat caca                                          24


<210>  22
<211>  29
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<212> DNA
<213> Artificial

<220>
<223> primer

<400> 22
gaagatcttc aaaaggttag gaatacggt 29

<210> 23
<211> 23
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 23
ccttttgaag atcgaccagt tgg 23

<210> 24
<211> 44
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 24
tacctggaat gctgttttcc cagggatcgc agtggtgagt aacc 44

<210> 25
<211> 28
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 25
cctgggaaaa cagcattcca ggtattag 28

<210> 26
<211> 23

<212> DNA
<213> Artificial

<220>
<223> primer

<400> 26
tgcaggtcga ctctagagga tcc 23

<210> 27
<211> 2028
<212> DNA
<213> Corynebacterium glutamicum

<220>
<221> CDS
<222> (1)..(2028)
<223>

<400> 27
atg gcg ttc tcc gta gag atg ccc gag ctg ggc gaa tca gta acc gaa 48
Met Ala Phe Ser Val Glu Met Pro Glu Leu Gly Glu Ser Val Thr Glu
1 5 10 15

ggc acg atc acc cag tgg ttg aag tct gtt ggt gac act gtt gag gta 96
Gly Thr Ile Thr Gln Trp Leu Lys Ser Val Gly Asp Thr Val Glu Val
20 25 30

gat gag ccg ttg ctc gag gtc tca act gac aag gtc gac acc gag att 144
Asp Glu Pro Leu Leu Glu Val Ser Thr Asp Lys Val Asp Thr Glu Ile
35 40 45

ccc tct cct gtc gcc ggt gtc atc cta gag att aag gct gaa gag gat 192
Pro Ser Pro Val Ala Gly Val Ile Leu Glu Ile Lys Ala Glu Glu Asp
50 55 60

gac acc gtc gac gtc ggc ggt gtc att gca ata atc ggc gat gct gat 240
Asp Thr Val Asp Val Gly Gly Val Ile Ala Ile Ile Gly Asp Ala Asp
65 70 75 80

gag act cct gcc aac gaa gct cct gcc gac gag gca cca gct cct gcc 288
Glu Thr Pro Ala Asn Glu Ala Pro Ala Asp Glu Ala Pro Ala Pro Ala
85 90 95

gaa gag gaa gaa cca gtt aag gaa gag cca aag aag gag gca gct cct 336
Glu Glu Glu Glu Pro Val Lys Glu Glu Pro Lys Lys Glu Ala Ala Pro
100 105 110

gaa gct cca gca gca act ggc gcc gca acc gat gtg gaa atg cca gaa 384
Glu Ala Pro Ala Ala Thr Gly Ala Ala Thr Asp Val Glu Met Pro Glu
115 120 125

ctc ggc gaa tcc gtc acc gaa ggc acc att acc cag tgg ctc aag gct 432
Leu Gly Glu Ser Val Thr Glu Gly Thr Ile Thr Gln Trp Leu Lys Ala
130 135 140

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gtc ggc gac acc gtc gaa gta gac gaa cca ctt ctt gag gtc tcc acc        480
Val Gly Asp Thr Val Glu Val Asp Glu Pro Leu Leu Glu Val Ser Thr
145                 150                 155                 160
gac aag gtc gac acc gaa atc cca tcc cca gta gca ggc acc atc gtg        528
Asp Lys Val Asp Thr Glu Ile Pro Ser Pro Val Ala Gly Thr Ile Val
                165                 170                 175
gag atc ctt gca gac gaa gac gac acc gtc gac gtc ggc gca gtc atc        576
Glu Ile Leu Ala Asp Glu Asp Asp Thr Val Asp Val Gly Ala Val Ile
            180                 185                 190
gcc cgc atc ggt gac gca aac gca gct gca gca cct gcc gaa gag gaa        624
Ala Arg Ile Gly Asp Ala Asn Ala Ala Ala Ala Pro Ala Glu Glu Glu
        195                 200                 205
gca gct cct gcc gaa gag gaa gaa cca gtt aag gaa gag cca aag aag        672
Ala Ala Pro Ala Glu Glu Glu Glu Pro Val Lys Glu Glu Pro Lys Lys
    210                 215                 220
gag gca gct cct gaa gct cca gca gca act ggc gcc gca acc gat gtg        720
Glu Ala Ala Pro Glu Ala Pro Ala Ala Thr Gly Ala Ala Thr Asp Val
225                 230                 235                 240
gaa atg cca gaa ctc ggc gaa tcc gtc acc gaa ggc acc att acc cag        768
Glu Met Pro Glu Leu Gly Glu Ser Val Thr Glu Gly Thr Ile Thr Gln
                245                 250                 255
tgg ctc aag gct gtc ggc gac acc gtc gaa gta gac gaa cca ctt ctt        816
Trp Leu Lys Ala Val Gly Asp Thr Val Glu Val Asp Glu Pro Leu Leu
            260                 265                 270
gag gtc tcc acc gac aag gtc gac acc gaa atc cca tcc cca gta gca        864
Glu Val Ser Thr Asp Lys Val Asp Thr Glu Ile Pro Ser Pro Val Ala
        275                 280                 285
ggc acc atc gtg gag atc ctt gca gac gaa gac gac acc gtc gac gtc        912
Gly Thr Ile Val Glu Ile Leu Ala Asp Glu Asp Asp Thr Val Asp Val
    290                 295                 300
ggc gca gtc atc gcc cgc atc ggt gac gca aac gca gct gca gca cct        960
Gly Ala Val Ile Ala Arg Ile Gly Asp Ala Asn Ala Ala Ala Ala Pro
305                 310                 315                 320
gcc gaa gag gaa gca gct cct gcc gaa gag gag gaa cca gtt aag gaa       1008
Ala Glu Glu Glu Ala Ala Pro Ala Glu Glu Glu Glu Pro Val Lys Glu
                325                 330                 335
gag cca aag aag gaa gag ccc aag aag gaa gag ccc aag aag gaa gca       1056
Glu Pro Lys Lys Glu Glu Pro Lys Lys Glu Glu Pro Lys Lys Glu Ala
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gct act aca cct gct gcg gca tcc gca act gtg tcc gct tct ggc gac       1104
Ala Thr Thr Pro Ala Ala Ala Ser Ala Thr Val Ser Ala Ser Gly Asp
        355                 360                 365
aac gtt cca tac gtc acc cca ctg gtg cgc aag ctt gct gaa aag cac       1152
Asn Val Pro Tyr Val Thr Pro Leu Val Arg Lys Leu Ala Glu Lys His
    370                 375                 380
ggc gtt gac ttg aac acc gtg acc ggt acc ggt atc ggt ggc cgt atc       1200
Gly Val Asp Leu Asn Thr Val Thr Gly Thr Gly Ile Gly Gly Arg Ile
385                 390                 395                 400
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cgc aag cag gat gtt ttg gct gct gcg aac ggc gag gct gca cct gct       1248
Arg Lys Gln Asp Val Leu Ala Ala Ala Asn Gly Glu Ala Ala Pro Ala
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gag gct gct gct cct gtt tcc gct tgg tcc act aag tct gtt gac cct       1296
Glu Ala Ala Ala Pro Val Ser Ala Trp Ser Thr Lys Ser Val Asp Pro
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gag aag gct aag ctc cgt ggt acc act cag aag gtc aac cgc atc cgt       1344
Glu Lys Ala Lys Leu Arg Gly Thr Thr Gln Lys Val Asn Arg Ile Arg
    435                 440                 445
gag atc acc gcg atg aag acc gtc gag gct ctg cag att tct gct cag       1392
Glu Ile Thr Ala Met Lys Thr Val Glu Ala Leu Gln Ile Ser Ala Gln
450                 455                 460
ctc acc cag ctg cac gag gtc gat atg act cgc gtt gct gag ctg cgt       1440
Leu Thr Gln Leu His Glu Val Asp Met Thr Arg Val Ala Glu Leu Arg
465                 470                 475                 480
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Lys Lys Asn Lys Pro Ala Phe Ile Glu Lys His Gly Val Asn Leu Thr
                485                 490                 495
tac ctg cca ttc ttc gtg aag gca gtt gtc gag gct ttg gtt tcc cat       1536
Tyr Leu Pro Phe Phe Val Lys Ala Val Val Glu Ala Leu Val Ser His
            500                 505                 510
cca aac gtc aac gcg tct ttc aac gcg aag acc aag gag atg acc tac       1584
Pro Asn Val Asn Ala Ser Phe Asn Ala Lys Thr Lys Glu Met Thr Tyr
    515                 520                 525
cac tcc tcc gtt aac ctc tcc atc gct gtt gat acc cca gct ggt ctg       1632
His Ser Ser Val Asn Leu Ser Ile Ala Val Asp Thr Pro Ala Gly Leu
530                 535                 540
ttg acc cca gtc att cac gat gct cag gat ctc tcc atc cca gag atc       1680
Leu Thr Pro Val Ile His Asp Ala Gln Asp Leu Ser Ile Pro Glu Ile
545                 550                 555                 560
gca aag gca att gtt gac ctg gct gat cgt tca cgc aac aac aag ctg       1728
Ala Lys Ala Ile Val Asp Leu Ala Asp Arg Ser Arg Asn Asn Lys Leu
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aag cca aac gat ctg tcc ggt ggc acc ttc acc atc acc aac att ggt       1776
Lys Pro Asn Asp Leu Ser Gly Gly Thr Phe Thr Ile Thr Asn Ile Gly
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tct gaa ggc gca ctg tct gat acc cca atc ctg gtt cca cca cag gct       1824
Ser Glu Gly Ala Leu Ser Asp Thr Pro Ile Leu Val Pro Pro Gln Ala
    595                 600                 605
ggc atc ttg ggc acc ggc gcg atc gtg aag cgt cca gtt gtc atc acc       1872
Gly Ile Leu Gly Thr Gly Ala Ile Val Lys Arg Pro Val Val Ile Thr
610                 615                 620
gag gat gga att gat tcc atc gcg atc cgt cag atg gtc ttc cta cca       1920
Glu Asp Gly Ile Asp Ser Ile Ala Ile Arg Gln Met Val Phe Leu Pro
625                 630                 635                 640
ctg acc tac gac cac cag gtt gta gat ggc gca gat gct ggt cgc ttc       1968
Leu Thr Tyr Asp His Gln Val Val Asp Gly Ala Asp Ala Gly Arg Phe
                645                 650                 655
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ctg acc acc atc aag gac cgc ctt gag acc gct aac ttc gaa ggc gat 2016
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ctg cag ctc taa 2028
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35 40 45
Pro Ser Pro Val Ala Gly Val Ile Leu Glu Ile Lys Ala Glu Glu Asp
50 55 60
Asp Thr Val Asp Val Gly Gly Val Ile Ala Ile Ile Gly Asp Ala Asp
65 70 75 80
Glu Thr Pro Ala Asn Glu Ala Pro Ala Asp Glu Ala Pro Ala Pro Ala
85 90 95
Glu Glu Glu Glu Pro Val Lys Glu Glu Pro Lys Lys Glu Ala Ala Pro
100 105 110
Glu Ala Pro Ala Ala Thr Gly Ala Ala Thr Asp Val Glu Met Pro Glu
115 120 125
Leu Gly Glu Ser Val Thr Glu Gly Thr Ile Thr Gln Trp Leu Lys Ala
130 135 140
Val Gly Asp Thr Val Glu Val Asp Glu Pro Leu Leu Glu Val Ser Thr
145 150 155 160
Asp Lys Val Asp Thr Glu Ile Pro Ser Pro Val Ala Gly Thr Ile Val
165 170 175
Glu Ile Leu Ala Asp Glu Asp Asp Thr Val Asp Val Gly Ala Val Ile
180 185 190
Ala Arg Ile Gly Asp Ala Asn Ala Ala Ala Ala Pro Ala Glu Glu Glu
195 200 205
Ala Ala Pro Ala Glu Glu Glu Glu Pro Val Lys Glu Glu Pro Lys Lys
210 215 220
Glu Ala Ala Pro Glu Ala Pro Ala Ala Thr Gly Ala Ala Thr Asp Val
225 230 235 240
Glu Met Pro Glu Leu Gly Glu Ser Val Thr Glu Gly Thr Ile Thr Gln
245 250 255
Trp Leu Lys Ala Val Gly Asp Thr Val Glu Val Asp Glu Pro Leu Leu
260 265 270

Glu Val Ser Thr Asp Lys Val Asp Thr Glu Ile Pro Ser Pro Val Ala
275 280 285

Gly Thr Ile Val Glu Ile Leu Ala Asp Glu Asp Asp Thr Val Asp Val
290 295 300

Gly Ala Val Ile Ala Arg Ile Gly Asp Ala Asn Ala Ala Ala Ala Pro
305 310 315 320

Ala Glu Glu Glu Ala Ala Pro Ala Glu Glu Glu Pro Val Lys Glu
325 330 335

Glu Pro Lys Lys Glu Glu Pro Lys Lys Glu Glu Pro Lys Lys Glu Ala
340 345 350

Ala Thr Thr Pro Ala Ala Ala Ser Ala Thr Val Ser Ala Ser Gly Asp
355 360 365

Asn Val Pro Tyr Val Thr Pro Leu Val Arg Lys Leu Ala Glu Lys His
370 375 380

Gly Val Asp Leu Asn Thr Val Thr Gly Thr Gly Ile Gly Gly Arg Ile
385 390 395 400

Arg Lys Gln Asp Val Leu Ala Ala Ala Asn Gly Glu Ala Ala Pro Ala
405 410 415

Glu Ala Ala Ala Pro Val Ser Ala Trp Ser Thr Lys Ser Val Asp Pro
420 425 430

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

Glu Ile Thr Ala Met Lys Thr Val Glu Ala Leu Gln Ile Ser Ala Gln
450 455 460

Leu Thr Gln Leu His Glu Val Asp Met Thr Arg Val Ala Glu Leu Arg
465 470 475 480

Lys Lys Asn Lys Pro Ala Phe Ile Glu Lys His Gly Val Asn Leu Thr
485 490 495

Tyr Leu Pro Phe Phe Val Lys Ala Val Val Glu Ala Leu Val Ser His
500 505 510

Pro Asn Val Asn Ala Ser Phe Asn Ala Lys Thr Lys Glu Met Thr Tyr
515 520 525

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

Leu Thr Pro Val Ile His Asp Ala Gln Asp Leu Ser Ile Pro Glu Ile
545 550 555 560

Ala Lys Ala Ile Val Asp Leu Ala Asp Arg Ser Arg Asn Asn Lys Leu
565 570 575

Lys Pro Asn Asp Leu Ser Gly Gly Thr Phe Thr Ile Thr Asn Ile Gly
580 585 590

Ser Glu Gly Ala Leu Ser Asp Thr Pro Ile Leu Val Pro Pro Gln Ala
595 600 605

Gly Ile Leu Gly Thr Gly Ala Ile Val Lys Arg Pro Val Val Ile Thr
610 615 620

Glu Asp Gly Ile Asp Ser Ile Ala Ile Arg Gln Met Val Phe Leu Pro
625 630 635 640

Leu Thr Tyr Asp His Gln Val Val Asp Gly Ala Asp Ala Gly Arg Phe
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Leu Gln Leu
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gctgcgctgc agtgcaccaa cagcggacac agtgccatgc atgcctggca tacccatgtg     180
cagctcgtgg gactctggga aggttcccag cgccatcaat gtggtgacaa ctggaatgcc     240
ggtgtgctca gcgaacgcac gaagctcttc gtgggcatca gccttgataa cgccgccgcc     300
aacgtaaagg acaggcttct tagactcacc gatcagtttg acagcctgct caatctgtcg     360
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agtaatcgcg aggtggaatg cctcagccaa tgcctgtgga atgtcgttgg ggttggtgac     540
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caagtttgca tcagcgattg gggtaaccaa gttggttgcg cctgggccag aggttgcaat     720
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cgtggcggga gtgggctgtt gagaagctgc cacattcacg actttctggc tcctttacta    1020
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agccctcatt taaaattgtt ccgacgcgga tgcgtgtgca cgcagtgcga cagatgtctg    1140
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gagtgttgtc gagggcgctt gacgagacga cttggaaggc cgttacggca ggcgccgcgc    1260
ggttactact acaagtcgaa taatggtcat ggtgtgtcat gctacacaca tcgagtttcc    1320
aattccacaa cgcacgaaaa ttcccacccc caaaactccc ccacttcggt taaggaatca    1380
ggattctcac aaagttcagg caggctcccg ctacttttca gcgctaatct tggctc atg    1439
                                                              Met
                                                              1

