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Identification of six open reading frames in the *Salmonella enterica* subsp. *enterica* ser. Typhi *viaB* locus involved in Vi antigen production

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The Vi antigen of *Salmonella enterica* subsp. *enterica* ser. Typhi (hereafter referred to as Typhi) is a capsular polysaccharide consisting of a homopolymer of α -1,4 2-deoxy-2N-acetyl galacturonic acid (Felix and Pitt, 1934). Determinants of Vi antigen occupy two widely separated chromosomal loci, designated *viaA* and *viaB*. The *viaB* locus, specific to Vi-expressing strains, maps at 92 min on the chromosome of Typhi (Johnson *et al.*, 1965). Cloning and molecular analysis of this chromosomal region were reported previously (Hashimoto *et al.*, 1991; Kolyva *et al.*, 1992). Here we report on the nucleotide sequence of a 9.3-kb fragment located within the Typhi strain Ty2*viaB* locus.

The dideoxy chain-termination method, using modified T7 DNA polymerase ("Sequenase"; USB Corp.) and universal forward and synthetic primers, was employed after subcloning of appropriate restriction fragments into M13 derivatives (Messing and Vieira, 1982). All the ends of restriction fragments used overlapped one another. DNA sequencing was performed at least twice on both strands. Nucleotide sequence data were analysed using the Lipman-Pearson program (Lipman and Pearson, 1985). The sequence data have been submitted to the EMBL data library and were assigned accession no. X67785.

As shown in figure 1, examination of the DNA sequence revealed six open reading frames (ORF), termed: *tviA* (Typhi Vi), *tviB*, *tviC*, *tviD*, *tviE* and *tviF*. All were transcribed in the same orientation. Their description is reported in table I. Significant homology was detected between TviB protein and AlgD (Deretic *et al.*, 1987), a GDP-mannose dehydrogenase of *Pseudomonas aeruginosa* (26 % identity and 71 % similarity in 288 amino acids overlap) and between TviC protein and StrE (Pisowotzki *et al.*, 1991), a TDP-glucose dehydratase of *Streptomyces griseus* (28 % identity and 68 % similarity in 326 amino acids overlap). A lipoprotein signal sequence (Hussain *et al.*, 1982) with a potential cleavage site for signal peptidase II (see fig. 1) was found in the TviF sequence. TviF protein shared significant homology to BexD (Kroll *et al.*, 1990) and CtrA (Frosch *et al.*, 1991) proteins (27 % identity and 72 % similarity in 280 amino acids overlap) which are involved in capsule export by *Haemophilus influenzae* and *Neisseria meningitidis*, respectively.

Studies designed to determine whether TviB and TviC proteins are involved in the biosynthesis, and TviF in the biogenesis, of the Vi antigen are presently under way in our laboratory.

Key-words: Vi antigen, ORF, *Salmonella* ser. Typhi; *viaB* locus, Nucleotides, Sequencing; Note.

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Table 1. Description of the six open reading frames identified within the 9.3-kb sequenced segment of the *viaB* locus.

Open reading frames	Location (nucleotide)		Expected protein	
	from:	to:	aa	mm
<i>tviA</i>	770	1306	179	21099
<i>tviB</i>	1554	2828	425	47612
<i>tviC</i>	2834	3877	348	39478
<i>tviD</i>	4285	6396	704	80402
<i>tviE</i>	6399	8132	578	64902
<i>tviF</i>	8180	9244	355	38877

aa = number of amino acids; mm = predicted molecular mass in dalton.

Identification de six phases ouvertes de lecture dans le locus *viaB* impliqué dans la production de l'antigène Vi chez *Salmonella enterica* subsp. *enterica* ser. Typhi

L'antigène Vi de *Salmonella enterica* subsp. *enterica* ser. Typhi est un polyside capsulaire dont l'expression est contrôlée par les loci chromosomiques *viaA* et *viaB*. La séquence d'un fragment (9,3 kb) du locus *viaB*, qui est spécifique des souches produisant l'antigène Vi, a été déterminée. Six phases ouvertes de lecture (*tviA*, *tviB*, *tviC*, *tviD*, *tviE* et *tviF*) codant respectivement pour des polypeptides de 21.099, 47.612, 39.478, 80.402, 64.902 et 38.877 daltons ont été mises en évidence. Sur la base des résultats de comparaison de séquence, les protéines TviB, TviC et TviF pourraient être impliquées dans la biosynthèse et la biogénèse de l'antigène Vi.

Mots-clés: Antigène Vi, ORF, *Salmonella* ser. Typhi; Locus *viaB*, Nucléotides, Séquençage; Note.

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Fig. 1. Nucleotide sequence of a 9.3-kb fragment of the *Salmonella* ser. Typhi Ty2*viaB* locus.

The putative Shine-Dalgarno sequences are underlined. The cleavage site of the lipoprotein signal peptide at amino acid position 17 of TviF is indicated with a star. These sequence data were assigned accession no. X67785 in the EMBL data library.

