

Article

Bioinformatic study on histidine decarboxylase[¶]

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Histidine decarboxylase (HDC) is an enzyme responsible for histamine production in living cells. It is of our aim to understand structure-function relationship of this enzyme in order to manipulate enzymatic activity for clinical usages. Firstly, structural aspects of HDC from variety of species were compared. Based upon the similarity of amino acid sequences, we presented the amino acid residues common among HDCs. Secondly, we presented intron-exon relationships based upon genomic information encoded for the enzyme. The exon information was reflected to the enzyme structure which was predicted based upon conformational similarity with 3,4-dihydroxyphenylalanine decarboxylase (also called aromatic amino acid decarboxylase, AroDC). This bioinformatic study should provide insights for evolutionary construction of HDC.

Keywords:

histidine decarboxylase, histamine, intron, motif

Histamine is a multifunctional biogenic amine and primarily expressed on mast cells, basophils, and histamine neurons in the brain (1-3). It has relevant roles in the intercellular communication, inflammatory processes, and highly prevalent pathologies (4-9). Histamine biosynthesis depends on a single decarboxylation step, carried out by an HDC activity (10, 11).

During the past few years, some advancement have been made in this field, including the generation and validation of the first three-dimensional model of mammalian histidine decarboxylase (12); however, its structural and functional characteristics still remain to be fully explored.

*Correspondence author: Phone No.: +81-742-20-3493, Fax No.: +81-742-20-3448, E-mail: hueno@cc.nara-wu.ac.jp, Abbreviations: AroDC, aromatic amino acid decarboxylase; PLP, pyridoxal 5'-phosphate; HDC, histidine decarboxylase.

[¶]Preliminary results of this study was reported at the National Meeting of Japanese Science Society of Biological Macromolecules in 2004 held in Hirakata, Osaka, Japan.

Sandmeier *et al.* classified PLP (pyridoxal 5'-phosphate)-dependent decarboxylases into four groups based upon their evolutionary origins (13). They have stated that a comparison of the amino acid sequences of nine different PLP-dependent amino acid decarboxylases, subdivided into four different groups, seems to be evolutionarily unrelated to each other. Four groups are as follows: group I is represented by glycine decarboxylase, a component of a multi-enzyme system; group II comprises glutamate, histidine, tyrosine, and aromatic-L-amino-acid decarboxylases; group III, prokaryotic ornithine and lysine decarboxylases as well as the prokaryotic biodegradative type of arginine decarboxylase; group IV, eukaryotic ornithine and arginine decarboxylases as well as the prokaryotic biosynthetic type of arginine decarboxylase and diaminopimelate decarboxylase. HDC belongs to group II; however, its tertiary structure is still undetermined.

When protein structures being elucidated, the relationships between protein structure modules and genetic segmentation, such as exon and intron boarder, has been recognized (14, 15). It is of interests to explore the relationship between structures of HDC gene and protein.

Materials and Methods

Amino acid sequences - Amino acid sequences of HDCs from different origin were obtained from the public databases via internet; the databases used are PIR and UNIPROT (Swiss-Prot/TrEMBL/TrEMBL_new).

Multiple sequence alignment - Multiple sequence alignment was carried out by using Clustal W (ver. 1.83) software available to public through GenomeNet (<http://www.genome.jp/>).

Exon-intron analysis - Information about

exon and intron were obtained by using Ensemble Genome Browser (<http://www.ensembl.org/>).

Motif analysis - A search of homologous motifs in a block of HDC gene was carried out with InterPro program (<http://www.ebi.ac.uk/interpro/>).

Molecular modeling - Protein structure coordinate files were obtained from Protein Data Bank (<http://www.rcsb.org/>). Molecular modeling study was carried out with MolFeat software (ver. 2.0.1.1, FiatLux Co., Tokyo).

Results and Discussion

Amino acid sequences of HDC from various species were obtained by searching currently available databases through internet, including Swiss-Prot and EMBL.

There are two kinds of HDC enzymes depending upon co-enzyme requirement: those that use PLP as a cofactor (13, 16, 17) and those that contain a covalently bound pyruvoyl residue (18). In this study, we have only focused on those require PLP. The PLP-dependent and pyruvoyl-dependent enzymes are clearly distinct in the evolutionary tree as they located in different branches. Table 1 lists 23 HDCs from different sources, in which the term, number of amino acid, included the pro-enzyme sequences.