att tta ggc gta ccc att caa tat ttg ctc tat tca ttg tgg aat tgg      1487
Ile Leu Gly Val Pro Ile Gln Tyr Leu Leu Tyr Ser Leu Trp Asn Trp
            5                   10                  15

att gtc gat acc ggt ttt gat gta gca att atc ctg gtc ttg gcg ttt      1535
Ile Val Asp Thr Gly Phe Asp Val Ala Ile Ile Leu Val Leu Ala Phe
        20                  25                  30
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ttg att cca cgt atc ggc cga ctg gcc atg cgt att atc aag cag cga 1583
Leu Ile Pro Arg Ile Gly Arg Leu Ala Met Arg Ile Ile Lys Gln Arg
35 40 45

gtg gag tct gca gcc gat gcg gac acc act aag aac cag ctc gcg ttc 1631
Val Glu Ser Ala Ala Asp Ala Asp Thr Thr Lys Asn Gln Leu Ala Phe
50 55 60 65

gct ggc gtt ggc gtt tat atc gcg caa att gtg gcg ttt ttc atg ctt 1679
Ala Gly Val Gly Val Tyr Ile Ala Gln Ile Val Ala Phe Phe Met Leu
70 75 80

gcc gtc tcc gcg atg cag gct ttt ggt ttc tct ctc gcg ggc gct gcg 1727
Ala Val Ser Ala Met Gln Ala Phe Gly Phe Ser Leu Ala Gly Ala Ala
85 90 95

att ccg gca acc att gcg tca gct gcc att ggt ctt ggt gcg cag tcg 1775
Ile Pro Ala Thr Ile Ala Ser Ala Ala Ile Gly Leu Gly Ala Gln Ser
100 105 110

att gtt gcg gac ttc ttg gcc gga ttt ttc atc ctg acg gaa aag caa 1823
Ile Val Ala Asp Phe Leu Ala Gly Phe Phe Ile Leu Thr Glu Lys Gln
115 120 125

ttc ggc gtg ggt gac tgg gtg cgc ttt gag ggc aac ggc atc gtt gtt 1871
Phe Gly Val Gly Asp Trp Val Arg Phe Glu Gly Asn Gly Ile Val Val
130 135 140 145

gaa ggc acc gtc att gag atc acc atg cgc gcg acc aaa att cgc acg 1919
Glu Gly Thr Val Ile Glu Ile Thr Met Arg Ala Thr Lys Ile Arg Thr
150 155 160

att gca caa gag acc gtg atc atc ccg aac tcc acg gcg aaa gtg tgc 1967
Ile Ala Gln Glu Thr Val Ile Ile Pro Asn Ser Thr Ala Lys Val Cys
165 170 175

atc aac aat tct aat aac tgg tcg cgt gcg gtt gtc gtt att ccg atc 2015
Ile Asn Asn Ser Asn Asn Trp Ser Arg Ala Val Val Val Ile Pro Ile
180 185 190

ccc atg ttg ggt tct gaa aac atc aca gat gtc atc gcg cgc tct gaa 2063
Pro Met Leu Gly Ser Glu Asn Ile Thr Asp Val Ile Ala Arg Ser Glu
195 200 205

gct gcg act cgt cgc gca ctt ggc cag gag aaa atc gca ccg gaa atc 2111
Ala Ala Thr Arg Arg Ala Leu Gly Gln Glu Lys Ile Ala Pro Glu Ile
210 215 220 225

ctc ggt gaa ctc gat gtg cac cca gcc acg gaa gtc aca ccg cca acg 2159
Leu Gly Glu Leu Asp Val His Pro Ala Thr Glu Val Thr Pro Pro Thr
230 235 240

gtg gtc ggc atg ccg tgg atg gtc acc atg cgt ttc ctc gtg caa gtc 2207
Val Val Gly Met Pro Trp Met Val Thr Met Arg Phe Leu Val Gln Val
245 250 255

acc gcc ggc aat caa tgg ctg gtc gaa cgc gcc atc cgc aca gaa atc 2255
Thr Ala Gly Asn Gln Trp Leu Val Glu Arg Ala Ile Arg Thr Glu Ile
260 265 270

atc aac gaa ttc tgg gaa gaa tac ggc agc gca acc act aca tcg gga 2303
Ile Asn Glu Phe Trp Glu Glu Tyr Gly Ser Ala Thr Thr Thr Ser Gly
275 280 285

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acc ctc att gat tcc tta cac gtt gag cat gaa gag cca aag acc tcg       2351
Thr Leu Ile Asp Ser Leu His Val Glu His Glu Glu Pro Lys Thr Ser
290                 295                 300                 305
ctt atc gac gcc tcc ccc cag gct ctt aag gaa ccg aag ccg gag gct       2399
Leu Ile Asp Ala Ser Pro Gln Ala Leu Lys Glu Pro Lys Pro Glu Ala
                310                 315                 320
gcg gcg acg gtt gca tcg cta gct gca tcg tct aac gac gat gca gac       2447
Ala Ala Thr Val Ala Ser Leu Ala Ala Ser Ser Asn Asp Asp Ala Asp
            325                 330                 335
aat gca gac gcc tcg gcg atc aat gca ggc aat cca gag aag gaa ctt       2495
Asn Ala Asp Ala Ser Ala Ile Asn Ala Gly Asn Pro Glu Lys Glu Leu
        340                 345                 350
gat tcc gat gtg ctg gaa caa gaa ctc tcc agc gaa gaa ccg gaa gaa       2543
Asp Ser Asp Val Leu Glu Gln Glu Leu Ser Ser Glu Glu Pro Glu Glu
    355                 360                 365
aca gca aaa cca gat cac tct ctc cga ggc ttc ttc cgc act gat tac       2591
Thr Ala Lys Pro Asp His Ser Leu Arg Gly Phe Phe Arg Thr Asp Tyr
370                 375                 380                 385
tac cca aat cgg tgg cag aag atc ctg tcg ttt ggc gga cgt gtc cgc       2639
Tyr Pro Asn Arg Trp Gln Lys Ile Leu Ser Phe Gly Gly Arg Val Arg
                390                 395                 400
atg agc act tcc ctg ttg ttg ggt gcg ctg ctc ttg ctg tca cta ttt       2687
Met Ser Thr Ser Leu Leu Leu Gly Ala Leu Leu Leu Leu Ser Leu Phe
            405                 410                 415
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Lys Val Met Thr Val Glu Pro Ser Glu Asn Trp Gln Asn Ser Ser Gly
        420                 425                 430
tgg ctg tca cca agc act gcc acc tca act gcg gtg acc acc tcc gaa       2783
Trp Leu Ser Pro Ser Thr Ala Thr Ser Thr Ala Val Thr Thr Ser Glu
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act tcc gcg cca gca agc acg cct tcg atg aca gtg ccc act acg gtg       2831
Thr Ser Ala Pro Ala Ser Thr Pro Ser Met Thr Val Pro Thr Thr Val
450                 455                 460                 465
gag gag acc cca acg atg gaa tct agc gtc gaa acg cag cag gaa acc       2879
Glu Glu Thr Pro Thr Met Glu Ser Ser Val Glu Thr Gln Gln Glu Thr
                470                 475                 480
tca acc cct gca acc gca acg ccc cag cga gcc gac acc atc gaa ccg       2927
Ser Thr Pro Ala Thr Ala Thr Pro Gln Arg Ala Asp Thr Ile Glu Pro
            485                 490                 495
acc gag gaa gcc acg tcg cag gag gaa acg act gca tcg cag acg cag       2975
Thr Glu Glu Ala Thr Ser Gln Glu Glu Thr Thr Ala Ser Gln Thr Gln
        500                 505                 510
tct cca gca gtg gaa gca cca acc gcg gtc caa gaa aca gtt gcg ccg       3023
Ser Pro Ala Val Glu Ala Pro Thr Ala Val Gln Glu Thr Val Ala Pro
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acg tcc acc cct taggacgctg attacagacg tgtcccattt ctttactact           3075
Thr Ser Thr Pro
530
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Phe Leu Ile Pro Arg Ile Gly Arg Leu Ala Met Arg Ile Ile Lys Gln
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Arg Val Glu Ser Ala Ala Asp Ala Asp Thr Thr Lys Asn Gln Leu Ala
50 55 60
Phe Ala Gly Val Gly Val Tyr Ile Ala Gln Ile Val Ala Phe Phe Met
65 70 75 80
Leu Ala Val Ser Ala Met Gln Ala Phe Gly Phe Ser Leu Ala Gly Ala
85 90 95
Ala Ile Pro Ala Thr Ile Ala Ser Ala Ala Ile Gly Leu Gly Ala Gln
100 105 110
Ser Ile Val Ala Asp Phe Leu Ala Gly Phe Phe Ile Leu Thr Glu Lys
115 120 125
Gln Phe Gly Val Gly Asp Trp Val Arg Phe Glu Gly Asn Gly Ile Val
130 135 140
Val Glu Gly Thr Val Ile Glu Ile Thr Met Arg Ala Thr Lys Ile Arg
145 150 155 160
Thr Ile Ala Gln Glu Thr Val Ile Ile Pro Asn Ser Thr Ala Lys Val
165 170 175
Cys Ile Asn Asn Ser Asn Asn Trp Ser Arg Ala Val Val Val Ile Pro
180 185 190
Ile Pro Met Leu Gly Ser Glu Asn Ile Thr Asp Val Ile Ala Arg Ser
195 200 205
Glu Ala Ala Thr Arg Arg Ala Leu Gly Gln Glu Lys Ile Ala Pro Glu
210 215 220
Ile Leu Gly Glu Leu Asp Val His Pro Ala Thr Glu Val Thr Pro Pro
225 230 235 240
Thr Val Val Gly Met Pro Trp Met Val Thr Met Arg Phe Leu Val Gln
245 250 255
Val Thr Ala Gly Asn Gln Trp Leu Val Glu Arg Ala Ile Arg Thr Glu
260 265 270

Ile Ile Asn Glu Phe Trp Glu Glu Tyr Gly Ser Ala Thr Thr Thr Ser
275 280 285
Gly Thr Leu Ile Asp Ser Leu His Val Glu His Glu Glu Pro Lys Thr
290 295 300
Ser Leu Ile Asp Ala Ser Pro Gln Ala Leu Lys Glu Pro Lys Pro Glu
305 310 315 320
Ala Ala Ala Thr Val Ala Ser Leu Ala Ala Ser Ser Asn Asp Asp Ala
325 330 335
Asp Asn Ala Asp Ala Ser Ala Ile Asn Ala Gly Asn Pro Glu Lys Glu
340 345 350
Leu Asp Ser Asp Val Leu Glu Gln Glu Leu Ser Ser Glu Glu Pro Glu
355 360 365
Glu Thr Ala Lys Pro Asp His Ser Leu Arg Gly Phe Phe Arg Thr Asp
370 375 380
Tyr Tyr Pro Asn Arg Trp Gln Lys Ile Leu Ser Phe Gly Gly Arg Val
385 390 395 400
Arg Met Ser Thr Ser Leu Leu Leu Gly Ala Leu Leu Leu Leu Ser Leu
405 410 415
Phe Lys Val Met Thr Val Glu Pro Ser Glu Asn Trp Gln Asn Ser Ser
420 425 430
Gly Trp Leu Ser Pro Ser Thr Ala Thr Ser Thr Ala Val Thr Thr Ser
435 440 445
Glu Thr Ser Ala Pro Ala Ser Thr Pro Ser Met Thr Val Pro Thr Thr
450 455 460
Val Glu Glu Thr Pro Thr Met Glu Ser Ser Val Glu Thr Gln Gln Glu
465 470 475 480
Thr Ser Thr Pro Ala Thr Ala Thr Pro Gln Arg Ala Asp Thr Ile Glu
485 490 495
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515 520 525
Pro Thr Ser Thr Pro
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cagctcgtgg gactctggga aggttcccag cgccatcaat gtggtgacaa ctggaatgcc    240
ggtgtgctca gcgaacgcac gaagctcttc gtgggcatca gccttgataa cgccgccgcc    300
aacgtaaagg acaggcttct tagactcacc gatcagtttg acagcctgct caatctgtcg    360
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caagtttgca tcagcgattg gggtaaccaa gttggttgcg cctgggccag aggttgcaat    720
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gagtgttgtc gagggcgctt gacgagacga cttggaaggc cgttacggca ggcgccgcgc   1260
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aattccacaa cgcacgaaaa ttcccacccc caaaactccc ccacttcggt taaggaatca   1380
ggattctcac aaagttcagg caggctcccg ctacttttca gcgctaatct tggctc atg   1439
                                                              Met
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att tta ggc gta ccc att caa tat ttg ctc tat tca ttg tgg aat tgg     1487
Ile Leu Gly Val Pro Ile Gln Tyr Leu Leu Tyr Ser Leu Trp Asn Trp
            5                   10                  15

att gtc gat acc ggt ttt gat gta gca att atc ctg gtc ttg gcg ttt     1535
Ile Val Asp Thr Gly Phe Asp Val Ala Ile Ile Leu Val Leu Ala Phe
        20                  25                  30

ttg att cca cgt atc ggc cga ctg gcc atg cgt att atc aag cag cga     1583
Leu Ile Pro Arg Ile Gly Arg Leu Ala Met Arg Ile Ile Lys Gln Arg
    35                  40                  45

gtg gag tct gca gcc gat gcg gac acc act aag aac cag ctc gcg ttc     1631
Val Glu Ser Ala Ala Asp Ala Asp Thr Thr Lys Asn Gln Leu Ala Phe
50                  55                  60                  65

gct ggc gtt ggc gtt tat atc gcg caa att gtg gcg ttt ttc atg ctt     1679
Ala Gly Val Gly Val Tyr Ile Ala Gln Ile Val Ala Phe Phe Met Leu
                70                  75                  80