30 60
 GAA TTC TGC AAA CCA GCC CTG TAC CAT CAA GTT CAT ATC CTC AGC GGA GGA AAT GCG TGA
 90 120
 AAT CCA GCG CAA CAC ACG GAG TAT CAC CCA CTA CCC AGG CAT CAT GAT TCT CAG AAA CCT
 150 180
 CAA ATG CTT CGC CGG CAT GAA TAA GGT ATT CAT TTC CGA AGC AGT CAC GCA CCA TCA TTT
 210 240
 CAC CGG AAA TTA TAA AAC CAG TAT GAC GTT CTG ACG GTT TTC CGG TCA TTA TTA ATG GGT
 270 300
 GAC TCT AAT GCA AAC ATC TAG CGA GAA AAT ATT TTG TAG ACA TCG TCA ACG GAA AAG TTA
 330 360
 ACT AAC AAT AGT CAT TAT CCA TAT CTT TAA TTT GAA ATG GAA ACA GGG CAA AGA GTA ATT
 390 420
 AAA ATA CAG CCT GTG ATT CTG TAC AGT TAA GCG TTA ACC CCA AAG GTG CAA ACA ATT AAA
 450 480
 TTT GTA ACA GAT TAT TTC AAA TAC GAT TAG GAA TAT TCT TAT TTT GAG GAA TGG CTT AGC
 510 540
 ATT TTT TAT GGT CGC CAG GAT TAA AAA ATA CGC CCT ATC CAA ACA ATT TAG CAT AAT TTA
 570 600
 TCA TTC GAT TTT CTA GAC TAA ATA AGA TTT TTT GAT AGG TAC AAA CAA TGA ATT GTG CAG
 630 660
 GTT TGA CAT CAA TTC TCT GTT GTG TAA AAA TCC CGT TTA GGC CGT TAG TAC TAT TAA AAT
 690 720
 TAG GGT AAT AAT TTT ATT GTT AGT TAA TTG TTA ACA GGA GCA AAG AAT TAG ATA TTG CTT
 750 781
 GTA CCT TTT CTA TGG ATG AAA TTA GGT TAT TTC AGC ATA AGGAG ACTTC ATG AGG TTT CAT
 Met Arg Phe His
 811 841
 CAT TTC TGG CCT CCG AAT GAT ATC TAT TTC GGG GTT GGA GCT GCT GGC ATT ATT GAA GAA
 His Phe Trp Pro Pro Asn Asp Ile Tyr Phe Gly Val Gly Ala Ala Gly Ile Ile Glu Glu
 871 901
 GTG TCA CTG ATA ACA AAT GAC AGA AAT TAT TTG TTT GTG AAC CTA AAT CGC TAC AGC CTG
 Val Ser Leu Ile Thr Asn Asp Arg Asn Tyr Leu Phe Val Asn Leu Asn Arg Tyr Ser Leu
 931 961
 TTA AAT GCC CTG AAT TTT TTC ACG CGA ATG AGT GAT ATT AAT AAA ATA ATC GTT ATC ATT
 Leu Asn Ala Leu Asn Phe Phe Thr Arg Met Ser Asp Ile Asn Lys Ile Ile Val Ile Ile
 991 1021
 TCA AGT TCG CGA CTA ATG CCC CTT GCA CGT TTT TGG TTG ACA GAG TGC AAA AAT GTT ATT
 Ser Ser Ser Arg Leu Met Pro Leu Ala Arg Phe Trp Leu Thr Glu Cys Lys Asn Val Ile
 1051 1081
 GCT GTT TTC GAT GCG GCA ACA TCA GTC CAG GAT ATT ATC AGA AAT GTC AGT CAA CAC CAA
 Ala Val Phe Asp Ala Ala Thr Ser Val Gln Asp Ile Ile Arg Asn Val Ser Gln His Gln
 1111 1141
 AGT GGT GAA AAG ATC TTG ACG GAG CAG AGA GAT TAT CGT TTC AGA ATT AAC CGT AAG GAT
 Ser Gly Glu Lys Ile Leu Thr Glu Gln Arg Asp Tyr Arg Phe Arg Ile Asn Arg Lys Asp
 1171 1201
 ATA GTA AAG ATG AAA TAT TTC CTT TCG GAA AGT GGT ATG GAA GAG CTT CAG GAT AGA TTT
 Ile Val Lys Met Lys Tyr Phe Leu Ser Glu Ser Gly Met Glu Glu Leu Gln Asp Arg Phe
 1231 1261
 ATG AAC TCA TCA TCG ACT ATG TAT CGC TGG AGA AAA GAA TTG GCA GTA AAA TTT GGA GTA
 Met Asn Ser Ser Ser Thr Met Tyr Arg Trp Arg Lys Glu Leu Ala Val Lys Phe Gly Val
 1291 1320
 CGT GAG CCG CGC TAT CTG TTA TTG CCG GAT TCA GTT ACT TTA CTG TAA TGC GGT AAT TT
 Arg Glu Pro Arg Tyr Leu Leu Leu Pro Asp Ser Val Thr Leu Leu
 1350 1380
 TTA TTG AGT AAA ACA CGG ACA AGT ATT TCG TTT CAG CAC AAA ATT ATT TTC GTT ACT CAT
 1410 1440
 TGG CGT TAA TAC ATA TAT TCT CAG CGA CTT CTG TTC TAT TCA AGT AAG AAA GGG GTA CGG
 1470 1500
 TTA TAC GTT TTC ATT AAC CAT ACT GGC TGC TAC GGC CAG GGG CGG TAG CGT ATC TGA ATA
 1530 1562
 AAC ACC TAG AAT TAA CTT TGT AAA TAT AAA ATT TTA GTA AAGGA TTAA TAAGA GTG TTC GGT
 Val Phe Gly
 1592 1622
 ATA GAC GAG GTA AAA ATC GCG ATT ATT GGG CTG GGA TAT GTT GGG CTT CCT CTG GCA GTT
 Ile Asp Glu Val Lys Ile Ala Ile Ile Gly Leu Gly Tyr Val Gly Leu Pro Leu Ala Val