Using CLUSTALW program, an evolutionary tree of HDC was drawn based on multiple alignments of amino acid sequences (Fig. 1). Those enzymes from animal, plants, and bacteria were grouped together, each belongs to different branches.

In order to examine the structural aspects on PLP-dependent HDCs, multiple alignments were performed. It was found that amino acid residues, as marked asterisk in Fig. 2, were conserved among 21 different species. Significant numbers

Table I Lists of HDC found in the databases

	Species	Class	ID	Accessing number	No. of amino acid
1	<i>Drosophila melanogaster</i> (Fruit fly)	Insecta	sp:DCHS_DROME ¹⁾	Q05733	847
2	<i>Enterobacter aerogenes</i> (<i>Aerobacter aerogenes</i>)	Bacteria	sp:DCHS_ENTAE	P28577	377
3	<i>Homo sapiens</i> (Human)	Mammalia	sp:DCHS_HUMAN	P19113	662
4	<i>Klebsiella planticola</i> (<i>Raoultella planticola</i>)	Bacteria	sp:DCHS_KLEPL	P28578	377
5	<i>Lycopersicon esculentum</i> (Tomato)	Spermatophyta	sp:DCHS_LYCES	P54772	413
6	<i>Morganella morganii</i> (<i>Proteus morganii</i>)	Bacteria	sp:DCHS_MORMO	P05034	377
7	<i>Mus musculus</i> (Mouse)	Mammalia	sp:DCHS_MOUSE	P23738	662
8	<i>Pseudomonas fluorescens</i> .	Bacteria	sp:DCHS_PSEFL	P95477	405
9	<i>Rattus norvegicus</i> (Rat)	Mammalia	sp:DCHS_RAT	P16453	656
10	<i>Rhizobium loti</i> (<i>Mesorhizobium loti</i>)	Bacteria	sp:DCHS_RHILO	Q98A07	369
11	<i>Vibrio anguillarum</i> (<i>Listonella anguillarum</i>)	Bacteria	sp:DCHS_VIBAN	Q56581	386
12	<i>Aeropyrum pernix</i> .	Archaea	tr:Q9YF28 ²⁾	Q9YF28	362
13	<i>Aplysia californica</i> (California sea hare)	Metazoa;	tr:Q86BW8	Q86BW8	926
14	<i>Oryza sativa</i> (<i>japonica</i> cultivar-group)	Spermatophyta	tr:Q7XHE6	Q7XHE6	467
15	<i>Arabidopsis thaliana</i> (Mouse-ear cress)	Spermatophyta	tr:Q9MA74	Q9MA74	482
16	<i>Oryza sativa</i> (Rice)	Spermatophyta	tr:Q8RV06	Q8RV06	467
17	<i>Vibrio anguillarum</i> (<i>Listonella anguillarum</i>)	Bacteria	tr:Q6W4S7	Q6W4S7	400
18	<i>Photobacterium phosphoreum</i>	Bacteria	tr:Q846V2	Q846V2	380
19	<i>Gloeobacter violaceus</i>	Bacteria	tr:Q7NIG4	Q7NIG4	382
20	<i>Clostridium tetani</i>	Bacteria	tr:Q894Q7	Q894Q7	575
21	<i>Mus musculus</i> (Mouse)	Mammalia	tr:Q7TMW5	Q7TMW5	662
22	<i>Vibrio anguillarum</i> (<i>Listonella anguillarum</i>)	Bacteria	trnew:AAR12533 ³⁾	AAR12533	400
23	<i>Vibrio anguillarum</i> (<i>Listonella anguillarum</i>)	Bacteria	trnew:AAO92385	AAO92385	386

Database: UniProt¹⁾ Sp:SWISS-PROT protein sequence database²⁾ Tr:TrEMBL protein sequence database³⁾ Trnew:TrEMBL_new protein sequence database

of the conserved amino acid residues were found in the range of 298-319, which number correlates the human HDC sequence number (19). To elucidate the significance of the conserved amino acid residues in the evolutionary process, we have explored exon/intron sequence of the enzyme. Fig. 2 also shows group of exons based upon exon/intron searches carried out at genomic DNA level. Exon 8 of human enzyme has a typical motif for PLP-dependent decarboxylases, which contains the active site Lys residue. The ϵ -amino group of the active site Lys binds to PLP to form an internal Schiff base.