gcc gtc tcc gcg atg cag gct ttt ggt ttc tct ctc gcg ggc gct gcg     1727
Ala Val Ser Ala Met Gln Ala Phe Gly Phe Ser Leu Ala Gly Ala Ala
            85                  90                  95

att ccg gca acc att gcg tca gct gcc att ggt ctt ggt gtg cag tcg     1775
Ile Pro Ala Thr Ile Ala Ser Ala Ala Ile Gly Leu Gly Val Gln Ser
        100                 105                 110

att gtt gcg gac ttc ttg gcc gga ttt ttc atc ctg acg gaa aag caa     1823
Ile Val Ala Asp Phe Leu Ala Gly Phe Phe Ile Leu Thr Glu Lys Gln
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    115                 120                 125
ttc ggc gtg ggt gac tgg gtg cgc ttt gag ggc aac ggc atc gtt gtt      1871
Phe Gly Val Gly Asp Trp Val Arg Phe Glu Gly Asn Gly Ile Val Val
130                 135                 140                 145
gaa ggc acc gtc att gag atc acc atg cgc gcg acc aaa att cgc acg      1919
Glu Gly Thr Val Ile Glu Ile Thr Met Arg Ala Thr Lys Ile Arg Thr
                150                 155                 160
att gca caa gag acc gtg atc atc ccg aac tcc acg gcg aaa gtg tgc      1967
Ile Ala Gln Glu Thr Val Ile Ile Pro Asn Ser Thr Ala Lys Val Cys
            165                 170                 175
atc aac aat tct aat aac tgg tcg cgt gcg gtt gtc gtt att ccg atc      2015
Ile Asn Asn Ser Asn Asn Trp Ser Arg Ala Val Val Val Ile Pro Ile
        180                 185                 190
ccc atg ttg ggt tct gaa aac atc aca gat gtc atc gcg cgc tct gaa      2063
Pro Met Leu Gly Ser Glu Asn Ile Thr Asp Val Ile Ala Arg Ser Glu
    195                 200                 205
gct gcg act cgt cgc gca ctt ggc cag gag aaa atc gca ccg gaa atc      2111
Ala Ala Thr Arg Arg Ala Leu Gly Gln Glu Lys Ile Ala Pro Glu Ile
210                 215                 220                 225
ctc ggt gaa ctc gat gtg cac cca gcc acg gaa gtc aca ccg cca acg      2159
Leu Gly Glu Leu Asp Val His Pro Ala Thr Glu Val Thr Pro Pro Thr
                230                 235                 240
gtg gtc ggc atg ccg tgg atg gtc acc atg cgt ttc ctc gtg caa gtc      2207
Val Val Gly Met Pro Trp Met Val Thr Met Arg Phe Leu Val Gln Val
            245                 250                 255
acc gcc ggc aat caa tgg ctg gtc gaa cgc gcc atc cgc aca gaa atc      2255
Thr Ala Gly Asn Gln Trp Leu Val Glu Arg Ala Ile Arg Thr Glu Ile
        260                 265                 270
atc aac gaa ttc tgg gaa gaa tac ggc agc gca acc act aca tcg gga      2303
Ile Asn Glu Phe Trp Glu Glu Tyr Gly Ser Ala Thr Thr Thr Ser Gly
    275                 280                 285
acc ctc att gat tcc tta cac gtt gag cat gaa gag cca aag acc tcg      2351
Thr Leu Ile Asp Ser Leu His Val Glu His Glu Glu Pro Lys Thr Ser
290                 295                 300                 305
ctt atc gac gcc tcc ccc cag gct ctt aag gaa ccg aag ccg gag gct      2399
Leu Ile Asp Ala Ser Pro Gln Ala Leu Lys Glu Pro Lys Pro Glu Ala
                310                 315                 320
gcg gcg acg gtt gca tcg cta gct gca tcg tct aac gac gat gca gac      2447
Ala Ala Thr Val Ala Ser Leu Ala Ala Ser Ser Asn Asp Asp Ala Asp
            325                 330                 335
aat gca gac gcc tcg gcg atc aat gca ggc aat cca gag aag gaa ctt      2495
Asn Ala Asp Ala Ser Ala Ile Asn Ala Gly Asn Pro Glu Lys Glu Leu
        340                 345                 350
gat tcc gat gtg ctg gaa caa gaa ctc tcc agc gaa gaa ccg gaa gaa      2543
Asp Ser Asp Val Leu Glu Gln Glu Leu Ser Ser Glu Glu Pro Glu Glu
    355                 360                 365
aca gca aaa cca gat cac tct ctc cga ggc ttc ttc cgc act gat tac      2591
Thr Ala Lys Pro Asp His Ser Leu Arg Gly Phe Phe Arg Thr Asp Tyr
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Tyr Pro Asn Arg Trp Gln Lys Ile Leu Ser Phe Gly Gly Arg Val Arg
                390                 395                 400
atg agc act tcc ctg ttg ttg ggt gcg ctg ctc ttg ctg tca cta ttt        2687
Met Ser Thr Ser Leu Leu Leu Gly Ala Leu Leu Leu Leu Ser Leu Phe
            405                 410                 415
aag gtc atg act gtg gaa cca agt gag aat tgg caa aac tcc agt gga        2735
Lys Val Met Thr Val Glu Pro Ser Glu Asn Trp Gln Asn Ser Ser Gly
        420                 425                 430
tgg ctg tca cca agc act gcc acc tca act gcg gtg acc acc tcc gaa        2783
Trp Leu Ser Pro Ser Thr Ala Thr Ser Thr Ala Val Thr Thr Ser Glu
    435                 440                 445
act tcc gcg cca gca agc acg cct tcg atg aca gtg ccc act acg gtg        2831
Thr Ser Ala Pro Ala Ser Thr Pro Ser Met Thr Val Pro Thr Thr Val
450                 455                 460                 465
gag gag acc cca acg atg gaa tct agc gtc gaa acg cag cag gaa acc        2879
Glu Glu Thr Pro Thr Met Glu Ser Ser Val Glu Thr Gln Gln Glu Thr
                470                 475                 480
tca acc cct gca acc gca acg ccc cag cga gcc gac acc atc gaa ccg        2927
Ser Thr Pro Ala Thr Ala Thr Pro Gln Arg Ala Asp Thr Ile Glu Pro
            485                 490                 495
acc gag gaa gcc acg tcg cag gag gaa acg act gca tcg cag acg cag        2975
Thr Glu Glu Ala Thr Ser Gln Glu Glu Thr Thr Ala Ser Gln Thr Gln
        500                 505                 510
tct cca gca gtg gaa gca cca acc gcg gtc caa gaa aca gtt gcg ccg        3023
Ser Pro Ala Val Glu Ala Pro Thr Ala Val Gln Glu Thr Val Ala Pro
    515                 520                 525
acg tcc acc cct taggacgctg attacagacg tgtcccattt ctttactact            3075
Thr Ser Thr Pro
530
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Trp Ile Val Asp Thr Gly Phe Asp Val Ala Ile Ile Leu Val Leu Ala
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            20                  25                  30
Phe Leu Ile Pro Arg Ile Gly Arg Leu Ala Met Arg Ile Ile Lys Gln
        35                  40                  45
Arg Val Glu Ser Ala Ala Asp Ala Asp Thr Thr Lys Asn Gln Leu Ala
    50                  55                  60
Phe Ala Gly Val Gly Val Tyr Ile Ala Gln Ile Val Ala Phe Phe Met
65                  70                  75                  80
Leu Ala Val Ser Ala Met Gln Ala Phe Gly Phe Ser Leu Ala Gly Ala
                85                  90                  95
Ala Ile Pro Ala Thr Ile Ala Ser Ala Ala Ile Gly Leu Gly Val Gln
            100                 105                 110
Ser Ile Val Ala Asp Phe Leu Ala Gly Phe Phe Ile Leu Thr Glu Lys
        115                 120                 125
Gln Phe Gly Val Gly Asp Trp Val Arg Phe Glu Gly Asn Gly Ile Val
    130                 135                 140
Val Glu Gly Thr Val Ile Glu Ile Thr Met Arg Ala Thr Lys Ile Arg
145                 150                 155                 160
Thr Ile Ala Gln Glu Thr Val Ile Ile Pro Asn Ser Thr Ala Lys Val
                165                 170                 175
Cys Ile Asn Asn Ser Asn Asn Trp Ser Arg Ala Val Val Val Ile Pro
            180                 185                 190
Ile Pro Met Leu Gly Ser Glu Asn Ile Thr Asp Val Ile Ala Arg Ser
        195                 200                 205
Glu Ala Ala Thr Arg Arg Ala Leu Gly Gln Glu Lys Ile Ala Pro Glu
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Ile Leu Gly Glu Leu Asp Val His Pro Ala Thr Glu Val Thr Pro Pro
225                 230                 235                 240
Thr Val Val Gly Met Pro Trp Met Val Thr Met Arg Phe Leu Val Gln
                245                 250                 255
Val Thr Ala Gly Asn Gln Trp Leu Val Glu Arg Ala Ile Arg Thr Glu
            260                 265                 270
Ile Ile Asn Glu Phe Trp Glu Glu Tyr Gly Ser Ala Thr Thr Thr Ser
        275                 280                 285
Gly Thr Leu Ile Asp Ser Leu His Val Glu His Glu Glu Pro Lys Thr
    290                 295                 300
Ser Leu Ile Asp Ala Ser Pro Gln Ala Leu Lys Glu Pro Lys Pro Glu
305                 310                 315                 320
Ala Ala Ala Thr Val Ala Ser Leu Ala Ala Ser Ser Asn Asp Asp Ala
                325                 330                 335
Asp Asn Ala Asp Ala Ser Ala Ile Asn Ala Gly Asn Pro Glu Lys Glu
            340                 345                 350
Leu Asp Ser Asp Val Leu Glu Gln Glu Leu Ser Ser Glu Glu Pro Glu
        355                 360                 365
Glu Thr Ala Lys Pro Asp His Ser Leu Arg Gly Phe Phe Arg Thr Asp
    370                 375                 380
Tyr Tyr Pro Asn Arg Trp Gln Lys Ile Leu Ser Phe Gly Gly Arg Val
385                 390                 395                 400
Arg Met Ser Thr Ser Leu Leu Leu Gly Ala Leu Leu Leu Leu Ser Leu
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                405                 410                 415
Phe Lys Val Met Thr Val Glu Pro Ser Glu Asn Trp Gln Asn Ser Ser
            420                 425                 430
Gly Trp Leu Ser Pro Ser Thr Ala Thr Ser Thr Ala Val Thr Thr Ser
        435                 440                 445
Glu Thr Ser Ala Pro Ala Ser Thr Pro Ser Met Thr Val Pro Thr Thr
    450                 455                 460
Val Glu Glu Thr Pro Thr Met Glu Ser Ser Val Glu Thr Gln Gln Glu
465                 470                 475                 480
Thr Ser Thr Pro Ala Thr Ala Thr Pro Gln Arg Ala Asp Thr Ile Glu
                485                 490                 495
Pro Thr Glu Glu Ala Thr Ser Gln Glu Glu Thr Thr Ala Ser Gln Thr
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Pro Thr Ser Thr Pro
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cgaagccacc tccaccctcg accccgccac cgaagccgtt atcctcaacg cctccgatcg 240
agtcactaag ggacgcacca gcatcatcgt cgcgcaccgc ttggcaaccg ctaaaagggc 300

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cgaccgtatt cttgttgttg aacaaggacg tatcattgag gacggatctc acgacgcgtt    360
gttgtctgct aacggcacct acgcccgcat gtggcattta atggcctgac acgttatttt    420
taggagaact gtcaacaaat ta atg cta caa ctg ggg ctt agg cat aat cag     472
                         Met Leu Gln Leu Gly Leu Arg His Asn Gln
                         1               5                   10

cca acg acc aac gtt aca gtg gat aaa ata aag ctc aat aaa ccc tca      520
Pro Thr Thr Asn Val Thr Val Asp Lys Ile Lys Leu Asn Lys Pro Ser
                15                  20                  25

aga agc aag gaa aag agg cga gta cct gcc gtg agc agc gct agt act      568
Arg Ser Lys Glu Lys Arg Arg Val Pro Ala Val Ser Ser Ala Ser Thr
            30                  35                  40

ttc ggc cag aat gcg tgg ctg gta gac gag atg ttc cag cag ttc cag      616
Phe Gly Gln Asn Ala Trp Leu Val Asp Glu Met Phe Gln Gln Phe Gln
        45                  50                  55

aag gac ccc aag tcc gtg gac aag gaa tgg aga gaa ctc ttt gag gcg      664
Lys Asp Pro Lys Ser Val Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala
    60                  65                  70

cag ggg gga cca aat gct acc ccc gct aca aca gaa gca cag cct tca      712
Gln Gly Gly Pro Asn Ala Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser
75                  80                  85                  90

gcg ccc aag gag tct gcg aaa cca gca cca aag gct gcc cct gca gcc      760
Ala Pro Lys Glu Ser Ala Lys Pro Ala Pro Lys Ala Ala Pro Ala Ala
                95                  100                 105

aag gca gca ccg cgc gta gaa acc aag ccg gcc gcc aag acc gcc cct      808
Lys Ala Ala Pro Arg Val Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro
            110                 115                 120

aag gcc aag gag tcc tca gtg cca cag caa cct aag ctt ccg gag cca      856
Lys Ala Lys Glu Ser Ser Val Pro Gln Gln Pro Lys Leu Pro Glu Pro
        125                 130                 135

gga caa acc cca atc agg ggt att ttc aag tcc atc gcg aag aac atg      904
Gly Gln Thr Pro Ile Arg Gly Ile Phe Lys Ser Ile Ala Lys Asn Met
    140                 145                 150

gat atc tcc ctg gaa atc cca acc gca acc tcg gtt cgc gat atg cca      952
Asp Ile Ser Leu Glu Ile Pro Thr Ala Thr Ser Val Arg Asp Met Pro
155                 160                 165                 170

gct cgc ctc atg ttc gaa aac cgc gcg atg gtc aac gat cag ctc aag      1000
Ala Arg Leu Met Phe Glu Asn Arg Ala Met Val Asn Asp Gln Leu Lys
                175                 180                 185

cgc acc cgc ggt ggc aag atc tcc ttc acc cac atc att ggc tac gcc      1048
Arg Thr Arg Gly Gly Lys Ile Ser Phe Thr His Ile Ile Gly Tyr Ala
            190                 195                 200

atg gtg aag gca gtc atg gct cac ccg gac atg aac aac tcc tac gac      1096
Met Val Lys Ala Val Met Ala His Pro Asp Met Asn Asn Ser Tyr Asp
        205                 210                 215

gtc atc gac ggc aag cca acc ctg atc gtg cct gag cac atc aac ctg      1144
Val Ile Asp Gly Lys Pro Thr Leu Ile Val Pro Glu His Ile Asn Leu
    220                 225                 230

ggc ctt gcc atc gac ctt cct cag aag gac ggc tcc cgc gca ctt gtc      1192
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235 240 245 250

gta gca gcc atc aag gaa acc gag aag atg aac ttc tcc gag ttc ctc 1240
Val Ala Ala Ile Lys Glu Thr Glu Lys Met Asn Phe Ser Glu Phe Leu
255 260 265

gca gca tac gaa gac atc gtg aca cgc tcc cgc aag ggc aag ctc acc 1288
Ala Ala Tyr Glu Asp Ile Val Thr Arg Ser Arg Lys Gly Lys Leu Thr
270 275 280

atg gat gac tac cag ggc gtt acc gtt tcc ttg acc aac cca ggt ggc 1336
Met Asp Asp Tyr Gln Gly Val Thr Val Ser Leu Thr Asn Pro Gly Gly
285 290 295

atc ggt acc cgc cac tct gtc cca cgt ctg acc aag ggc cag ggc acc 1384
Ile Gly Thr Arg His Ser Val Pro Arg Leu Thr Lys Gly Gln Gly Thr
300 305 310

atc atc ggt gtc ggt tcc atg gat tac cca gca gag ttc cag ggc gct 1432
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315 320 325 330

tcc gaa gac cgc ctt gca gag ctc ggc gtt gga aag ctt gtc acc atc 1480
Ser Glu Asp Arg Leu Ala Glu Leu Gly Val Gly Lys Leu Val Thr Ile
335 340 345