1652 1682
 GAA TTT GGC AAA TCT CGT CAG GTT GTT GGC TTC GAC GTT AAT AAA AAG CGT ATT CTT GAA
 Glu Phe Gly Lys Ser Arg Gln Val Val Gly Phe Asp Val Asn Lys Lys Arg Ile Leu Glu
 1712 1742
 TTA AAG AAT GGG GTG GAT GTC AAT CTG GAA ACC ACT GAA GAA GAA TTA CGT GAG GCT CCG
 Leu Lys Asn Gly Val Asp Val Asn Leu Glu Thr Thr Glu Glu Glu Leu Arg Glu Ala Arg
 1772 1802
 TAT CTG AAA TTT ACT TCC GAG ATT GAG AAG ATC AAA GAA TGT AAT TTT TAC ATC ATC ACC
 Tyr Leu Lys Phe Thr Ser Glu Ile Glu Lys Ile Lys Glu Cys Asn Phe Tyr Ile Ile Thr
 1832 1862
 GTC CCG ACG CCG ATA AAT ACC TAC AGG CAA CCA GAC CTC ACC CCA CTA ATC AAG GCC AGT
 Val Pro Thr Pro Ile Asn Thr Tyr Lys Gln Pro Asp Leu Thr Pro Leu Ile Lys Ala Ser
 1892 1922
 GAA ACC GTT GGT ACA GTG CTG AAT CGG GGA GAT ATT GTG GTA TAT GAA TCT ACG GTA TAT
 Glu Thr Val Gly Thr Val Leu Asn Arg Gly Asp Ile Val Val Tyr Glu Ser Thr Val Tyr
 1952 1982
 CCG GGA TGT ACC GAA GAA GAA TGC GTG CCG ATC CTT GCT CGT ATG TCC GGA ATG ACT TTC
 Pro Gly Cys Thr Glu Glu Glu Cys Val Pro Ile Leu Ala Arg Met Ser Gly Met Thr Phe
 2012 2042
 AAC CAG GAT TTC TAT GTC GGT TAT AGC CCG GAA AGG ATC AAT CCC GGT GAT AAA AAG CAC
 Asn Gln Asp Phe Tyr Val Gly Tyr Ser Pro Glu Arg Ile Asn Pro Gly Asp Lys Lys His
 2072 2102
 CGT TTA ACC AAC ATC AAG AAA ATC ACC TCC GGT TCA ACC GCA CAG ATC GCC GAA CTT ATC
 Arg Leu Thr Asn Ile Lys Lys Ile Thr Ser Gly Ser Thr Ala Gln Ile Ala Glu Leu Ile
 2132 2162
 GAT GAA GTA TAT CAG CAG ATC ATC AGC GCA GGT ACA TAT AAA GCA GAG AGC ATC AAA GTT
 Asp Glu Val Tyr Gln Gln Ile Ile Ser Ala Gly Thr Tyr Lys Ala Glu Ser Ile Lys Val
 2192 2222
 GCT GAG GCA GCG AAG GTG ATT GAA AAT ACG CAA CGC GAT CTG AAT ATT GCC TTG GTC AAT
 Ala Glu Ala Ala Lys Val Ile Glu Asn Thr Gln Arg Asp Leu Asn Ile Ala Leu Val Asn
 2252 2282
 GAG CTG GCG ATT ATT TTT AAT CGT TTA AAT ATC GAT ACT GAA GCC GTG CTA CGT GCC GCT
 Glu Leu Ala Ile Ile Phe Asn Arg Leu Asn Ile Asp Thr Glu Ala Val Leu Arg Ala Ala
 2312 2342
 GGC AGC AAA TGG AAT TTC CTG CCA TTC CGT CCG GGA CTG GTC GGT GGT CAC TGT ATT GGC
 Gly Ser Lys Trp Asn Phe Leu Pro Phe Arg Pro Gly Leu Val Gly Gly His Cys Ile Gly
 2372 2402
 GTA GAT CCC TAT TAT CTG ACA CAT AAA TCT CAG GGC ATT GGC TAT TAT CCA GAA ATC ATA
 Val Asp Pro Tyr Tyr Leu Thr His Lys Ser Gln Gly Ile Gly Tyr Tyr Pro Glu Ile Ile
 2432 2462
 CTT GCA GGA CGC CGC CTG AAC GAC ATG GGC AAC TAT GTC TCC GAG CAG TTG ATC AAA
 Leu Ala Gly Arg Arg Leu Asn Asp Asn Met Gly Asn Tyr Val Ser Glu Gln Leu Ile Lys
 2492 2522
 GCA ATG ATC AAA AAA GGA ATT AAC GTT GAG GGT TCC AGC GTG CTG ATT CTC GGC TTT ACC
 Ala Met Ile Lys Lys Gly Ile Asn Val Glu Gly Ser Ser Val Leu Ile Leu Gly Phe Thr
 2552 2582
 TTT AAA GAA AAC TGT CCG GAC ATC AGA AAT ACA CGC ATT ATT GAT GTG GTA AAG GAA CTC
 Phe Lys Glu Asn Cys Pro Asp Ile Arg Asn Thr Arg Ile Ile Asp Val Val Lys Glu Leu
 2612 2642
 GGT AAA TAT AGT TGT AAA GTG GAT ATT TTT GAT CCA TGG GTG GAT GCC GAA GAG GTA AGA
 Gly Lys Tyr Ser Cys Lys Val Asp Ile Phe Asp Pro Trp Val Asp Ala Glu Glu Val Arg
 2672 2702
 CGA GAG TAT GGC ATT ATC CCG GTA TCG GAA GTC AAA TCA AGC CAC TAC GAT GCG ATC ATT
 Arg Glu Tyr Gly Ile Ile Pro Val Ser Glu Val Lys Ser Ser His Tyr Asp Ala Ile Ile
 2732 2762
 GTT GCA GTA GGA CAT CAG CAA TTT AAA CAG ATG GCA AGT CAG GAT ATT CGC GGC TTC GGA
 Val Ala Val Gly His Gln Gln Phe Lys Gln Met Gly Ser Glu Asp Ile Arg Gly Phe Gly
 2792 2822
 AAA GAT AAA CAT GTA CTT TAT GAT TTG AAG TAT GTT CTT CCG GCT GAG CAG TCA GAT GTG
 Lys Asp Lys His Val Leu Tyr Asp Leu Lys Tyr Val Leu Pro Ala Glu Gln Ser Asp Val
 2851 2881
 AGA TTG TAA TC ATG ACG GCT TAC GAA GAA CTA CGG ACC AAA CTG GTT CTG GCA CCA AAG
 Arg Leu Met Thr Ala Tyr Glu Glu Leu Arg Thr Lys Leu Val Leu Ala Pro Lys
 2911 2941
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 Arg Trp Leu Ile Thr Gly Val Ala Gly Phe Ile Gly Ser Gly Leu Leu Glu Glu Leu Leu