PLP-dependent decarboxylase motif is also found in other decarboxylases, such as 3,4-dihydroxyphenylalanine (also called aromatic amino acid) decarboxylase (AroDC), glutamate decarboxylase (GAD), and tyrosine decarboxylase (YDC). Because having similar motifs, those decarboxylases are grouped as group II (16, 17, 20).

As of now, there is no solved crystal structure for any PLP-dependent HDC. Obtaining stable

crystals of HDC is still difficult due to the instability of HDC protein, especially in the highly purified preparations (21, 22). However, crystalline structure for pig AroDC was reported (12, 23). Pig AroDC exhibits high sequence homology to mammalian HDCs; thus, it is quite likely to predict three-dimensional model structure for human HDC by overlaying the amino acid sequence of HDC over AroDC (21).

We have employed the method described by Rodriguez-Caso *et al.* (21) to predict the human HDC structure, and result is shown in Fig. 3 (<http://www-cryst.bioc.cam.ac.uk/~jiye/evoltrace/evoltrace.html>). Each exons as indicated in Fig. 2 are color coded as described in Fig. 2. It is apparent that PLP molecule is situated just adjacent to Exon 8 (pink colored), which is translated into two helical structures that contain a typical motif for the active site sequence of group II decarboxylases. HDC, as a typical PLP-dependent enzyme, situates an active site Lys residue (Lys-305) in the helical region derived from Exon 8. This Lys residue forms a covalent

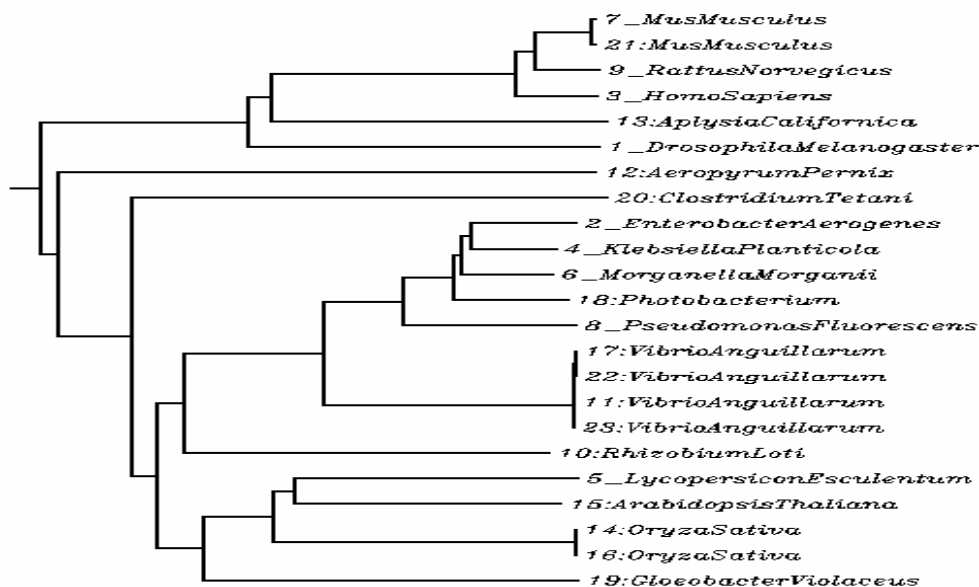


Fig. 1 Evolutionary tree of PLP-dependent HDCs. Numbers indicated correspond to those of Table I.