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Thr Ser Thr Tyr Asp His Arg Val Ile Gln Gly Ala Val Ser Gly Glu
350 355 360

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365 370 375

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Glu Ile Phe Asp Ala Met Asn Val Pro Tyr Thr Pro Met Arg Trp Ala
380 385 390

cag gac gtt cca aac acc ggt gtt gat aag aac acc cgc gtc atg cag 1672
Gln Asp Val Pro Asn Thr Gly Val Asp Lys Asn Thr Arg Val Met Gln
395 400 405 410

ctc att gag gca tac cgc tcc cgt gga cac ctc atc gct gac acc aac 1720
Leu Ile Glu Ala Tyr Arg Ser Arg Gly His Leu Ile Ala Asp Thr Asn
415 420 425

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Pro Leu Ser Trp Val Gln Pro Gly Met Pro Val Pro Asp His Arg Asp
430 435 440

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Phe Ser Val Gly Gly Phe Gly Gly Lys Glu Thr Met Thr Leu Arg Glu
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475 480 485 490

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Tyr Thr His Ile Leu Asp Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg
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Leu Glu Ala Gly Met Pro Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile
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Leu Gln Lys Leu Asn Ala Ala Glu Ala Phe Glu Asn Phe Leu Gln Thr
        525                 530                 535
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atc cca ctg atg gac tcc gcc atc gac acc gcc gca ggc cag ggc ctc       2152
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Asp Glu Val Val Ile Gly Met Pro His Arg Gly Arg Leu Asn Val Leu
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Phe Asn Ile Val Gly Lys Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu
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ggc caa atg gag cag ggc cag atc ggt ggc tcc ggt gac gtg aag tac       2296
Gly Gln Met Glu Gln Gly Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr
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cac ctc ggt tcc gaa ggc cag cac ctg cag atg ttc ggc gac ggc gag       2344
His Leu Gly Ser Glu Gly Gln His Leu Gln Met Phe Gly Asp Gly Glu
    620                 625                 630
atc aag gtc tcc ctg act gct aac ccg tcc cac ctg gaa gct gtt aac       2392
Ile Lys Val Ser Leu Thr Ala Asn Pro Ser His Leu Glu Ala Val Asn
635                 640                 645                 650
cca gtg atg gaa ggt atc gtc cgc gca aag cag gac tac ctg gac aag       2440
Pro Val Met Glu Gly Ile Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys
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ggc gta gac ggc aag act gtt gtg cca ctg ctg ctc cac ggt gac gct       2488
Gly Val Asp Gly Lys Thr Val Val Pro Leu Leu Leu His Gly Asp Ala
            670                 675                 680
gca ttc gca ggc ctg ggc atc gtg cca gaa acc atc aac ctg gct aag       2536
Ala Phe Ala Gly Leu Gly Ile Val Pro Glu Thr Ile Asn Leu Ala Lys
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ctg cgt cgacgtcgga ggcaccatcc acatcgtggt gaacaaccag atcggcttca       2592
Leu Arg
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Gly Ile Phe Lys Ser Ile Ala Lys Asn Met Asp Ile Ser Leu Glu Ile
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Pro Gln Lys Asp Gly Ser Arg Ala Leu Val Val Ala Ala Ile Lys Glu
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Met Pro His Arg Gly Arg Leu Asn Val Leu Phe Asn Ile Val Gly Lys
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Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu Gly Gln Met Glu Gln Gly
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Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr His Leu Gly Ser Glu Gly
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Gln His Leu Gln Met Phe Gly Asp Gly Glu Ile Lys Val Ser Leu Thr
625                 630                 635                 640
Ala Asn Pro Ser His Leu Glu Ala Val Asn Pro Val Met Glu Gly Ile
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Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys Gly Val Asp Gly Lys Thr
            660                 665                 670
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Ile Val Pro Glu Thr Ile Asn Leu Ala Lys Leu Arg
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Pro Thr Thr Asn Val Thr Val Asp Lys Ile Lys Leu Asn Lys Pro Ser
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aga agc aag gaa aag agg cga gta cct gcc gtg agc agc gct agt act       568
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aag gac ccc aag tcc gtg gac aag gaa tgg aga gaa ctc ttt gag gcg      664
Lys Asp Pro Lys Ser Val Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala
        60                  65                  70

cag ggg gga cca aat gct acc ccc gct aca aca gaa gca cag cct tca      712
Gln Gly Gly Pro Asn Ala Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser
75                  80                  85                  90

gcg ccc aag gag tct gcg aaa cca gca cca aag gct gcc cct gca gcc      760
Ala Pro Lys Glu Ser Ala Lys Pro Ala Pro Lys Ala Ala Pro Ala Ala
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aag gca gca ccg cgc gta gaa acc aag ccg gcc gcc aag acc gcc cct      808
Lys Ala Ala Pro Arg Val Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro
            110                 115                 120

aag gcc aag gag tcc tca gtg cca cag caa cct aag ctt ccg gag cca      856
Lys Ala Lys Glu Ser Ser Val Pro Gln Gln Pro Lys Leu Pro Glu Pro
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gga caa acc cca atc agg ggt att ttc aag tcc atc gcg aag aac atg      904
Gly Gln Thr Pro Ile Arg Gly Ile Phe Lys Ser Ile Ala Lys Asn Met
    140                 145                 150

gat atc tcc ctg gaa atc cca acc gca acc tcg gtt cgc gat atg cca      952
Asp Ile Ser Leu Glu Ile Pro Thr Ala Thr Ser Val Arg Asp Met Pro
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gct cgc ctc atg ttc gaa aac cgc gcg atg gtc aac gat cag ctc aag      1000
Ala Arg Leu Met Phe Glu Asn Arg Ala Met Val Asn Asp Gln Leu Lys
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cgc acc cgc ggt ggc aag atc tcc ttc acc cac atc att ggc tac gcc      1048
Arg Thr Arg Gly Gly Lys Ile Ser Phe Thr His Ile Ile Gly Tyr Ala
            190                 195                 200

atg gtg aag gca gtc atg gct cac ccg gac atg aac aac tcc tac gac      1096
Met Val Lys Ala Val Met Ala His Pro Asp Met Asn Asn Ser Tyr Asp
        205                 210                 215

gtc atc gac ggc aag cca acc ctg atc gtg cct gag cac atc aac ctg      1144
Val Ile Asp Gly Lys Pro Thr Leu Ile Val Pro Glu His Ile Asn Leu
    220                 225                 230

ggc ctt gcc atc gac ctt cct cag aag gac ggc tcc cgc gca ctt gtc      1192
Gly Leu Ala Ile Asp Leu Pro Gln Lys Asp Gly Ser Arg Ala Leu Val
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gta gca gcc atc aag gaa acc gag aag atg aac ttc tcc gag ttc ctc      1240
Val Ala Ala Ile Lys Glu Thr Glu Lys Met Asn Phe Ser Glu Phe Leu
                255                 260                 265

gca gca tac gaa gac atc gtg aca cgc tcc cgc aag ggc aag ctc acc      1288
Ala Ala Tyr Glu Asp Ile Val Thr Arg Ser Arg Lys Gly Lys Leu Thr
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315 320 325 330

tcc gaa gac cgc ctt gca gag ctc ggc gtt gga aag ctt gtc acc atc 1480
Ser Glu Asp Arg Leu Ala Glu Leu Gly Val Gly Lys Leu Val Thr Ile
335 340 345

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Phe Leu Arg Thr Met Ser Arg Leu Leu Thr Asp Asp Ser Phe Trp Asp
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Glu Ile Phe Asp Ala Met Asn Val Pro Tyr Thr Pro Met Arg Trp Ala
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Gln Asp Val Pro Asn Thr Gly Val Asp Lys Asn Thr Arg Val Met Gln
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Pro Leu Ser Trp Val Gln Pro Gly Met Pro Val Pro Asp His Arg Asp
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gac gaa gtt gtc atc ggt atg cca cac cgt ggt cgc ctc aac gtg ctg      2200
Asp Glu Val Val Ile Gly Met Pro His Arg Gly Arg Leu Asn Val Leu
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ttc aac atc gtg ggc aag cca ctg gca tcc atc ttc aac gag ttt gaa      2248
Phe Asn Ile Val Gly Lys Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu
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ggc caa atg gag cag ggc cag atc ggt ggc tcc ggt gac gtg aag tac      2296
Gly Gln Met Glu Gln Gly Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr
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cac ctc ggt tcc gaa ggc cag cac ctg cag atg ttc ggc gac ggc gag      2344
His Leu Gly Ser Glu Gly Gln His Leu Gln Met Phe Gly Asp Gly Glu
    620                 625                 630

atc aag gtc tcc ctg act gct aac ccg tcc cac ctg gaa gct gtt aac      2392
Ile Lys Val Ser Leu Thr Ala Asn Pro Ser His Leu Glu Ala Val Asn
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cca gtg atg gaa ggt atc gtc cgc gca aag cag gac tac ctg gac aag      2440
Pro Val Met Glu Gly Ile Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys
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Gly Val Asp Gly Lys Thr Val Val Pro Leu Leu Leu His Gly Asp Ala
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Ala Phe Ala Gly Leu Gly Ile Val Pro Glu Thr Ile Asn Leu Ala Lys
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ctg cgt ctc gac gtc gga ggc acc atc cac atc gtg gtg aac aac cag      2584
Leu Arg Leu Asp Val Gly Gly Thr Ile His Ile Val Val Asn Asn Gln
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atc ggc ttc acc acc acc cca gac tcc agc cgc tcc atg cac tac gca      2632
Ile Gly Phe Thr Thr Thr Pro Asp Ser Ser Arg Ser Met His Tyr Ala
715                 720                 725                 730

acc gac tac gcc aag gca ttc ggc tgc cca gtc ttc cac gtc aat ggt      2680
Thr Asp Tyr Ala Lys Ala Phe Gly Cys Pro Val Phe His Val Asn Gly
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gat gac cca gag gca gtt gtc tgg gtt ggc cag ctg gca acc gag tac      2728
Asp Asp Pro Glu Ala Val Val Trp Val Gly Gln Leu Ala Thr Glu Tyr
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Arg Arg Arg Phe Gly Lys Asp Val Phe Ile Asp Leu Val Cys Tyr Arg
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Val Val Arg Asp Phe His Asp Gln Met Glu Ser Val Phe Asn Glu Val
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Tyr His Pro Arg Val Ala Pro Val Ala Lys Lys Arg Val Ser Ser Val
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Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala Gln Gly Gly Pro Asn Ala
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Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro Lys Ala Lys Glu Ser Ser
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Pro Thr Ala Thr Ser Val Arg Asp Met Pro Ala Arg Leu Met Phe Glu
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Asn Arg Ala Met Val Asn Asp Gln Leu Lys Arg Thr Arg Gly Gly Lys
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Ala His Pro Asp Met Asn Asn Ser Tyr Asp Val Ile Asp Gly Lys Pro
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Thr Leu Ile Val Pro Glu His Ile Asn Leu Gly Leu Ala Ile Asp Leu
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Thr Glu Lys Met Asn Phe Ser Glu Phe Leu Ala Ala Tyr Glu Asp Ile
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Val Thr Arg Ser Arg Lys Gly Lys Leu Thr Met Asp Asp Tyr Gln Gly
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Val Pro Arg Leu Thr Lys Gly Gln Gly Thr Ile Ile Gly Val Gly Ser
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Met Asp Tyr Pro Ala Glu Phe Gln Gly Ala Ser Glu Asp Arg Leu Ala
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Glu Leu Gly Val Gly Lys Leu Val Thr Ile Thr Ser Thr Tyr Asp His

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Asn Val Pro Tyr Thr Pro Met Arg Trp Ala Gln Asp Val Pro Asn Thr
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Gly Val Asp Lys Asn Thr Arg Val Met Gln Leu Ile Glu Ala Tyr Arg
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Ser Arg Gly His Leu Ile Ala Asp Thr Asn Pro Leu Ser Trp Val Gln
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Pro Gly Met Pro Val Pro Asp His Arg Asp Leu Asp Ile Glu Thr His
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Ser Leu Thr Ile Trp Asp Leu Asp Arg Thr Phe Ser Val Gly Gly Phe
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Gly Gly Lys Glu Thr Met Thr Leu Arg Glu Val Leu Ser Arg Leu Arg
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Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg Leu Glu Ala Gly Met Pro
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Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile Leu Gln Lys Leu Asn Ala
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Met Pro His Arg Gly Arg Leu Asn Val Leu Phe Asn Ile Val Gly Lys
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Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu Gly Gln Met Glu Gln Gly
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Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys Gly Val Asp Gly Lys Thr
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Pro Val Ala Lys Lys Arg Val Ser Ser Val Thr Glu Gly Gly Ile Asp
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Gln Arg His Ala Val Ala Ile Asp Pro Ala Thr Ala Glu Glu Phe Asn
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Pro Leu His Glu Leu Ala Gln Ser Lys Gly Asn Asn Gly Lys Phe Leu
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Gly Tyr Ser Val Gly Asn Glu Asp Ser Val Val Ala Trp Glu Ala Gln
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Phe Gly Asp Phe Ala Asn Gly Ala Gln Thr Ile Ile Asp Glu Tyr
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gttgtctgct aacggcacct acgcccgcat gtggcattta atggcctgac acgttatttt 420
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Met Leu Gln Leu Gly Leu Arg His Asn Gln
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Phe Gly Gln Asn Ala Trp Leu Val Asp Glu Met Phe Gln Gln Phe Gln
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Lys Asp Pro Lys Ser Val Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala
60 65 70

cag ggg gga cca aat gct acc ccc gct aca aca gaa gca cag cct tca 712
Gln Gly Gly Pro Asn Ala Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser
75 80 85 90

gcg ccc aag gag tct gcg aaa cca gca cca aag gct gcc cct gca gcc 760
Ala Pro Lys Glu Ser Ala Lys Pro Ala Pro Lys Ala Ala Pro Ala Ala
95 100 105

aag gca gca ccg cgc gta gaa acc aag ccg gcc gcc aag acc gcc cct 808
Lys Ala Ala Pro Arg Val Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro
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aag gcc aag gag tcc tca gtg cca cag caa cct aag ctt ccg gag cca 856
Lys Ala Lys Glu Ser Ser Val Pro Gln Gln Pro Lys Leu Pro Glu Pro
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gga caa acc cca atc agg ggt att ttc aag tcc atc gcg aag aac atg 904
Gly Gln Thr Pro Ile Arg Gly Ile Phe Lys Ser Ile Ala Lys Asn Met
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gat atc tcc ctg gaa atc cca acc gca acc tcg gtt cgc gat atg cca 952
Asp Ile Ser Leu Glu Ile Pro Thr Ala Thr Ser Val Arg Asp Met Pro
155 160 165 170