2971 3001
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 Phe Leu Asn Gln Thr Val Ile Gly Leu Asp Asn Phe Ser Thr Gly Tyr Gln His Asn Leu
 3031 3061
 GAC GAC GTT CGC ACG TCC GTC AGT GAG GAG CAA TGG TCG CGA TTT ATT TTT ATT CAG GGT
 Asp Asp Val Arg Thr Ser Val Ser Glu Glu Gln Trp Ser Arg Phe Ile Phe Ile Gln Gly
 3091 3121
 GAC ATC AGG AAA TTT ACT GAC TGT CAG AAA GCG TGT AAG AAC GTT GAC TAT GTT CTC CAC
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 3151 3181
 CAA GCC GCG CTA GCG AGC GTG CCA CGT TCC CTA AAG GAT CCC ATC GCG ACT AAT AGC GCC
 Gln Ala Ala Leu Glu Ser Val Pro Arg Ser Leu Lys Asp Pro Ile Ala Thr Asn Ser Ala
 3211 3241
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 Asn Ile Asp Gly Phe Leu Asn Met Leu Thr Ala Ala Arg Asp Ala His Val Ser Ser Phe
 3271 3301
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 Thr Tyr Ala Ala Ser Ser Ser Thr Tyr Gly Asp His Pro Asp Leu Pro Lys Ile Glu Glu
 3331 3361
 CGG ATC GGT CGA CCA CTC AGC CCG TAT GCG GTA ACA AAA TAC GTC AAT GAA TTG TAC GCT
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 3391 3421
 GAT GTG TTT GCA CGT AGC TAT GAA TTT AAC GCT AAT GGC CTA CGC TAC TTT AAT GTC TTT
 Asp Val Phe Ala Arg Val Tyr Glu Phe Asn Ala Ile Gly Leu Arg Tyr Phe Asn Val Phe
 3451 3481
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 Gly Arg Arg Gln Asn Val Asn Gly Ala Tyr Ser Ala Val Ile Pro Arg Trp Ile Leu Ser
 3511 3541
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 3571 3601
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 Tyr Ile Glu Asn Val Ile Gln Ala Asn Leu Leu Ser Ala Thr Thr Asn Asp Leu Ala Ser
 3631 3661
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 3691 3721
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 Leu Ile Arg Asp Gly Leu Asn Leu Trp Arg Asn Glu Gln Ser Arg Ala Glu Pro Ile Tyr
 3751 3781
 AAA GAT TTT CGT GAC GGT AAC GTT AAG CAT AGC CAG GCA GAT ATT ACC AAA ATA AAA ACA
 Lys Asp Phe Arg Asp Gly Asp Val Lys His Ser Gln Ala Asp Ile Thr Lys Ile Lys Thr
 3811 3841
 TTT CTT TCA TAT GAG CCT GAA TTT GAT ATC AAA GAA GGA CTT AAG CAG ACT CTA AAA TGG
 Phe Leu Ser Tyr Glu Pro Glu Phe Asp Ile Lys Glu Gly Leu Lys Gln Thr Leu Lys Trp
 3871 3901
 TAT ATC GAT AAA CAT TAT ACT TTG TAT TCC TCG GTA TAA CTA CTC ACT TTC CTT TCA CGT
 Tyr Ile Asp Lys His Ser Thr Leu Tyr Ser Ser Val
 3931 3961
 GGA TGA ATT TAA TGA AAT GGT CAG GGA TGT TTA CGC TTA CAG CCA TTG GCA GTT GCC GTA
 3991 4021
 TTG TGA GTC CGG TAA AAT GAG CTC AGC CTT ATT TTA ATT TTC AGG CAA ACT TTA AGA GAA
 4051 4081
 TAT ATG GTT TTA GCG TGA GCA GCG AGG CAT TAC AGC AGA TTC GGT TTA TTT TGG GCT
 4111 4141
 TGA TAG ACA TTC CTC AAG TCC GAC CAT TTA TTT TTA GAC CTA ATG TAA ACT ATT CAA
 4171 4201
 ACA CCG ACG TAC ATA GTC GTT CTG ATT TCT ATA TCA TTG AGA TTT CAA GTC AGA AGA AGA
 4231 4261
 TTA TGG CCT ATG GGT TCT GCT TAC AAA TAA ATT ATT TAA CTC GTC ATT TCT ATG AAT TTT
 tvid 4290 4320
 TT AGC CAA AC AGG CGG GCG TGC ATG TAC TGG TCG TTG GCC ACG CAA GGA AAT CGA CAC
 Met Tyr Trp Ser Leu Ala Thr Gln Gly Asn Arg His
 4350 4380
 AAA CTG CTG GCC TAT CTC AAA GAC GAT CCC TGT TTT GCC GGA ATG TCG GAA GAC GAT CGT
 Lys Leu Leu Ala Tyr Leu Lys Asp Asp Pro Cys Phe Ala Gly Met Ser Glu Asp Asp Arg