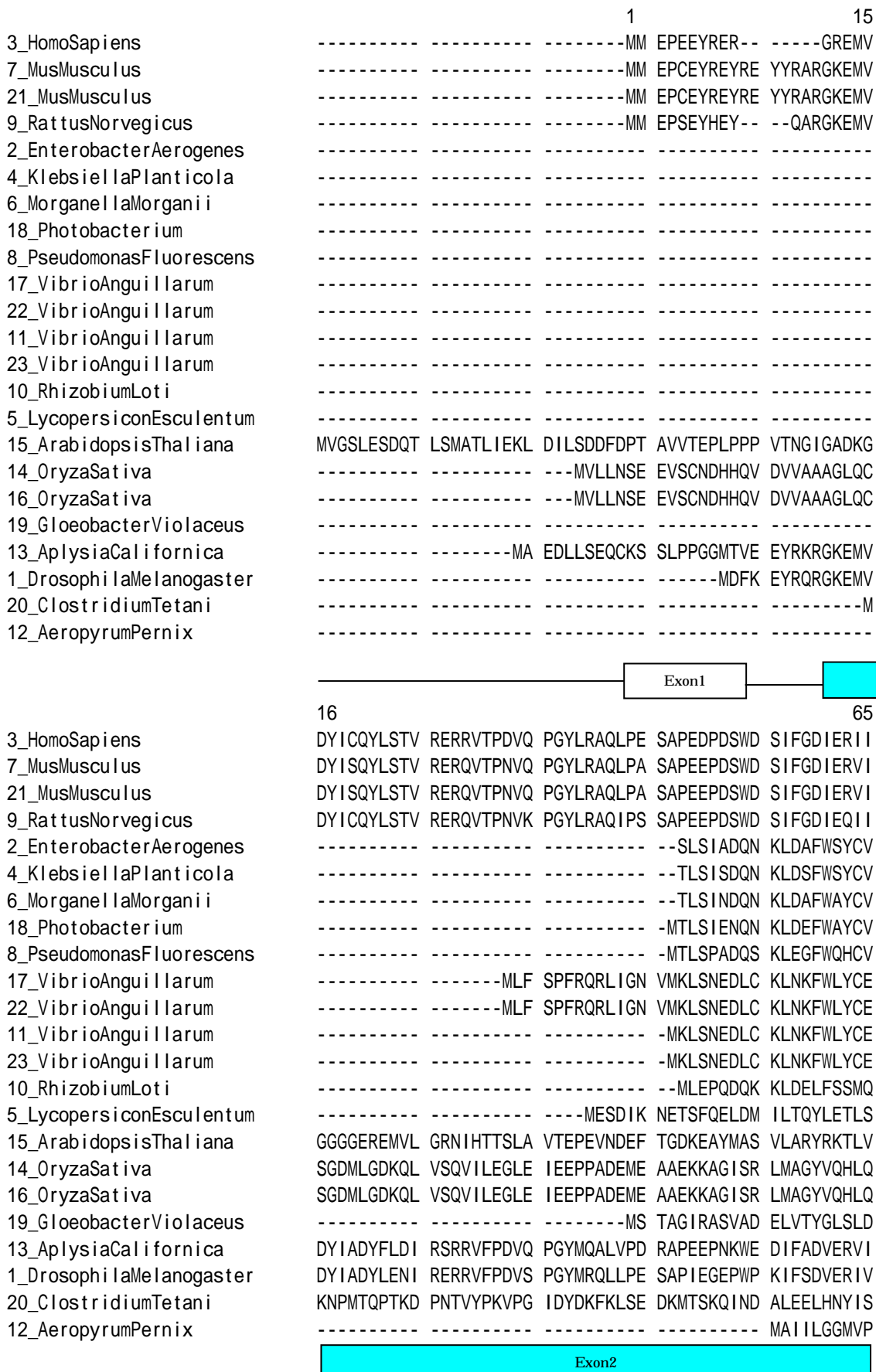


Fig. 2 Homology alignment of HDCs. CLUSTAL W (1.83) multiple sequence alignment was employed. '*' indicates a fully conserved residue. ':' indicates a residue having Gonnet Pam250 matrix score > 0.5, *i.e.*, STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW. '.' indicates the score ≤ 0.5, *i.e.*, CSA, ATV, SAG, STNK, STPA, SGND, SNDEQK, NDEQHK, NEQHRK, FVLIM, HFY.