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175 180 185

cgc acc cgc ggt ggc aag atc tcc ttc acc cac atc att ggc tac gcc 1048
Arg Thr Arg Gly Gly Lys Ile Ser Phe Thr His Ile Ile Gly Tyr Ala
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atg gtg aag gca gtc atg gct cac ccg gac atg aac aac tcc tac gac 1096
Met Val Lys Ala Val Met Ala His Pro Asp Met Asn Asn Ser Tyr Asp
205 210 215

gtc atc gac ggc aag cca acc ctg atc gtg cct gag cac atc aac ctg 1144
Val Ile Asp Gly Lys Pro Thr Leu Ile Val Pro Glu His Ile Asn Leu
220 225 230

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Gly Leu Ala Ile Asp Leu Pro Gln Lys Asp Gly Ser Arg Ala Leu Val
235 240 245 250

gta gca gcc atc aag gaa acc gag aag atg aac ttc tcc gag ttc ctc 1240
Val Ala Ala Ile Lys Glu Thr Glu Lys Met Asn Phe Ser Glu Phe Leu
255 260 265

gca gca tac gaa gac atc gtg aca cgc tcc cgc aag ggc aag ctc acc 1288
Ala Ala Tyr Glu Asp Ile Val Thr Arg Ser Arg Lys Gly Lys Leu Thr
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Ile Gly Thr Arg His Ser Val Pro Arg Leu Thr Lys Gly Gln Gly Thr
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Ile Ile Gly Val Gly Ser Met Asp Tyr Pro Ala Glu Phe Gln Gly Ala
315                 320                 325                 330
tcc gaa gac cgc ctt gca gag ctc ggc gtt gga aag ctt gtc acc atc     1480
Ser Glu Asp Arg Leu Ala Glu Leu Gly Val Gly Lys Leu Val Thr Ile
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acc tcc acc tac gat cac cgc gtg atc cag ggt gct gtg tcc ggt gaa     1528
Thr Ser Thr Tyr Asp His Arg Val Ile Gln Gly Ala Val Ser Gly Glu
            350                 355                 360
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Phe Leu Arg Thr Met Ser Arg Leu Leu Thr Asp Asp Ser Phe Trp Asp
        365                 370                 375
gag atc ttc gac gca atg aac gtt cct tac acc cca atg cgt tgg gca     1624
Glu Ile Phe Asp Ala Met Asn Val Pro Tyr Thr Pro Met Arg Trp Ala
    380                 385                 390
cag gac gtt cca aac acc ggt gtt gat aag aac acc cgc gtc atg cag     1672
Gln Asp Val Pro Asn Thr Gly Val Asp Lys Asn Thr Arg Val Met Gln
395                 400                 405                 410
ctc att gag gca tac cgc tcc cgt gga cac ctc atc gct gac acc aac     1720
Leu Ile Glu Ala Tyr Arg Ser Arg Gly His Leu Ile Ala Asp Thr Asn
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Pro Leu Ser Trp Val Gln Pro Gly Met Pro Val Pro Asp His Arg Asp
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ctc gac atc gag acc cac agc ctg acc atc tgg gat ctg gac cgt acc     1816
Leu Asp Ile Glu Thr His Ser Leu Thr Ile Trp Asp Leu Asp Arg Thr
        445                 450                 455
ttc agc gtc ggt ggc ttc ggc ggc aag gag acc atg acc ctg cgc gag     1864
Phe Ser Val Gly Gly Phe Gly Gly Lys Glu Thr Met Thr Leu Arg Glu
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gta ctg tcc cgc ctg cgc gct gcc tac acc ttg aag gtc ggc tcc gaa     1912
Val Leu Ser Arg Leu Arg Ala Ala Tyr Thr Leu Lys Val Gly Ser Glu
475                 480                 485                 490
tac acc cac atc ctg gac cgc gac gag cgc acc tgg ctg cag gac cgc     1960
Tyr Thr His Ile Leu Asp Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg
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ctc gaa gcc gga atg cca aag cca acc cag gca gag cag aag tac atc     2008
Leu Glu Ala Gly Met Pro Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile
            510                 515                 520
ctg cag aag ctg aac gcc gca gag gct ttc gag aac ttc ctg cag acc     2056
Leu Gln Lys Leu Asn Ala Ala Glu Ala Phe Glu Asn Phe Leu Gln Thr
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aag tac gtc ggc cag aag cgc ttc tcc ctc gaa ggt gca gaa gct ctc     2104
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atc cca ctg atg gac tcc gcc atc gac acc gcc gca ggc cag ggc ctc      2152
Ile Pro Leu Met Asp Ser Ala Ile Asp Thr Ala Ala Gly Gln Gly Leu
555                 560                 565                 570

gac gaa gtt gtc atc ggt atg cca cac cgt ggt cgc ctc aac gtg ctg      2200
Asp Glu Val Val Ile Gly Met Pro His Arg Gly Arg Leu Asn Val Leu
                575                 580                 585

ttc aac atc gtg ggc aag cca ctg gca tcc atc ttc aac gag ttt gaa      2248
Phe Asn Ile Val Gly Lys Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu
            590                 595                 600

ggc caa atg gag cag ggc cag atc ggt ggc tcc ggt gac gtg aag tac      2296
Gly Gln Met Glu Gln Gly Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr
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cac ctc ggt tcc gaa ggc cag cac ctg cag atg ttc ggc gac ggc gag      2344
His Leu Gly Ser Glu Gly Gln His Leu Gln Met Phe Gly Asp Gly Glu
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atc aag gtc tcc ctg act gct aac ccg tcc cac ctg gaa gct gtt aac      2392
Ile Lys Val Ser Leu Thr Ala Asn Pro Ser His Leu Glu Ala Val Asn
635                 640                 645                 650

cca gtg atg gaa ggt atc gtc cgc gca aag cag gac tac ctg gac aag      2440
Pro Val Met Glu Gly Ile Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys
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ggc gta gac ggc aag act gtt gtg cca ctg ctg ctc cac ggt gac gct      2488
Gly Val Asp Gly Lys Thr Val Val Pro Leu Leu Leu His Gly Asp Ala
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gca ttc gca ggc ctg ggc atc gtg cca gaa acc atc aac ctg gct aaa      2536
Ala Phe Ala Gly Leu Gly Ile Val Pro Glu Thr Ile Asn Leu Ala Lys
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agc tgc gtc gac gtc gga ggc acc atc cac atc gtg gtg aac aac cag      2584
Ser Cys Val Asp Val Gly Gly Thr Ile His Ile Val Val Asn Asn Gln
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atc ggc ttc acc acc acc cca gac tcc agc cgc tcc atg cac tac gca      2632
Ile Gly Phe Thr Thr Thr Pro Asp Ser Ser Arg Ser Met His Tyr Ala
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acc gac tac gcc aag gca ttc ggc tgc cca gtc ttc cac gtc aat ggt      2680
Thr Asp Tyr Ala Lys Ala Phe Gly Cys Pro Val Phe His Val Asn Gly
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gat gac cca gag gca gtt gtc tgg gtt ggc cag ctg gca acc gag tac      2728
Asp Asp Pro Glu Ala Val Val Trp Val Gly Gln Leu Ala Thr Glu Tyr
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cgt cgt cgc ttc ggc aag gac gtc ttc atc gac ctc gtt tgc tac cgc      2776
Arg Arg Arg Phe Gly Lys Asp Val Phe Ile Asp Leu Val Cys Tyr Arg
        765                 770                 775

ctc cgc ggc cac aac gaa gct gat gat cct tcc atg acc cag cca aag      2824
Leu Arg Gly His Asn Glu Ala Asp Asp Pro Ser Met Thr Gln Pro Lys
    780                 785                 790

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815 820 825

gtc gtc cgc gac ttc cac gac cag atg gaa tct gtg ttc aac gaa gtc 2968
Val Val Arg Asp Phe His Asp Gln Met Glu Ser Val Phe Asn Glu Val
830 835 840

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Lys Glu Gly Gly Lys Lys Gln Ala Glu Ala Gln Thr Gly Ile Thr Gly
845 850 855

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875 880 885 890

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Tyr His Pro Arg Val Ala Pro Val Ala Lys Lys Arg Val Ser Ser Val
895 900 905

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Thr Glu Gly Gly Ile Asp Trp Ala Trp Gly Glu Leu Leu Ala Phe Gly
910 915 920

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Ser Leu Ala Asn Ser Gly Arg Leu Val Arg Leu Ala Gly Glu Asp Ser
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Ala Asn His Phe His Leu Leu Arg Arg His Ala Leu Ser Asp Leu
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Lys Arg Pro Leu Val Ile Phe Thr Pro Lys Ser Met Leu Arg Asn
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cgt atc gaa atg ctc cac cca att ccg ttc aac cgc atc tcc gag      3988
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gat gag cca gca aac cag ggc cca tgg ccg ttc tac cag gag cac      4078
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Arg Arg Ala Gln Ser Ser Thr Ala Thr Gly Val Ala Lys Val His
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Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala Gln Gly Gly Pro Asn Ala
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Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro Lys Ala Lys Glu Ser Ser
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Val Pro Gln Gln Pro Lys Leu Pro Glu Pro Gly Gln Thr Pro Ile Arg
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Gly Ile Phe Lys Ser Ile Ala Lys Asn Met Asp Ile Ser Leu Glu Ile
145 150 155 160
Pro Thr Ala Thr Ser Val Arg Asp Met Pro Ala Arg Leu Met Phe Glu
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Asn Arg Ala Met Val Asn Asp Gln Leu Lys Arg Thr Arg Gly Gly Lys
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Ala His Pro Asp Met Asn Asn Ser Tyr Asp Val Ile Asp Gly Lys Pro
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Thr Leu Ile Val Pro Glu His Ile Asn Leu Gly Leu Ala Ile Asp Leu
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Thr Glu Lys Met Asn Phe Ser Glu Phe Leu Ala Ala Tyr Glu Asp Ile
260 265 270
Val Thr Arg Ser Arg Lys Gly Lys Leu Thr Met Asp Asp Tyr Gln Gly
275 280 285
Val Thr Val Ser Leu Thr Asn Pro Gly Gly Ile Gly Thr Arg His Ser
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Glu Leu Gly Val Gly Lys Leu Val Thr Ile Thr Ser Thr Tyr Asp His

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

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785 790 795 800
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Gln Arg His Ala Val Ala Ile Asp Pro Ala Thr Ala Glu Glu Phe Asn
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Gly Tyr Ser Val Gly Asn Glu Asp Ser Val Val Ala Trp Glu Ala Gln
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gttgtctgct aacggcacct acgcccgcat gtggcattta atggcctgac acgttatttt 420
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Met Leu Gln Leu Gly Leu Arg His Asn Gln
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Pro Thr Thr Asn Val Thr Val Asp Lys Ile Lys Leu Asn Lys Pro Ser
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Phe Gly Gln Asn Ala Trp Leu Val Asp Glu Met Phe Gln Gln Phe Gln
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Lys Asp Pro Lys Ser Val Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala
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cag ggg gga cca aat gct acc ccc gct aca aca gaa gca cag cct tca 712
Gln Gly Gly Pro Asn Ala Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser
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gcg ccc aag gag tct gcg aaa cca gca cca aag gct gcc cct gca gcc 760
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Lys Ala Ala Pro Arg Val Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro
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Lys Ala Lys Glu Ser Ser Val Pro Gln Gln Pro Lys Leu Pro Glu Pro
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gga caa acc cca atc agg ggt att ttc aag tcc atc gcg aag aac atg 904
Gly Gln Thr Pro Ile Arg Gly Ile Phe Lys Ser Ile Ala Lys Asn Met
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Asp Ile Ser Leu Glu Ile Pro Thr Ala Thr Ser Val Arg Asp Met Pro
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Ala Arg Leu Met Phe Glu Asn Arg Ala Met Val Asn Asp Gln Leu Lys
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cgc acc cgc ggt ggc aag atc tcc ttc acc cac atc att ggc tac gcc 1048
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Met Val Lys Ala Val Met Ala His Pro Asp Met Asn Asn Ser Tyr Asp
205 210 215
gtc atc gac ggc aag cca acc ctg atc gtg cct gag cac atc aac ctg 1144
Val Ile Asp Gly Lys Pro Thr Leu Ile Val Pro Glu His Ile Asn Leu
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Gly Leu Ala Ile Asp Leu Pro Gln Lys Asp Gly Ser Arg Ala Leu Val
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gta gca gcc atc aag gaa acc gag aag atg aac ttc tcc gag ttc ctc 1240
Val Ala Ala Ile Lys Glu Thr Glu Lys Met Asn Phe Ser Glu Phe Leu
255 260 265
gca gca tac gaa gac atc gtg aca cgc tcc cgc aag ggc aag ctc acc 1288
Ala Ala Tyr Glu Asp Ile Val Thr Arg Ser Arg Lys Gly Lys Leu Thr
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atg gat gac tac cag ggc gtt acc gtt tcc ttg acc aac cca ggt ggc 1336
Met Asp Asp Tyr Gln Gly Val Thr Val Ser Leu Thr Asn Pro Gly Gly