4410
 GCC TTA TTA AGC AAT ATC AAT GTC GAG CAG ATG GAT GAG CAT GCT ATC GAA CAG GAT ATG
 Ala Leu Leu Ser Asn Ile Asn Val Glu Gln Met Asp Glu His Ala Ile Glu Gln Asp Met
 4470
 ATG GAA ATC GTT CAG CTT CTT GGT CGC GAT CGC GTT ATG TTT ATG ACA CAT GTT GAT GCC
 Met Glu Ile Val Gln Leu Leu Gly Arg Asp Arg Val Met Phe Met Thr His Val Asp Ala
 4530
 GTG ACT CGT GCT GGA ACC GTC ATT CTA TCC CGT AGT CGG TTG ATT AAA AAT GTC GAC ACC
 Val Thr Arg Ala Gly Thr Val Ile Leu Ser Arg Ser Arg Leu Ile Lys Asn Val Asp Thr
 4590
 ATC GCC GCC AGG ATG GAT ATT CCC TGC GTT AAC CCG ACA AAT TTG ATG GAA AAG TGG GGG
 Ile Ala Ala Arg Met Asp Ile Pro Cys Val Asn Pro Thr Asn Leu Met Glu Lys Trp Gly
 4650
 CAG AAA CGA GCC CTG GAA AAA AAT GGC GAC GAT CTT ACT CAT TAT ACC GAT ATG TTT GGT
 Gln Lys Arg Ala Leu Glu Lys Asn Gly Asp Asp Leu Thr His Tyr Thr Asp Met Phe Gly
 4710
 GAC GCG ATC GTT GCG GCT ATT TTT AAG GGA GTG ATC AAT AAT ACT AAT CAT CAT CTT GAT
 Asp Ala Ile Val Ala Ala Ile Phe Lys Gly Val Ile Asn Asn Thr Asn His His Leu Asp
 4770
 GAG GGG CGA CAA GAG AAA CAG GAC CAA ATC AGT GAG ATT ACC TTA TCG ATC ACT AAG CAG
 Glu Gly Arg Gln Glu Lys Gln Asp Gln Ile Ser Glu Ile Thr Leu Ser Ile Thr Lys Gln
 4830
 CTT GCA GAT GGC GAC ATT ATT GCT GCA TCA CAA CAA CTT TTT GCC GCA TTA AGA AAT CAG
 Leu Ala Asp Gly Asp Ile Ile Ala Ala Ser Gln Gln Leu Phe Ala Ala Leu Arg Asn Gln
 4890
 CAG CAA GAT CCC GTT CTA ATC CAA CTT CGG TCC GTA ATC TTC AGC CAT TTA GGT TAT TAT
 Gln Gln Asp Pro Val Leu Ile Gln Leu Arg Ser Val Ile Phe Ser His Leu Gly Tyr Tyr
 4950
 GAA CAG GCT TAT CAG GAT ATT AGT GAT GTT GAG AAA ATT ATC GGT ACG ACT GAC AGT ACA
 Glu Gln Ala Tyr Gln Asp Ile Ser Asp Val Glu Lys Ile Ile Gly Thr Thr Asp Ser Thr
 5010
 TTA CGT TGT CGG CTG AGG TCT CTA CAT GGA TTA GCG CGT TGG CGG GAA GCC TTA TCG ACG
 Leu Arg Cys Arg Leu Arg Ser Leu His Gly Leu Ala Arg Trp Arg Glu Ala Leu Ser Thr
 5070
 GCA GAG ATG ATG CTT TCC AAT GAA ATT GAA GAT GAA GAA GTC CTT ACC GTT GCC GCC GGC
 Ala Glu Met Met Leu Ser Asn Glu Ile Glu Asp Glu Glu Val Leu Thr Val Ala Ala Gly
 5130
 TCA GCC GAT GCT TTA CAG CTG TTT GAT AAG TCA TAT CAT TAT TGG AAA CGT GTA CTA TTA
 Ser Ala Asp Ala Leu Gln Leu Phe Asp Lys Ser Tyr His Tyr Trp Lys Arg Val Leu Leu
 5190
 TTG AAT CCT GAA ACT CAA AGC GGA TGG GTT AAT TTC CTG AGC AGC ACG CAA TAT TTC AAT
 Leu Asn Pro Glu Thr Gln Ser Gly Trp Val Asn Phe Leu Ser Ser Thr Gln Tyr Phe Asn
 5250
 GAT GGC AAC GCA TTC TCT GAA GCT TTC CAT GCC GGC ATT CAA TCG CAG CGC CTA AAT GAT
 Asp Gly Asn Ala Phe Ser Glu Ala Phe His Ala Gly Ile Gln Ser Gln Arg Leu Asn Asp
 5310
 ACG TTT ATG GAA ACG GCG TTA TCT TTG GCA ATC AAA TTC AGT GAT GAA TTG ATT TTC ATG
 Thr Phe Met Glu Thr Ala Leu Ser Leu Ala Ile Lys Phe Ser Asp Glu Leu Ile Phe Met
 5370
 CAT GCG CTC GAG CAG CTA CTC CGC CAT GAG TCA GAA TTT GCG CTG ACG GTA TTG TCG ACG
 His Ala Leu Glu Gln Leu Leu Arg His Glu Ser Glu Phe Ala Leu Thr Val Leu Ser Thr
 5430
 ATT CAT GAT ACC GGT CTC GTT ATC CGC ACA GCT TTC TGC ATC AAG AAT ATG AGC TAT CAT
 Ile His Asp Thr Gly Leu Val Ile Arg Thr Ala Phe Cys Ile Lys Asn Met Ser Tyr His
 5490
 CAA GCG CTT CGC ACC TCG TAT AAA GAT AAA ATC CAC GAC GTT TTT GAG GCA TGG AAC AAT
 Gln Ala Leu Arg Thr Ser Tyr Lys Asp Lys Ile His Asp Val Phe Glu Ala Trp Asn Asn
 5550
 ACC GCG CTG TCG CTA CAT TCG GTT GAT GAT TTT GTC TCA CTG AGC ACT TCG CTA GCC TAT
 Thr Ala Leu Ser Leu His Ser Val Asp Asp Phe Val Ser Leu Ser Thr Ser Leu Ala Tyr
 5610
 AGC TAC TCT GCA TTT ATG GTT TAT CCC CAT TCA CGT ATT TCT CGC TTT AAT AAT GAA GTT
 Ser Tyr Ser Ala Phe Met Val Tyr Pro His Ser Arg Ile Ser Arg Phe Asn Asn Glu Val
 5670
 AAA ATG GCA TGG CGC GAT AAA TTA AGA GAA ATG TAT GAG CGT GAG GAT TAT GAA AAT ATC
 Lys Met Ala Trp Arg Asp Lys Leu Arg Glu Met Tyr Glu Arg Glu Asp Tyr Glu Asn Ile