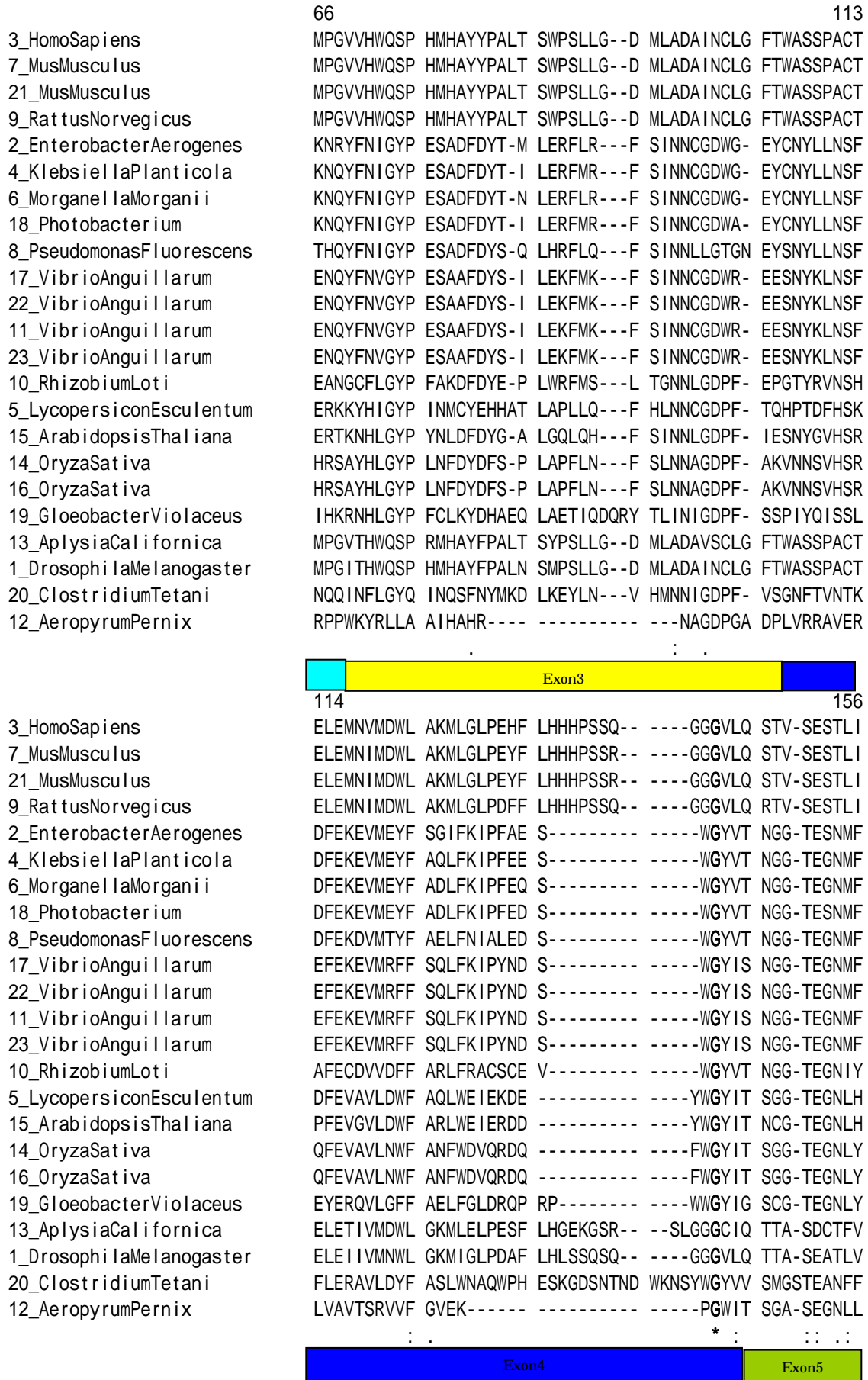


Fig. 2 (continued)