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Ile Ile Gly Val Gly Ser Met Asp Tyr Pro Ala Glu Phe Gln Gly Ala
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Ser Glu Asp Arg Leu Ala Glu Leu Gly Val Gly Lys Leu Val Thr Ile
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acc tcc acc tac gat cac cgc gtg atc cag ggt gct gtg tcc ggt gaa      1528
Thr Ser Thr Tyr Asp His Arg Val Ile Gln Gly Ala Val Ser Gly Glu
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Phe Leu Arg Thr Met Ser Arg Leu Leu Thr Asp Asp Ser Phe Trp Asp
        365                 370                 375
gag atc ttc gac gca atg aac gtt cct tac acc cca atg cgt tgg gca      1624
Glu Ile Phe Asp Ala Met Asn Val Pro Tyr Thr Pro Met Arg Trp Ala
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cag gac gtt cca aac acc ggt gtt gat aag aac acc cgc gtc atg cag      1672
Gln Asp Val Pro Asn Thr Gly Val Asp Lys Asn Thr Arg Val Met Gln
395                 400                 405                 410
ctc att gag gca tac cgc tcc cgt gga cac ctc atc gct gac acc aac      1720
Leu Ile Glu Ala Tyr Arg Ser Arg Gly His Leu Ile Ala Asp Thr Asn
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cca ctt tca tgg gtt cag cct ggc atg cca gtt cca gac cac cgc gac      1768
Pro Leu Ser Trp Val Gln Pro Gly Met Pro Val Pro Asp His Arg Asp
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ctc gac atc gag acc cac agc ctg acc atc tgg gat ctg gac cgt acc      1816
Leu Asp Ile Glu Thr His Ser Leu Thr Ile Trp Asp Leu Asp Arg Thr
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ttc agc gtc ggt ggc ttc ggc ggc aag gag acc atg acc ctg cgc gag      1864
Phe Ser Val Gly Gly Phe Gly Gly Lys Glu Thr Met Thr Leu Arg Glu
    460                 465                 470
gta ctg tcc cgc ctg cgc gct gcc tac acc ttg aag gtc ggc tcc gaa      1912
Val Leu Ser Arg Leu Arg Ala Ala Tyr Thr Leu Lys Val Gly Ser Glu
475                 480                 485                 490
tac acc cac atc ctg gac cgc gac gag cgc acc tgg ctg cag gac cgc      1960
Tyr Thr His Ile Leu Asp Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg
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ctc gaa gcc gga atg cca aag cca acc cag gca gag cag aag tac atc      2008
Leu Glu Ala Gly Met Pro Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile
            510                 515                 520
ctg cag aag ctg aac gcc gca gag gct ttc gag aac ttc ctg cag acc      2056
Leu Gln Lys Leu Asn Ala Ala Glu Ala Phe Glu Asn Phe Leu Gln Thr
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gac gaa gtt gtc atc ggt atg cca cac cgt ggt cgc ctc aac gtg ctg       2200
Asp Glu Val Val Ile Gly Met Pro His Arg Gly Arg Leu Asn Val Leu
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ttc aac atc gtg ggc aag cca ctg gca tcc atc ttc aac gag ttt gaa       2248
Phe Asn Ile Val Gly Lys Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu
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ggc caa atg gag cag ggc cag atc ggt ggc tcc ggt gac gtg aag tac       2296
Gly Gln Met Glu Gln Gly Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr
        605                 610                 615
cac ctc ggt tcc gaa ggc cag cac ctg cag atg ttc ggc gac ggc gag       2344
His Leu Gly Ser Glu Gly Gln His Leu Gln Met Phe Gly Asp Gly Glu
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atc aag gtc tcc ctg act gct aac ccg tcc cac ctg gaa gct gtt aac       2392
Ile Lys Val Ser Leu Thr Ala Asn Pro Ser His Leu Glu Ala Val Asn
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cca gtg atg gaa ggt atc gtc cgc gca aag cag gac tac ctg gac aag       2440
Pro Val Met Glu Gly Ile Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys
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ggc gta gac ggc aag act gtt gtg cca ctg ctg ctc cac ggt gac gct       2488
Gly Val Asp Gly Lys Thr Val Val Pro Leu Leu Leu His Gly Asp Ala
            670                 675                 680
gca ttc gca ggc ctg ggc atc gtg cca gaa acc atc aac ctg gct ata       2536
Ala Phe Ala Gly Leu Gly Ile Val Pro Glu Thr Ile Asn Leu Ala Ile
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agc tgc gtc gac gtc gga ggc acc atc cac atc gtg gtg aac aac cag       2584
Ser Cys Val Asp Val Gly Gly Thr Ile His Ile Val Val Asn Asn Gln
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atc ggc ttc acc acc acc cca gac tcc agc cgc tcc atg cac tac gca       2632
Ile Gly Phe Thr Thr Thr Pro Asp Ser Ser Arg Ser Met His Tyr Ala
715                 720                 725                 730
acc gac tac gcc aag gca ttc ggc tgc cca gtc ttc cac gtc aat ggt       2680
Thr Asp Tyr Ala Lys Ala Phe Gly Cys Pro Val Phe His Val Asn Gly
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gat gac cca gag gca gtt gtc tgg gtt ggc cag ctg gca acc gag tac       2728
Asp Asp Pro Glu Ala Val Val Trp Val Gly Gln Leu Ala Thr Glu Tyr
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cgt cgt cgc ttc ggc aag gac gtc ttc atc gac ctc gtt tgc tac cgc       2776
Arg Arg Arg Phe Gly Lys Asp Val Phe Ile Asp Leu Val Cys Tyr Arg
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ctc cgc ggc cac aac gaa gct gat gat cct tcc atg acc cag cca aag       2824
Leu Arg Gly His Asn Glu Ala Asp Asp Pro Ser Met Thr Gln Pro Lys
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atg tat gag ctc atc acc ggc cgc gag acc gtt cgt gct cag tac acc       2872
Met Tyr Glu Leu Ile Thr Gly Arg Glu Thr Val Arg Ala Gln Tyr Thr
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gtc gtc cgc gac ttc cac gac cag atg gaa tct gtg ttc aac gaa gtc      2968
Val Val Arg Asp Phe His Asp Gln Met Glu Ser Val Phe Asn Glu Val
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aag gaa ggc ggc aag aag cag gct gag gca cag acc ggc atc acc ggc      3016
Lys Glu Gly Gly Lys Lys Gln Ala Glu Ala Gln Thr Gly Ile Thr Gly
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Ser Gln Lys Leu Pro His Gly Leu Glu Thr Asn Ile Ser Arg Glu Glu
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ctc ctg gaa ctg gga cag gct ttc gcc aac acc cca gaa ggc ttc aac      3112
Leu Leu Glu Leu Gly Gln Ala Phe Ala Asn Thr Pro Glu Gly Phe Asn
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tac cac cca cgt gtg gct cca gtt gct aag aag cgc gtc tcc tct gtc      3160
Tyr His Pro Arg Val Ala Pro Val Ala Lys Lys Arg Val Ser Ser Val
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acc gaa ggt ggc atc gac tgg gca tgg ggc gag ctc ctc gcc ttc ggt      3208
Thr Glu Gly Gly Ile Asp Trp Ala Trp Gly Glu Leu Leu Ala Phe Gly
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tcc ctg gct aac tcc ggc cgc ttg gtt cgc ctt gca ggt gaa gat tcc      3256
Ser Leu Ala Asn Ser Gly Arg Leu Val Arg Leu Ala Gly Glu Asp Ser
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cgc cgc ggt acc ttc acc cag cgc cac gca gtt gcc atc gac cca gcg      3304
Arg Arg Gly Thr Phe Thr Gln Arg His Ala Val Ala Ile Asp Pro Ala
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Thr Ala Glu Glu Phe Asn Pro Leu His Glu Leu Ala Gln Ser Lys Gly
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Gly Met Gly Phe Glu Tyr Gly Tyr Ser Val Gly Asn Glu Asp  Ser Val
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Val Ala Trp  Glu Ala Gln Phe Gly  Asp Phe Ala Asn Gly  Ala Gln
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acc atc atc  gat gag tac gtc tcc  tca ggc gaa gct aag  tgg ggc       3538
Thr Ile Ile  Asp Glu Tyr Val Ser  Ser Gly Glu Ala Lys  Trp Gly
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Gln Thr Ser  Lys Leu Ile Leu Leu  Leu Pro His Gly Tyr  Glu Gly
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Gln Gly Pro  Asp His Ser Ser Ala  Arg Ile Glu Arg Phe  Leu Gln
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Ala Asn His  Phe His Leu Leu Arg  Arg His Ala Leu Ser  Asp Leu
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Lys Arg Pro  Leu Val Ile Phe Thr  Pro Lys Ser Met Leu  Arg Asn
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Val Lys Lys  Val Met Leu Val Ser  Gly Lys Leu Tyr Tyr  Glu Leu
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Ala Lys Arg  Lys Glu Lys Asp Gly  Arg Asp Asp Ile Ala  Ile Val
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Arg Ile Glu  Met Leu His Pro Ile  Pro Phe Asn Arg Ile  Ser Glu
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gct ctt gcc  ggc tac cct aac gct  gag gaa gtc ctc ttc  gtt cag      4033
Ala Leu Ala  Gly Tyr Pro Asn Ala  Glu Glu Val Leu Phe  Val Gln
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Asp Glu Pro  Ala Asn Gln Gly Pro  Trp Pro Phe Tyr Gln  Glu His
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Leu Pro Glu  Leu Ile Pro Asn Met  Pro Lys Met Arg Arg  Val Ser
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Glu Thr Lys Pro Ala Ala Lys Thr Ala Pro Lys Ala Lys Glu Ser Ser
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Pro Thr Ala Thr Ser Val Arg Asp Met Pro Ala Arg Leu Met Phe Glu
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Asn Arg Ala Met Val Asn Asp Gln Leu Lys Arg Thr Arg Gly Gly Lys
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Ile Ser Phe Thr His Ile Ile Gly Tyr Ala Met Val Lys Ala Val Met
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Ala His Pro Asp Met Asn Asn Ser Tyr Asp Val Ile Asp Gly Lys Pro
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Thr Leu Ile Val Pro Glu His Ile Asn Leu Gly Leu Ala Ile Asp Leu
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Pro Gln Lys Asp Gly Ser Arg Ala Leu Val Val Ala Ala Ile Lys Glu
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Thr Glu Lys Met Asn Phe Ser Glu Phe Leu Ala Ala Tyr Glu Asp Ile
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Val Thr Arg Ser Arg Lys Gly Lys Leu Thr Met Asp Asp Tyr Gln Gly
275 280 285
Val Thr Val Ser Leu Thr Asn Pro Gly Gly Ile Gly Thr Arg His Ser
290 295 300
Val Pro Arg Leu Thr Lys Gly Gln Gly Thr Ile Ile Gly Val Gly Ser
305 310 315 320
Met Asp Tyr Pro Ala Glu Phe Gln Gly Ala Ser Glu Asp Arg Leu Ala
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Glu Leu Gly Val Gly Lys Leu Val Thr Ile Thr Ser Thr Tyr Asp His
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Arg Val Ile Gln Gly Ala Val Ser Gly Glu Phe Leu Arg Thr Met Ser

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Gly Val Asp Lys Asn Thr Arg Val Met Gln Leu Ile Glu Ala Tyr Arg
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Ser Arg Gly His Leu Ile Ala Asp Thr Asn Pro Leu Ser Trp Val Gln
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Ser Leu Thr Ile Trp Asp Leu Asp Arg Thr Phe Ser Val Gly Gly Phe
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465                 470                 475                 480
Ala Ala Tyr Thr Leu Lys Val Gly Ser Glu Tyr Thr His Ile Leu Asp
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Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg Leu Glu Ala Gly Met Pro
            500                 505                 510
Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile Leu Gln Lys Leu Asn Ala
        515                 520                 525
Ala Glu Ala Phe Glu Asn Phe Leu Gln Thr Lys Tyr Val Gly Gln Lys
    530                 535                 540
Arg Phe Ser Leu Glu Gly Ala Glu Ala Leu Ile Pro Leu Met Asp Ser
545                 550                 555                 560
Ala Ile Asp Thr Ala Ala Gly Gln Gly Leu Asp Glu Val Val Ile Gly
                565                 570                 575
Met Pro His Arg Gly Arg Leu Asn Val Leu Phe Asn Ile Val Gly Lys
            580                 585                 590
Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu Gly Gln Met Glu Gln Gly
        595                 600                 605
Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr His Leu Gly Ser Glu Gly
    610                 615                 620
Gln His Leu Gln Met Phe Gly Asp Gly Glu Ile Lys Val Ser Leu Thr
625                 630                 635                 640
Ala Asn Pro Ser His Leu Glu Ala Val Asn Pro Val Met Glu Gly Ile
                645                 650                 655
Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys Gly Val Asp Gly Lys Thr
            660                 665                 670
Val Val Pro Leu Leu Leu His Gly Asp Ala Ala Phe Ala Gly Leu Gly
        675                 680                 685
Ile Val Pro Glu Thr Ile Asn Leu Ala Ile Ser Cys Val Asp Val Gly
    690                 695                 700
Gly Thr Ile His Ile Val Val Asn Asn Gln Ile Gly Phe Thr Thr Thr
705                 710                 715                 720
Pro Asp Ser Ser Arg Ser Met His Tyr Ala Thr Asp Tyr Ala Lys Ala
                725                 730                 735
Phe Gly Cys Pro Val Phe His Val Asn Gly Asp Asp Pro Glu Ala Val
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740 745 750

Val Trp Val Gly Gln Leu Ala Thr Glu Tyr Arg Arg Arg Phe Gly Lys

755 760 765

Asp Val Phe Ile Asp Leu Val Cys Tyr Arg Leu Arg Gly His Asn Glu

770 775 780

Ala Asp Asp Pro Ser Met Thr Gln Pro Lys Met Tyr Glu Leu Ile Thr

785 790 795 800

Gly Arg Glu Thr Val Arg Ala Gln Tyr Thr Glu Asp Leu Leu Gly Arg

805 810 815

Gly Asp Leu Ser Asn Glu Asp Ala Glu Ala Val Val Arg Asp Phe His

820 825 830

Asp Gln Met Glu Ser Val Phe Asn Glu Val Lys Glu Gly Gly Lys Lys

835 840 845

Gln Ala Glu Ala Gln Thr Gly Ile Thr Gly Ser Gln Lys Leu Pro His

850 855 860

Gly Leu Glu Thr Asn Ile Ser Arg Glu Glu Leu Leu Glu Leu Gly Gln

865 870 875 880

Ala Phe Ala Asn Thr Pro Glu Gly Phe Asn Tyr His Pro Arg Val Ala

885 890 895

Pro Val Ala Lys Lys Arg Val Ser Ser Val Thr Glu Gly Gly Ile Asp

900 905 910

Trp Ala Trp Gly Glu Leu Leu Ala Phe Gly Ser Leu Ala Asn Ser Gly

915 920 925

Arg Leu Val Arg Leu Ala Gly Glu Asp Ser Arg Arg Gly Thr Phe Thr

930 935 940

Gln Arg His Ala Val Ala Ile Asp Pro Ala Thr Ala Glu Glu Phe Asn

945 950 955 960

Pro Leu His Glu Leu Ala Gln Ser Lys Gly Asn Asn Gly Lys Phe Leu

965 970 975

Val Tyr Asn Ser Ala Leu Thr Glu Tyr Ala Gly Met Gly Phe Glu Tyr

980 985 990

Gly Tyr Ser Val Gly Asn Glu Asp Ser Val Val Ala Trp Glu Ala Gln

995 1000 1005

Phe Gly Asp Phe Ala Asn Gly Ala Gln Thr Ile Ile Asp Glu Tyr

1010 1015 1020

Val Ser Ser Gly Glu Ala Lys Trp Gly Gln Thr Ser Lys Leu Ile

1025 1030 1035

Leu Leu Leu Pro His Gly Tyr Glu Gly Gln Gly Pro Asp His Ser

1040 1045 1050

Ser Ala Arg Ile Glu Arg Phe Leu Gln Leu Cys Ala Glu Gly Ser

1055 1060 1065

Met Thr Val Ala Gln Pro Ser Thr Pro Ala Asn His Phe His Leu

1070 1075 1080

Leu Arg Arg His Ala Leu Ser Asp Leu Lys Arg Pro Leu Val Ile

1085 1090 1095

Phe Thr Pro Lys Ser Met Leu Arg Asn Lys Ala Ala Ala Ser Ala

1100 1105 1110

Pro Glu Asp Phe Thr Glu Val Thr Lys Phe Gln Ser Val Ile Asp

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Asp Pro Asn Val Ala Asp Ala Ala Lys Val Lys Lys Val Met Leu
    1130                1135                1140
Val Ser Gly Lys Leu Tyr Tyr Glu Leu Ala Lys Arg Lys Glu Lys
    1145                1150                1155
Asp Gly Arg Asp Asp Ile Ala Ile Val Arg Ile Glu Met Leu His
    1160                1165                1170
Pro Ile Pro Phe Asn Arg Ile Ser Glu Ala Leu Ala Gly Tyr Pro
    1175                1180                1185
Asn Ala Glu Glu Val Leu Phe Val Gln Asp Glu Pro Ala Asn Gln
    1190                1195                1200
Gly Pro Trp Pro Phe Tyr Gln Glu His Leu Pro Glu Leu Ile Pro
    1205                1210                1215
Asn Met Pro Lys Met Arg Arg Val Ser Arg Arg Ala Gln Ser Ser
    1220                1225                1230
Thr Ala Thr Gly Val Ala Lys Val His Gln Leu Glu Glu Lys Gln
    1235                1240                1245
Leu Ile Asp Glu Ala Phe Glu Ala
    1250                1255