5730
 CTG GCA GGG GCG AAA ATA GTG TGG CCA CTT CTG AAG TTT GAT CCC GTT GGC ACC GTA TAT
 Leu Ala Gly Ala Lys Ile Val Trp Pro Leu Leu Lys Phe Asp Pro Val Gly Thr Val Tyr
 5790
 TGT GCA AGA ACG CTG GTG AAT CTT GGT GCC TGG AAA GAC GCG TGC ACG TTG GCC CAC ATG
 Cys Ala Arg Thr Leu Val Asn Leu Gly Ala Trp Lys Asp Ala Cys Thr Leu Ala His Met
 5850
 ACC TTG ATT CGT AAC TCG AAC ATT ACC AGC CTG CAG TCG ATT ATG TTA CGC AGC ATA CGT
 Thr Leu Ile Arg Asn Ser Asn Ile Thr Ser Leu Gln Ser Ile Met Leu Arg Ser Ile Arg
 5910
 CAT ATT AAC AAC ATT CCG TTC CTC ATT GAT TTG ATT GCT AAC GTC ATG AGC ATT ACT CTA
 His Ile Asn Asn Ile Pro Phe Leu Ile Asp Leu Ile Ala Asn Val Met Ser Ile Thr Leu
 5970
 TCA TTC CAG AAT GCC TCA ATG AAC AAG TTG TTT GAG AAA GAG TGT CGC AAT GTT GCA ACC
 Ser Phe Gln Asn Ala Ser Met Asn Lys Leu Phe Glu Lys Glu Cys Arg Asn Val Ala Thr
 6030
 AGA GCC CTT AAA TAT GTA CGC CAG AAG AAA ACT GAA GGG CGT CTG GAT GAA GCA TTG TCT
 Arg Ala Leu Lys Tyr Val Arg Gln Lys Lys Thr Glu Gly Arg Leu Asp Glu Ala Leu Ser
 6090
 GTA TTG ATT AGC CTG AAA CGA ATT GAG CCT GAT GTT TCT CGT CTG ATG CGT GAA TAT AAG
 Val Leu Ile Ser Leu Lys Arg Ile Glu Pro Asp Val Ser Arg Leu Met Arg Glu Tyr Lys
 6150
 CAA ATT ATC AGA TTA TTT AAT GAG TCA CGG AAG GAT GGC GGT AGC ACT ATC ACG TCT TAT
 Gln Ile Ile Arg Leu Phe Asn Glu Ser Arg Lys Asp Gly Gly Ser Thr Ile Thr Ser Tyr
 6210
 GAA CAT CTA GAC TAT GCG AAA AAA TTA CTC GTT TTT GAT AGC GAA AAT GCC TAT GCC TTG
 Glu His Leu Asp Tyr Ala Lys Lys Leu Leu Val Phe Asp Ser Glu Asn Ala Tyr Ala Leu
 6270
 AAA TAT GCC GCA TTA AAT GCA ATG CAT TTA CGC GAC TAC ACG CAG GCT TTG CAG TAT TGG
 Lys Tyr Ala Ala Leu Asn Ala Met His Leu Arg Asp Tyr Thr Gln Ala Leu Gln Tyr Trp
 6330
 CAG CGA CTG GAG AAA GTG AAT GGA CCA ACG GAG CCG GTG ACA AGG CAG ATC TCG ACC TGC
 Gln Arg Leu Glu Lys Val Asn Gly Pro Thr Glu Pro Val Thr Arg Gln Ile Ser Thr Cys
 6390
 ATA ACC GCA TTA CAA AAA AAT ACA TCA GGG AAG TCG TA ATG ATT ACG CAG GAA GAA AAG
 Ile Thr Ala Leu Gln Lys Asn Thr Ser Gly Lys Ser Met Ile Thr Gln Glu Glu Lys
 6449
 TTA GCT GCA CTA GGA AAA ACG TGT TTA ACA TTA APA CAA GAG AAG AAG CTT GCG CAA GCT
 Leu Ala Ala Leu Gly Lys Thr Cys Leu Thr Leu Lys Gln Glu Lys Lys Leu Ala Gln Ala
 6509
 GTT GCG TTA ATT GAC AGT GAA TTA CCG ACT GAG GCT TTA ACT TCA TTA GCG ATG CTA AAA
 Val Ala Leu Ile Asp Ser Glu Leu Pro Thr Glu Ala Leu Thr Ser Leu Ala Met Leu Lys
 6569
 AAA GCA GAG TTT CTT CAT GAT GTC AAT GAA ACG GAG CGT GCA TAC GCG CTC TAC GAA ACG
 Lys Ala Glu Phe Leu His Asp Val Asn Glu Thr Glu Arg Ala Tyr Ala Leu Tyr Glu Thr
 6629
 CTG ATT GCA CAA AAC AAT GAT GAA GCA CGT TAT GAG TAT GCA CGT CGT TTA TAT AAT ACG
 Leu Ile Ala Gln Asn Asn Asp Glu Ala Arg Tyr Glu Tyr Ala Arg Arg Leu Tyr Asn Thr
 6689
 GGG CTA GCC AAA GAT GCT CAG CTA ATT CTT AAA AAG GTT AGC AAT GGT GTG CAG AAA AAA
 Gly Leu Ala Lys Asp Ala Gln Leu Ile Leu Lys Lys Val Ser Asn Gly Val Gln Lys Lys
 6749
 TAT AAC AAT TAT TTA GGC AAA ATA AAT AAG ATC TGT SAT TTG CTT GAA CGC CTT GAA GGG
 Tyr Asn Asn Tyr Leu Gly Lys Ile Asn Lys Ile Cys Asp Leu Leu Glu Arg Leu Glu Gly
 6809
 AAA GCG ATC CCT GTG GGG ACC AAC ACC TGT ATT ATT GCA ATG AAG CAT GCC ATC TTG TTC
 Lys Ala Ile Pro Val Gly Thr Asn Thr Cys Ile Ile Ala Met Lys His Ala Ile Leu Phe
 6869
 TAT AGA AAT CGT CAA CCC AGG CAG CTT CCC GTC GGG TCT TTC GGT CGT CTT GCG CTC TGT
 Tyr Arg Asn Arg Gln Pro Arg Gln Leu Pro Val Gly Ser Phe Gly Arg Leu Ala Leu Cys
 6929
 ACT GGC TCG CTA GGT AGC GGT GGT GCA GAG CGT CAG ATT TCC AGG CTG GCT ATC GAA ATC
 Thr Gly Ser Leu Gly Ser Gly Gly Ala Glu Arg Gln Ile Ser Arg Leu Ala Ile Glu Ile
 6989
 GCC AGA AAA TAT CGG CAA AAG GGG AAA ATT GGC GGC CTG AAA GTA GAA GAA CCG GTA G A
 Ala Arg Lys Tyr Arg Gln Lys Gly Lys Ile Gly Gly Leu Lys Val Glu Glu Pro Val C

7049 7079
 CTA ATT ATT CGC TCC CTG ACA CCG GAA CTC AGG CAA GAC TTT TTC CTG AAA GAA GTG CTG
 Leu Ile Ile Arg Ser Leu Thr Pro Glu Leu Arg Gln Asp Phe Phe Leu Lys Glu Val Leu
 7109 7139
 GAA GAA CAG GTC GAG GTT CTT GAA ATC GCG AAG ATT ACC GGA AAC TTG TTT GAC GAT GCG
 Glu Glu Gln Val Glu Val Leu Glu Ile Ala Lys Ile Thr Gly Asn Leu Phe Asp Asp Ala
 7169 7199
 ACA ATA GAA TCT CCA GAG TTG CGC TTA TTG CTA TCG CAT CTA CCG CCG GTG TGT AAA TAC
 Thr Ile Glu Ser Pro Glu Leu Arg Leu Leu Ser His Leu Pro Pro Val Cys Lys Tyr
 7229 7259
 GGC ATC AAG CAT CTG GTC CCC CAT TTA TGC GAG CGC AAG CTG GAT TAT CTC TCC GTT TGG
 Gly Ile Lys His Leu Val Pro His Leu Cys Glu Arg Lys Leu Asp Tyr Leu Ser Val Trp
 7289 7319
 CAG GAT GGC GCT TGT CTG ATG ATT GCG CTT GCA GCA TTG ATT GCT GGC GTG CCC AGA ATT
 Gln Asp Gly Ala Cys Leu Met Ile Ala Leu Ala Ala Leu Ile Ala Gly Val Pro Arg Ile
 7349 7379
 CAA CTG GGA TTA CGT GGG TTA CCG CCG GTG GTT AGA AAG CGT CTG TTC AAG CCG GAA TAT
 Gln Leu Gly Leu Arg Gly Leu Pro Pro Val Val Arg Lys Arg Leu Phe Lys Pro Glu Tyr
 7409 7439
 GAG CCT CTC TAC CAG GCG CTG GCG GTC GTG CCT GGC GTT GAT TTT ATG AGT AAC AAC CAT
 Glu Pro Leu Tyr Gln Ala Leu Ala Val Val Pro Gly Val Asp Phe Met Ser Asn Asn His
 7479 7499
 TGT GTG ACT CGC CAT TAT GCC GAC TGG CTG AAG TTG GAG GCG AAC GAC TTC CAG GTT GTA
 Cys Val Thr Arg His Tyr Ala Asp Trp Leu Lys Leu Glu Ala Asn Asp Phe Gln Val Val
 7529 7559
 TAT AAC GGC GTC TTA CCG CCA TCT ACT GAA CCC TCT TCT GAG GTG CCA CAT AAA ATC TGG
 Tyr Asn Gly Val Leu Pro Pro Ser Thr Glu Pro Ser Ser Glu Val Pro His Lys Ile Trp
 7589 7619
 CAG CAG TTT ACG CAA AAA ACC CAG GAT GCG GAC ACG ACT ATT GGT GGC GTT TTC CGC TTT
 Gln Gln Phe Thr Gln Lys Thr Gln Asp Ala Asp Thr Thr Ile Gly Gly Val Phe Arg Phe
 7649 7679
 GTA GGC GAT AAG AAC CCT TTT GCA TGG ATT GAT TTT GCA GCA CGC TAT TTA CAA CAC CAC
 Val Gly Asp Lys Asn Pro Phe Ala Trp Ile Asp Phe Ala Ala Arg Tyr Leu Gln His His
 7709 7739
 CCC GCC ACG CGC TTT GTG CTG GTA GGC GAT GGT GAT TTA CGC GCT GAA GCG CAG AAA CGC
 Pro Ala Thr Arg Phe Val Leu Val Gly Asp Gly Asp Leu Arg Ala Glu Ala Gln Lys Arg
 7769 7799
 GCC GAA CAG TTA GGG ATT CTG GAG AGA ATA CTA TTC GTT GGC GCC TCG CGT GAC GTA GGG
 Ala Glu Gln Leu Gly Ile Leu Glu Arg Ile Leu Phe Val Gly Ala Ser Arg Asp Val Gly
 7829 7859
 TAT TGG CTG CAA AAA ATG AAT GTA TTC ATT TTG TTT TCG CGT TAT GAA GGG CTA CCT AAT
 Tyr Trp Leu Gln Lys Met Asn Val Phe Ile Leu Phe Ser Arg Tyr Glu Gly Leu Pro Asn
 7889 7919
 GTG CTT ATT GAA GCA CAA ATG GTC GGG GTG CCG GTG ATT TCA ACC CCT GCA GGT GGA TCG
 Val Leu Ile Glu Ala Gly Met Val Gly Val Pro Val Ile Ser Thr Pro Ala Gly Gly Ser
 7949 7979
 GCA GAA TGC TTT ATT GAG GGT GTT TCG GGT TTC ATT CTT GAT GAT GCA CAG ACG GTC AAT
 Ala Glu Cys Phe Ile Glu Gly Val Ser Gly Phe Ile Leu Asp Asp Ala Gln Thr Val Asn
 8009 8039
 CTT GAC CAG GCT TGC CGC TAT GCA GAA AAG TTG GTC AAT TTA TGG CGC AGC AGA ACC GGT
 Leu Asp Gln Ala Cys Arg Tyr Ala Glu Lys Leu Val Asn Leu Trp Arg Ser Arg Thr Gly
 8069 8099
 ATT TGC CAA CAG ACG CAG TCA TTT TTA CAA GAA CGC TTC ACC GTG GAA CAT ATG GTG GGA
 Ile Cys Gln Gln Thr Gln Ser Phe Leu Gln Glu Arg Phe Thr Val Glu His Met Val Gly
 8129 8160
 ACG TTT GTA AAA ACC ATT GCC TCT CAG CCT CGT TAA TTA ATG GGC ATC ATT TTT CAG CTAT
 Thr Phe Val Lys Thr Ile Ala Ser Gln Pro Arg
tvfF 8191 8221
 TTCA TTT ATA AAA TAA GTT ATG AAA AAA ATC ATC ATA TTA CTA ACG ACA TTT TTC CTG CTT
 Met Lys Lys Ile Ile Ile Leu Leu Thr Thr Phe Phe Leu Leu
 * 8251 8281
 TCG GGA TGC ACT ATT CCC AGG GCG GTA TTT AAA TCC AGC CTT ATT AAT CAG GAC GAT CCT
 Ser Gly Cys Thr Ile Pro Arg Ala Val Phe Lys Ser Ser Leu Ile Asn Gln Asp Asp Pro
 8311 8341
 CGT TAT AAT CTG GTC GAA GTC ACG CCG ACA TTA AAA CTA AGC GCT CCC GAT ACT GTG CCG
 Arg Tyr Asn Leu Val Glu Val Thr Pro Thr Leu Lys Leu Ser Ala Pro Asp Thr Val Pro