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1               5                   10                  15
gtg gat aaa aca aag ctc aat aaa ccc tca aga agc aag gaa aag agg        96
Val Asp Lys Thr Lys Leu Asn Lys Pro Ser Arg Ser Lys Glu Lys Arg
            20                  25                  30
cga gta cct gcc gtg agc agc gct agt act ttc ggc cag aat gcg tgg       144
Arg Val Pro Ala Val Ser Ser Ala Ser Thr Phe Gly Gln Asn Ala Trp
        35                  40                  45
ctg gta gac gag atg ttc cag cag ttc cag aag gac ccc aag tcc gtg       192
Leu Val Asp Glu Met Phe Gln Gln Phe Gln Lys Asp Pro Lys Ser Val
    50                  55                  60
gac aag gaa tgg aga gaa ctc ttt gag gcg cag ggg gga cca aat act       240
Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala Gln Gly Gly Pro Asn Thr
65                  70                  75                  80
acc ccc gct aca aca gaa gca cag cct tca gcg ccc aag gag tct gcg       288
Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser Ala Pro Lys Glu Ser Ala
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                 85                  90                  95
aaa cca gca cca aag gct gcc cct gca gcc aag gca gca ccg cgc gta      336
Lys Pro Ala Pro Lys Ala Ala Pro Ala Ala Lys Ala Ala Pro Arg Val
            100                 105                 110
gaa acc aag ccg gcc gac aag acc gcc cct aag gcc aag gag tcc tca      384
Glu Thr Lys Pro Ala Asp Lys Thr Ala Pro Lys Ala Lys Glu Ser Ser
        115                 120                 125
gtg cca cag caa cct aag ctt ccg gag cca gga caa acc cca atc agg      432
Val Pro Gln Gln Pro Lys Leu Pro Glu Pro Gly Gln Thr Pro Ile Arg
    130                 135                 140
ggt att ttc aag tcc atc gcg aag aac atg gat atc tcc ctg gaa atc      480
Gly Ile Phe Lys Ser Ile Ala Lys Asn Met Asp Ile Ser Leu Glu Ile
145                 150                 155                 160
cca acc gca acc tcg gtt cgc gat atg cca gct cgc ctc atg ttc gaa      528
Pro Thr Ala Thr Ser Val Arg Asp Met Pro Ala Arg Leu Met Phe Glu
                165                 170                 175
aac cgc gcg atg gtc aac gat cag ctc aag cgc acc cgc ggt ggc aag      576
Asn Arg Ala Met Val Asn Asp Gln Leu Lys Arg Thr Arg Gly Gly Lys
            180                 185                 190
atc tcc ttc acc cac atc att ggc tac gcc atg gtg aag gca gtc atg      624
Ile Ser Phe Thr His Ile Ile Gly Tyr Ala Met Val Lys Ala Val Met
        195                 200                 205
gct cac ccg gac atg aac aac tcc tac gac gtc atc gac ggc aag cca      672
Ala His Pro Asp Met Asn Asn Ser Tyr Asp Val Ile Asp Gly Lys Pro
    210                 215                 220
acc ctg atc gtg cct gag cac atc aac ctg ggc ctt gct atc gac ctt      720
Thr Leu Ile Val Pro Glu His Ile Asn Leu Gly Leu Ala Ile Asp Leu
225                 230                 235                 240
cct cag aag gac ggc tcc cgc gca ctt gtc gta gca gcc atc aag gaa      768
Pro Gln Lys Asp Gly Ser Arg Ala Leu Val Val Ala Ala Ile Lys Glu
                245                 250                 255
acc gag aag atg aac ttc tcc gag ttc ctc gca gcc tac gaa gac atc      816
Thr Glu Lys Met Asn Phe Ser Glu Phe Leu Ala Ala Tyr Glu Asp Ile
            260                 265                 270
gtg gca cgc tcc cgc aag ggc aag ctc acc atg gat gac tac cag ggc      864
Val Ala Arg Ser Arg Lys Gly Lys Leu Thr Met Asp Asp Tyr Gln Gly
        275                 280                 285
gtt acc gtt tcc ttg acc aac cca ggt ggc atc ggt acc cgc cac tct      912
Val Thr Val Ser Leu Thr Asn Pro Gly Gly Ile Gly Thr Arg His Ser
    290                 295                 300
gtt cca cgt cta acc aag ggc cag ggc acc atc atc ggt gtc ggt tcc      960
Val Pro Arg Leu Thr Lys Gly Gln Gly Thr Ile Ile Gly Val Gly Ser
305                 310                 315                 320
atg gat tac cca gca gag ttc cag ggc gct tca gaa gac cgc ctt gca     1008
Met Asp Tyr Pro Ala Glu Phe Gln Gly Ala Ser Glu Asp Arg Leu Ala
                325                 330                 335
gag ctc ggc gtt ggc aaa ctt gtc acc atc acc tcc acc tac gat cac     1056
Glu Leu Gly Val Gly Lys Leu Val Thr Ile Thr Ser Thr Tyr Asp His
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340 345 350
cgc gtg atc cag ggt gct gtg tcc ggt gaa ttc ctg cgc acc atg tct 1104
Arg Val Ile Gln Gly Ala Val Ser Gly Glu Phe Leu Arg Thr Met Ser
355 360 365
cgc ctg ctc acc gat gat tcc ttc tgg gat gag atc ttc gac gca atg 1152
Arg Leu Leu Thr Asp Asp Ser Phe Trp Asp Glu Ile Phe Asp Ala Met
370 375 380
aac gtt cct tac acc cca atg cgt tgg gca cag gac gtt cca aac acc 1200
Asn Val Pro Tyr Thr Pro Met Arg Trp Ala Gln Asp Val Pro Asn Thr
385 390 395 400
ggt gtt gat aag aac acc cgc gtc atg cag ctc att gag gca tac cgc 1248
Gly Val Asp Lys Asn Thr Arg Val Met Gln Leu Ile Glu Ala Tyr Arg
405 410 415
tcc cgt gga cac ctc atc gct gac acc aac cca ctt tca tgg gtt cag 1296
Ser Arg Gly His Leu Ile Ala Asp Thr Asn Pro Leu Ser Trp Val Gln
420 425 430
cct ggc atg cca gtt cca gac cac cgc gac ctc gac atc gag acc cac 1344
Pro Gly Met Pro Val Pro Asp His Arg Asp Leu Asp Ile Glu Thr His
435 440 445
aac ctg acc atc tgg gat ctg gac cgt acc ttc aac gtc ggt ggc ttc 1392
Asn Leu Thr Ile Trp Asp Leu Asp Arg Thr Phe Asn Val Gly Gly Phe
450 455 460
ggc ggc aag gag acc atg acc ctg cgc gag gta ctg tcc cgc ctc cgc 1440
Gly Gly Lys Glu Thr Met Thr Leu Arg Glu Val Leu Ser Arg Leu Arg
465 470 475 480
gct gcg tac acc ctc aag gtc ggc tcc gaa tac acc cac atc ctg gac 1488
Ala Ala Tyr Thr Leu Lys Val Gly Ser Glu Tyr Thr His Ile Leu Asp
485 490 495
cgc gac gag cgc acc tgg ctg cag gac cgc ctc gag gcc gga atg cca 1536
Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg Leu Glu Ala Gly Met Pro
500 505 510
aag cca acc cag gca gag cag aag tac atc ctg cag aag ctg aac gcc 1584
Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile Leu Gln Lys Leu Asn Ala
515 520 525
gcg gag gct ttc gag aac ttc ctg cag acc aag tac gtc ggc cag aag 1632
Ala Glu Ala Phe Glu Asn Phe Leu Gln Thr Lys Tyr Val Gly Gln Lys
530 535 540
cgc ttc tcc ctc gaa ggt gca gaa gca ctt atc cca ctg atg gac tcc 1680
Arg Phe Ser Leu Glu Gly Ala Glu Ala Leu Ile Pro Leu Met Asp Ser
545 550 555 560
gcc atc gac acc gcc gca ggc caa ggc ctc gac gaa gtt gtc atc ggt 1728
Ala Ile Asp Thr Ala Ala Gly Gln Gly Leu Asp Glu Val Val Ile Gly
565 570 575
atg cca cac cgt ggt cgc ctc aac gtg ctg ttc aac atc gtg ggc aag 1776
Met Pro His Arg Gly Arg Leu Asn Val Leu Phe Asn Ile Val Gly Lys
580 585 590
cca ctg gca tcc atc ttc aac gag ttt gaa ggc caa atg gag cag ggc 1824
Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu Gly Gln Met Glu Gln Gly

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        595                 600                 605
cag atc ggt ggc tcc ggt gac gtg aag tac cac ctc ggt tcc gaa ggc      1872
Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr His Leu Gly Ser Glu Gly
    610                 615                 620
cag cac ctg cag atg ttc ggc gac ggc gag atc aag gtc tcc ctg act      1920
Gln His Leu Gln Met Phe Gly Asp Gly Glu Ile Lys Val Ser Leu Thr
625                 630                 635                 640
gct aac ccg tcc cac ctg gaa gct gtt aac cca gtg atg gaa ggt atc      1968
Ala Asn Pro Ser His Leu Glu Ala Val Asn Pro Val Met Glu Gly Ile
                645                 650                 655
gtc cgc gca aag cag gac tac ctg gac aag ggc gta gac ggc aag act      2016
Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys Gly Val Asp Gly Lys Thr
            660                 665                 670
gtt gtg cca ctg ctg ctc cac ggt gac gct gca ttc gca ggc ctg ggc      2064
Val Val Pro Leu Leu Leu His Gly Asp Ala Ala Phe Ala Gly Leu Gly
        675                 680                 685
atc gtg cca gaa acc atc aac ctg gct aag ctg cgt ggc tac gac gtc      2112
Ile Val Pro Glu Thr Ile Asn Leu Ala Lys Leu Arg Gly Tyr Asp Val
    690                 695                 700
ggc ggc acc atc cac atc gtg gtg aac aac cag atc ggc ttc acc acc      2160
Gly Gly Thr Ile His Ile Val Val Asn Asn Gln Ile Gly Phe Thr Thr
705                 710                 715                 720
acc cca gac tcc agc cgc tcc atg cac tac gca acc gac tac gcc aag      2208
Thr Pro Asp Ser Ser Arg Ser Met His Tyr Ala Thr Asp Tyr Ala Lys
                725                 730                 735
gca ttc ggc tgc cca gtc ttc cac gtc aac ggc gac gac cca gag gca      2256
Ala Phe Gly Cys Pro Val Phe His Val Asn Gly Asp Asp Pro Glu Ala
            740                 745                 750
gtt gtc tgg gtt ggc cag ctg gcc acc gag tac cgt cgt cgc ttc ggc      2304
Val Val Trp Val Gly Gln Leu Ala Thr Glu Tyr Arg Arg Arg Phe Gly
        755                 760                 765
aag gac gtc ttc atc gac ctc gtc tgc tac cgc ctc cgc ggc cac aac      2352
Lys Asp Val Phe Ile Asp Leu Val Cys Tyr Arg Leu Arg Gly His Asn
    770                 775                 780
gaa gct gat gat cct tcc atg acc cag cca aag atg tat gag ctc atc      2400
Glu Ala Asp Asp Pro Ser Met Thr Gln Pro Lys Met Tyr Glu Leu Ile
785                 790                 795                 800
acc ggc cgc gag acc gtt cgt gct cag tac acc gaa gac ctg ctc gga      2448
Thr Gly Arg Glu Thr Val Arg Ala Gln Tyr Thr Glu Asp Leu Leu Gly
                805                 810                 815
cgt gga gac ctc tcc aac gaa gat gca gaa gca gtc gtc cgc gac ttc      2496
Arg Gly Asp Leu Ser Asn Glu Asp Ala Glu Ala Val Val Arg Asp Phe
            820                 825                 830
cac gac cag atg gaa tct gtg ttc aac gaa gtc aag gaa ggc ggc aag      2544
His Asp Gln Met Glu Ser Val Phe Asn Glu Val Lys Glu Gly Gly Lys
        835                 840                 845
aag cag gct gag gca cag acc ggc atc acc ggc tcc cag aag ctt cca      2592
Lys Gln Ala Glu Ala Gln Thr Gly Ile Thr Gly Ser Gln Lys Leu Pro
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    850                 855                 860
cac ggc ctt gag acc aac atc tcc cgt gaa gag ctc ctg gaa ctg gga       2640
His Gly Leu Glu Thr Asn Ile Ser Arg Glu Glu Leu Leu Glu Leu Gly
865                 870                 875                 880
cag gct ttc gcc aac acc cca gaa ggc ttc aac tac cac cca cgt gtg       2688
Gln Ala Phe Ala Asn Thr Pro Glu Gly Phe Asn Tyr His Pro Arg Val
                885                 890                 895
gct ccc gtt gct aag aag cgc gtc tcc tct gtc acc gaa ggt ggc atc       2736
Ala Pro Val Ala Lys Lys Arg Val Ser Ser Val Thr Glu Gly Gly Ile
            900                 905                 910
gac tgg gca tgg ggc gag ctc ctc gcc ttc ggt tcc ctg gct aac tcc       2784
Asp Trp Ala Trp Gly Glu Leu Leu Ala Phe Gly Ser Leu Ala Asn Ser
        915                 920                 925
ggc cgc ttg gtt cgc ctt gca ggt gaa gat tcc cgc cgc ggt acc ttc       2832
Gly Arg Leu Val Arg Leu Ala Gly Glu Asp Ser Arg Arg Gly Thr Phe
    930                 935                 940
acc cag cgc cac gca gtt gcc atc gac cca gcg acc gct gaa gag ttc       2880
Thr Gln Arg His Ala Val Ala Ile Asp Pro Ala Thr Ala Glu Glu Phe
945                 950                 955                 960
aac cca ctc cac gag ctt gca cag tcc aag ggc aac aac ggt aag ttc       2928
Asn Pro Leu His Glu Leu Ala Gln Ser Lys Gly Asn Asn Gly Lys Phe
                965                 970                 975
ctg gtc tac aac tcc gca ctg acc gag tac gca ggc atg ggc ttc gag       2976
Leu Val Tyr Asn Ser Ala Leu Thr Glu Tyr Ala Gly Met Gly Phe Glu
            980                 985                 990
tac ggc tac tcc gta gga aac gaa  gac tcc atc gtt gca  tgg gaa gca     3024
Tyr Gly Tyr Ser Val Gly Asn Glu  Asp Ser Ile Val Ala  Trp Glu Ala
        995                 1000                 1005
cag ttc  ggc gac ttc gcc aac  ggc gct cag acc atc  atc gat gag        3069
Gln Phe  Gly Asp Phe Ala Asn  Gly Ala Gln Thr Ile  Ile Asp Glu
    1010                 1015                 1020
tac gtc  tcc tca ggc gaa gct  aag tgg ggc cag acc  tcc aag ctg        3114
Tyr Val  Ser Ser Gly Glu Ala  Lys Trp Gly Gln Thr  Ser Lys Leu
    1025                 1030                 1035
atc ctt  ctg ctg cct cac ggc  tac gaa ggc cag ggc  cca gac cac        3159
Ile Leu  Leu Leu Pro His Gly  Tyr Glu Gly Gln Gly  Pro Asp His
    1040                 1045                 1050
tct tcc  gca cgt atc gag cgc  ttc ctg cag ctg tgc  gct gag ggt        3204
Ser Ser  Ala Arg Ile Glu Arg  Phe Leu Gln Leu Cys  Ala Glu Gly
    1055                 1060                 1065
tcc atg  act gtt gct cag cca  tcc acc cca gca aac  cac ttc cac        3249
Ser Met  Thr Val Ala Gln Pro  Ser Thr Pro Ala Asn  His Phe His
    1070                 1075                 1080
cta ctg  cgt cgt cac gct ctg  tcc gac ctg aag cgt  cca ctg gtt        3294
Leu Leu  Arg Arg His Ala Leu  Ser Asp Leu Lys Arg  Pro Leu Val
    1085                 1090                 1095
atc ttc  acc ccg aag tcc atg  ctg cgt aac aag gct  gct gcc tcc        3339
Ile Phe  Thr Pro Lys Ser Met  Leu Arg Asn Lys Ala  Ala Ala Ser
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    1100                1105                1110
gca cca  gaa gac ttc act gag  gtc acc aag ttc cag  tcc gtg atc      3384
Ala Pro  Glu Asp Phe Thr Glu  Val Thr Lys Phe Gln  Ser Val Ile
    1115                1120                1125
aac gat  cca aac gtt gca gat  gca gcc aag gtg aag  aag gtc atg      3429
Asn Asp  Pro Asn Val Ala Asp  Ala Ala Lys Val Lys  Lys Val Met
    1130                1135                1140
ctg gtc  tcc ggc aag ctg tac  tac gaa ttg gca aag  cgc aag gag      3474
Leu Val  Ser Gly Lys Leu Tyr  Tyr Glu Leu Ala Lys  Arg Lys Glu
    1145                1150                1155
aag gac  gga cgc gac gac atc  gcg atc gtt cgt atc  gaa atg ctc      3519
Lys Asp  Gly Arg Asp Asp Ile  Ala Ile Val Arg Ile  Glu Met Leu
    1160                1165                1170
cac cca  att ccg ttc aac cgc  atc tcc gag gct ctt  gcc ggc tac      3564
His Pro  Ile Pro Phe Asn Arg  Ile Ser Glu Ala Leu  Ala Gly Tyr
    1175                1180                1185
cct aac  gct gag gaa gtc ctc  ttc gtt cag gat gag  cca gca aac      3609
Pro Asn  Ala Glu Glu Val Leu  Phe Val Gln Asp Glu  Pro Ala Asn
    1190                1195                1200
cag ggc  cca tgg ccg ttc tac  cag gag cac ctc cca  gag ctg atc      3654
Gln Gly  Pro Trp Pro Phe Tyr  Gln Glu His Leu Pro  Glu Leu Ile
    1205                1210                1215
ccg aac  atg cca aag atg cgc  cgc gtt tcc cgc cgc  gct cag tcc      3699
Pro Asn  Met Pro Lys Met Arg  Arg Val Ser Arg Arg  Ala Gln Ser
    1220                1225                1230
tcc acc  gca act ggt gtt gcc  aag gtg cac cag ctg  gag gag aag      3744
Ser Thr  Ala Thr Gly Val Ala  Lys Val His Gln Leu  Glu Glu Lys
    1235                1240                1245
cag ctt  atc gac gag gct ttc  gag gct taa                          3774
Gln Leu  Ile Asp Glu Ala Phe  Glu Ala
    1250                1255