8371 8401
 AAA ACT ATT GTC GAT CCG GTT TTT GCC GCA AAT AAC TGG CAC TGG ACA TCT TTG GCT AAA
 Lys Thr Ile Val Asp Pro Val Phe Ala Ala Asn Asn Trp His Trp Thr Ser Leu Ala Lys
 8431 8461
 GGC GAT GTG CTG CAT ATC ACT ATT TTA TCC TCG GGC GGG GCT GGA TAT TTA TCC AAT AAC
 Gly Asp Val Leu His Ile Thr Ile Leu Ser Ser Gly Gly Ala Gly Tyr Leu Ser Asn Asn
 8491 8521
 GCG AGC GGC GAC CGT GCG GAT TTT GAA AAT ATT CTT GTG ACT GAC AGT AAT ACC GTT CAG
 Ala Ser Gly Asp Arg Ala Asp Phe Glu Asn Ile Leu Val Thr Asp Ser Asn Thr Val Gln
 8551 8581
 GTG CCT TAT GCC GGG ACA ATC CCG GTT TCT GGA TTG GAT GTG ACG CAA CTG GCT GAT GAG
 Val Pro Tyr Ala Gly Thr Ile Pro Val Ser Gly Leu Asp Val Thr Gln Leu Ala Asp Glu
 8611 8641
 ATC AAA AAG CGA CTT TCG CGC GTT GTC CTG AAT CCT CAG GTG ATT GTG ACA CTT ACC GCC
 Ile Lys Lys Arg Leu Ser Arg Val Val Leu Asn Pro Gln Val Ile Val Thr Leu Thr Ala
 8671 8701
 CGC ACC GGA GCC ATG GTG ACG GTC GAG GGC AGC GGG AAA ACG GGT CGA TAC CCT CTC GAA
 Arg Thr Gly Ala Met Val Thr Val Glu Gly Ser Gly Lys Thr Gly Arg Tyr Pro Leu Glu
 8731 8761
 CAG AGT ATG AAT CGT CTG AGT CAT CTT TTG GCA ACG GCA GTG GCA GTA GAA AAT ACC AGC
 Gln Ser Met Asn Arg Leu Ser His Leu Leu Ala Thr Ala Val Ala Val Glu Asn Thr Ser
 8791 8821
 ACA GAT ATG ATG GAA GTT CAC GTG ACG CGC CAG CAG CAT TAT TTC ACT GCG CGA CTG TCA
 Thr Asp Met Met Glu Val His Val Thr Arg Gln Gln His Tyr Phe Thr Ala Arg Leu Ser
 8851 8881
 GAT ATT TAT CAG TAT CCC GGA TTG GAT ATT GCC TTA CAG CCG GAT GAC CGT ATC ACT CTG
 Asp Ile Tyr Gln Tyr Pro Gly Leu Asp Ile Ala Leu Gln Pro Asp Asp Arg Ile Thr Leu
 8911 8941
 CGT CAA GTG ACC GAG TAT GTT AAT GTG CTC GGC GCA GCA GGT GTT CAG GGG AAA CAT GCT
 Arg Gln Val Thr Glu Tyr Val Asn Val Leu Gly Ala Ala Gly Val Gln Gly Lys His Ala
 8971 9001
 CTG GTT CAG CGT CAT TCC AGC GTC GTG GAT GCT TTG GCG CTC GCG AAA GGA TTA AAT GAC
 Leu Val Gln Arg His Ser Ser Val Val Asp Ala Leu Ala Leu Ala Lys Gly Leu Asn Asp
 9031 9061
 AAT CTT GCC GAT CCG CAA GCG ATT TTT CTG TAC AAG CAT AAC GAA GCG GAA CAG GCG AAA
 Asn Leu Ala Asp Pro Gln Ala Ile Phe Leu Tyr Lys His Asn Glu Ala Glu Gln Ala Lys
 9091 9121
 CAG CAG ATG CGT AAG CTG AAT ATC TAT CAT GTC GAT ATG AGC CAA CCT AAC TCG GTG TTT
 Gln Gln Met Arg Lys Leu Asn Ile Tyr His Val Asp Met Ser Gln Pro Asn Ser Val Phe
 9151 9181
 TTA GCG CAG GCC ATA CGA GTG GAC AAC GGC GAT GTT ATC TAT ATC TCG AAC GCC TCT TTG
 Leu Ala Gln Ala Ile Arg Val Asp Asn Gly Asp Val Ile Tyr Ile Ser Asn Ala Ser Leu
 9211 9241
 ACT GAT TTC GCT AAG GTG AAA GCC GCA TTC GAT AGC TTT TTG ACC CGC GGC ACT AAT TCT
 Thr Asp Phe Ala Lys Val Lys Ala Ala Phe Asp Ser Phe Leu Thr Arg Gly Thr Asn Ser
 9271 9301
 TTC TAA TGT CGC CAT ATG AAT ATT TTG AAA AAT AAT TCT TAT TAT TTT ATG AAA CTC ATT
 Phe