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            20                  25                  30
Arg Val Pro Ala Val Ser Ser Ala Ser Thr Phe Gly Gln Asn Ala Trp
        35                  40                  45
Leu Val Asp Glu Met Phe Gln Gln Phe Gln Lys Asp Pro Lys Ser Val
    50                  55                  60
Asp Lys Glu Trp Arg Glu Leu Phe Glu Ala Gln Gly Gly Pro Asn Thr
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65                  70                  75                  80
Thr Pro Ala Thr Thr Glu Ala Gln Pro Ser Ala Pro Lys Glu Ser Ala
                85                  90                  95
Lys Pro Ala Pro Lys Ala Ala Pro Ala Ala Lys Ala Ala Pro Arg Val
            100                 105                 110
Glu Thr Lys Pro Ala Asp Lys Thr Ala Pro Lys Ala Lys Glu Ser Ser
        115                 120                 125
Val Pro Gln Gln Pro Lys Leu Pro Glu Pro Gly Gln Thr Pro Ile Arg
    130                 135                 140
Gly Ile Phe Lys Ser Ile Ala Lys Asn Met Asp Ile Ser Leu Glu Ile
145                 150                 155                 160
Pro Thr Ala Thr Ser Val Arg Asp Met Pro Ala Arg Leu Met Phe Glu
                165                 170                 175
Asn Arg Ala Met Val Asn Asp Gln Leu Lys Arg Thr Arg Gly Gly Lys
            180                 185                 190
Ile Ser Phe Thr His Ile Ile Gly Tyr Ala Met Val Lys Ala Val Met
        195                 200                 205
Ala His Pro Asp Met Asn Asn Ser Tyr Asp Val Ile Asp Gly Lys Pro
    210                 215                 220
Thr Leu Ile Val Pro Glu His Ile Asn Leu Gly Leu Ala Ile Asp Leu
225                 230                 235                 240
Pro Gln Lys Asp Gly Ser Arg Ala Leu Val Val Ala Ala Ile Lys Glu
                245                 250                 255
Thr Glu Lys Met Asn Phe Ser Glu Phe Leu Ala Ala Tyr Glu Asp Ile
            260                 265                 270
Val Ala Arg Ser Arg Lys Gly Lys Leu Thr Met Asp Asp Tyr Gln Gly
        275                 280                 285
Val Thr Val Ser Leu Thr Asn Pro Gly Gly Ile Gly Thr Arg His Ser
    290                 295                 300
Val Pro Arg Leu Thr Lys Gly Gln Gly Thr Ile Ile Gly Val Gly Ser
305                 310                 315                 320
Met Asp Tyr Pro Ala Glu Phe Gln Gly Ala Ser Glu Asp Arg Leu Ala
                325                 330                 335
Glu Leu Gly Val Gly Lys Leu Val Thr Ile Thr Ser Thr Tyr Asp His
            340                 345                 350
Arg Val Ile Gln Gly Ala Val Ser Gly Glu Phe Leu Arg Thr Met Ser
        355                 360                 365
Arg Leu Leu Thr Asp Asp Ser Phe Trp Asp Glu Ile Phe Asp Ala Met
    370                 375                 380
Asn Val Pro Tyr Thr Pro Met Arg Trp Ala Gln Asp Val Pro Asn Thr
385                 390                 395                 400
Gly Val Asp Lys Asn Thr Arg Val Met Gln Leu Ile Glu Ala Tyr Arg
                405                 410                 415
Ser Arg Gly His Leu Ile Ala Asp Thr Asn Pro Leu Ser Trp Val Gln
            420                 425                 430
Pro Gly Met Pro Val Pro Asp His Arg Asp Leu Asp Ile Glu Thr His
        435                 440                 445
Asn Leu Thr Ile Trp Asp Leu Asp Arg Thr Phe Asn Val Gly Gly Phe
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    450                 455                 460
Gly Gly Lys Glu Thr Met Thr Leu Arg Glu Val Leu Ser Arg Leu Arg
465                 470                 475                 480
Ala Ala Tyr Thr Leu Lys Val Gly Ser Glu Tyr Thr His Ile Leu Asp
                485                 490                 495
Arg Asp Glu Arg Thr Trp Leu Gln Asp Arg Leu Glu Ala Gly Met Pro
            500                 505                 510
Lys Pro Thr Gln Ala Glu Gln Lys Tyr Ile Leu Gln Lys Leu Asn Ala
        515                 520                 525
Ala Glu Ala Phe Glu Asn Phe Leu Gln Thr Lys Tyr Val Gly Gln Lys
    530                 535                 540
Arg Phe Ser Leu Glu Gly Ala Glu Ala Leu Ile Pro Leu Met Asp Ser
545                 550                 555                 560
Ala Ile Asp Thr Ala Ala Gly Gln Gly Leu Asp Glu Val Val Ile Gly
                565                 570                 575
Met Pro His Arg Gly Arg Leu Asn Val Leu Phe Asn Ile Val Gly Lys
            580                 585                 590
Pro Leu Ala Ser Ile Phe Asn Glu Phe Glu Gly Gln Met Glu Gln Gly
        595                 600                 605
Gln Ile Gly Gly Ser Gly Asp Val Lys Tyr His Leu Gly Ser Glu Gly
    610                 615                 620
Gln His Leu Gln Met Phe Gly Asp Gly Glu Ile Lys Val Ser Leu Thr
625                 630                 635                 640
Ala Asn Pro Ser His Leu Glu Ala Val Asn Pro Val Met Glu Gly Ile
                645                 650                 655
Val Arg Ala Lys Gln Asp Tyr Leu Asp Lys Gly Val Asp Gly Lys Thr
            660                 665                 670
Val Val Pro Leu Leu Leu His Gly Asp Ala Ala Phe Ala Gly Leu Gly
        675                 680                 685
Ile Val Pro Glu Thr Ile Asn Leu Ala Lys Leu Arg Gly Tyr Asp Val
    690                 695                 700
Gly Gly Thr Ile His Ile Val Val Asn Asn Gln Ile Gly Phe Thr Thr
705                 710                 715                 720
Thr Pro Asp Ser Ser Arg Ser Met His Tyr Ala Thr Asp Tyr Ala Lys
                725                 730                 735
Ala Phe Gly Cys Pro Val Phe His Val Asn Gly Asp Asp Pro Glu Ala
            740                 745                 750
Val Val Trp Val Gly Gln Leu Ala Thr Glu Tyr Arg Arg Arg Phe Gly
        755                 760                 765
Lys Asp Val Phe Ile Asp Leu Val Cys Tyr Arg Leu Arg Gly His Asn
    770                 775                 780
Glu Ala Asp Asp Pro Ser Met Thr Gln Pro Lys Met Tyr Glu Leu Ile
785                 790                 795                 800
Thr Gly Arg Glu Thr Val Arg Ala Gln Tyr Thr Glu Asp Leu Leu Gly
                805                 810                 815
Arg Gly Asp Leu Ser Asn Glu Asp Ala Glu Ala Val Val Arg Asp Phe
            820                 825                 830
His Asp Gln Met Glu Ser Val Phe Asn Glu Val Lys Glu Gly Gly Lys
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        835                 840                 845
Lys Gln Ala Glu Ala Gln Thr Gly Ile Thr Gly Ser Gln Lys Leu Pro
    850                 855                 860
His Gly Leu Glu Thr Asn Ile Ser Arg Glu Glu Leu Leu Glu Leu Gly
865                 870                 875                 880
Gln Ala Phe Ala Asn Thr Pro Glu Gly Phe Asn Tyr His Pro Arg Val
                885                 890                 895
Ala Pro Val Ala Lys Lys Arg Val Ser Ser Val Thr Glu Gly Gly Ile
            900                 905                 910
Asp Trp Ala Trp Gly Glu Leu Leu Ala Phe Gly Ser Leu Ala Asn Ser
        915                 920                 925
Gly Arg Leu Val Arg Leu Ala Gly Glu Asp Ser Arg Arg Gly Thr Phe
    930                 935                 940
Thr Gln Arg His Ala Val Ala Ile Asp Pro Ala Thr Ala Glu Glu Phe
945                 950                 955                 960
Asn Pro Leu His Glu Leu Ala Gln Ser Lys Gly Asn Asn Gly Lys Phe
                965                 970                 975
Leu Val Tyr Asn Ser Ala Leu Thr Glu Tyr Ala Gly Met Gly Phe Glu
            980                 985                 990
Tyr Gly Tyr Ser Val Gly Asn Glu  Asp Ser Ile Val Ala  Trp Glu Ala
        995                1000                1005
Gln Phe  Gly Asp Phe Ala Asn  Gly Ala Gln Thr Ile  Ile Asp Glu
    1010                 1015                 1020
Tyr Val  Ser Ser Gly Glu Ala  Lys Trp Gly Gln Thr  Ser Lys Leu
    1025                 1030                 1035
Ile Leu  Leu Leu Pro His Gly  Tyr Glu Gly Gln Gly  Pro Asp His
    1040                 1045                 1050
Ser Ser  Ala Arg Ile Glu Arg  Phe Leu Gln Leu Cys  Ala Glu Gly
    1055                 1060                 1065
Ser Met  Thr Val Ala Gln Pro  Ser Thr Pro Ala Asn  His Phe His
    1070                 1075                 1080
Leu Leu  Arg Arg His Ala Leu  Ser Asp Leu Lys Arg  Pro Leu Val
    1085                 1090                 1095
Ile Phe  Thr Pro Lys Ser Met  Leu Arg Asn Lys Ala  Ala Ala Ser
    1100                 1105                 1110
Ala Pro  Glu Asp Phe Thr Glu  Val Thr Lys Phe Gln  Ser Val Ile
    1115                 1120                 1125
Asn Asp  Pro Asn Val Ala Asp  Ala Ala Lys Val Lys  Lys Val Met
    1130                 1135                 1140
Leu Val  Ser Gly Lys Leu Tyr  Tyr Glu Leu Ala Lys  Arg Lys Glu
    1145                 1150                 1155
Lys Asp  Gly Arg Asp Asp Ile  Ala Ile Val Arg Ile  Glu Met Leu
    1160                 1165                 1170
His Pro  Ile Pro Phe Asn Arg  Ile Ser Glu Ala Leu  Ala Gly Tyr
    1175                 1180                 1185
Pro Asn  Ala Glu Glu Val Leu  Phe Val Gln Asp Glu  Pro Ala Asn
    1190                 1195                 1200
Gln Gly  Pro Trp Pro Phe Tyr  Gln Glu His Leu Pro  Glu Leu Ile
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    1205                1210                1215
Pro Asn  Met Pro Lys Met Arg  Arg Val Ser Arg Arg  Ala Gln Ser
    1220                1225                1230
Ser Thr  Ala Thr Gly Val Ala  Lys Val His Gln Leu  Glu Glu Lys
    1235                1240                1245
Gln Leu  Ile Asp Glu Ala Phe  Glu Ala
    1250                1255
```