	157		185		
3_HomoSapiens	ALLAARKNKI	LEMKTSEPDA	DESCLNARL	-----	-----
7_MusMusculus	ALLAARKNKI	LAMTACEPDA	NESSLNARL	-----	-----
21_MusMusculus	ALLAARKNKI	LAMKACEPDA	NESSLNARL	-----	-----
9_RattusNorvegicus	ALLAARKNKI	LEMKAHEPNA	DESSLNARL	-----	-----
2_EnterobacterAerogenes	GCYLG----	-----	--RELFPEG-	-----	-----
4_KlebsiellaPlanticola	GCYLG----	-----	--REIFPNG-	-----	-----
6_MorganeliaMorganii	GCYLG----	-----	--REIFPDG-	-----	-----
18_Photobacterium	GCYLG----	-----	--RELFPDG-	-----	-----
8_PseudomonasFluorescens	GCYLG----	-----	--RELFPDG-	-----	-----
17_VibrioAnguillarum	SCYLA----	-----	--REIFPTA-	-----	-----
22_VibrioAnguillarum	SCYLA----	-----	--REIFPTA-	-----	-----
11_VibrioAnguillarum	SCYLA----	-----	--REIFPTA-	-----	-----
23_VibrioAnguillarum	SCYLA----	-----	--REIFPTA-	-----	-----
10_RhizobiumLoti	GLYLA----	-----	--RELYPNA-	-----	-----
5_LycopersiconEsculentum	GFWLGR----	-----	--RELLPNG-	-----	-----
15_ArabidopsisThaliana	GILVG----	-----	--REMFPDG-	-----	-----
14_OryzaSativa	GLLVG----	-----	--RELFPDG-	-----	-----
16_OryzaSativa	GLLVG----	-----	--RELFPDG-	-----	-----
19_GloeobacterViolaceus	GLLL-----	-----	--RLAQPEG-	-----	-----
13_AplysiaCalifornica	TLLAARTDAI	ARYKA IHPDK	DEAWINGRL	-----	-----
1_DrosophilaMelanogaster	CLLAGRTRAI	QRFHERHPGY	QDAEINARL	-----	-----
20_ClostridiumTetani	GIWNARDYLS	GKALLLDTST	HKRAKSASIN	GNPQSVEPRV	LNYQAKSLED
12_AeropyrumPernix	ALYTLR----	-----	--EEGYRR--	-----	-----

Exon5

	186		209		
3_HomoSapiens	-----VAY	ASDQAHSSVE	KAGLISLVKM	K-----	-----
7_MusMusculus	-----VAY	TSDQAHSSVE	KAGLISLVKI	R-----	-----
21_MusMusculus	-----VAY	TSDQAHSSVE	KAGLISLVKI	R-----	-----
9_RattusNorvegicus	-----VAY	ASDQAHSSVE	KAGLISLVKI	K-----	-----
2_EnterobacterAerogenes	-----TLY	YSKDTHTSVA	KIVKLLRIKS	Q-----	-----
4_KlebsiellaPlanticola	-----TLY	YSKDTHTSVA	KIVKLLRIKS	T-----	-----
6_MorganeliaMorganii	-----TLY	YSKDTHTSVA	KIVKLLRIKS	Q-----	-----
18_Photobacterium	-----TLY	YSKDTHTSVA	KIVKLLRIKS	Q-----	-----
8_PseudomonasFluorescens	-----TLY	YSKDTHTSVA	KIVKLLRIKC	R-----	-----
17_VibrioAnguillarum	-----YIY	YSEETHYSVD	KIVRLLNIPA	R-----	-----
22_VibrioAnguillarum	-----YIY	YSEETHYSVD	KIVRLLNIPA	R-----	-----
11_VibrioAnguillarum	-----YIY	YSEETHYSVD	KIVRLLNIPA	R-----	-----
23_VibrioAnguillarum	-----YIY	YSEETHYSVD	KIVRLLNIPA	R-----	-----
10_RhizobiumLoti	-----VAY	FSQDHTYSVS	KGVRLRLLEH	S-----	-----
5_LycopersiconEsculentum	-----YLY	ASKDSHYSIF	KAARMYRMEL	Q-----	-----
15_ArabidopsisThaliana	-----ILY	ASRESHYSVF	KAARMYRMEC	E-----	-----
14_OryzaSativa	-----ILY	ASNSHYSVF	KAAMKMYRVKC	I-----	-----
16_OryzaSativa	-----ILY	ASNSHYSVF	KAAMKMYRVKC	I-----	-----
19_GloeobacterViolaceus	-----ILY	FSEAAHYSVG	KAARMFRMPY	R-----	-----
13_AplysiaCalifornica	-----IGY	CSDQAHSSVE	KAGLIGLVKM	R-----	-----
1_DrosophilaMelanogaster	-----VAY	CSDQAHSSVE	KAALIGLVRM	R-----	-----
20_ClostridiumTetani	NPNMYTPIAF	YSQDHTYSII	KGMRILNFTT	FNEAGSGKFE	CPLKYPEDYP
12_AeropyrumPernix	-----VV	AFDTSHTYSIK	KSALTLSMEL	D-----	-----

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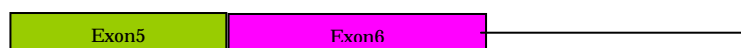


Fig. 2 (continued)

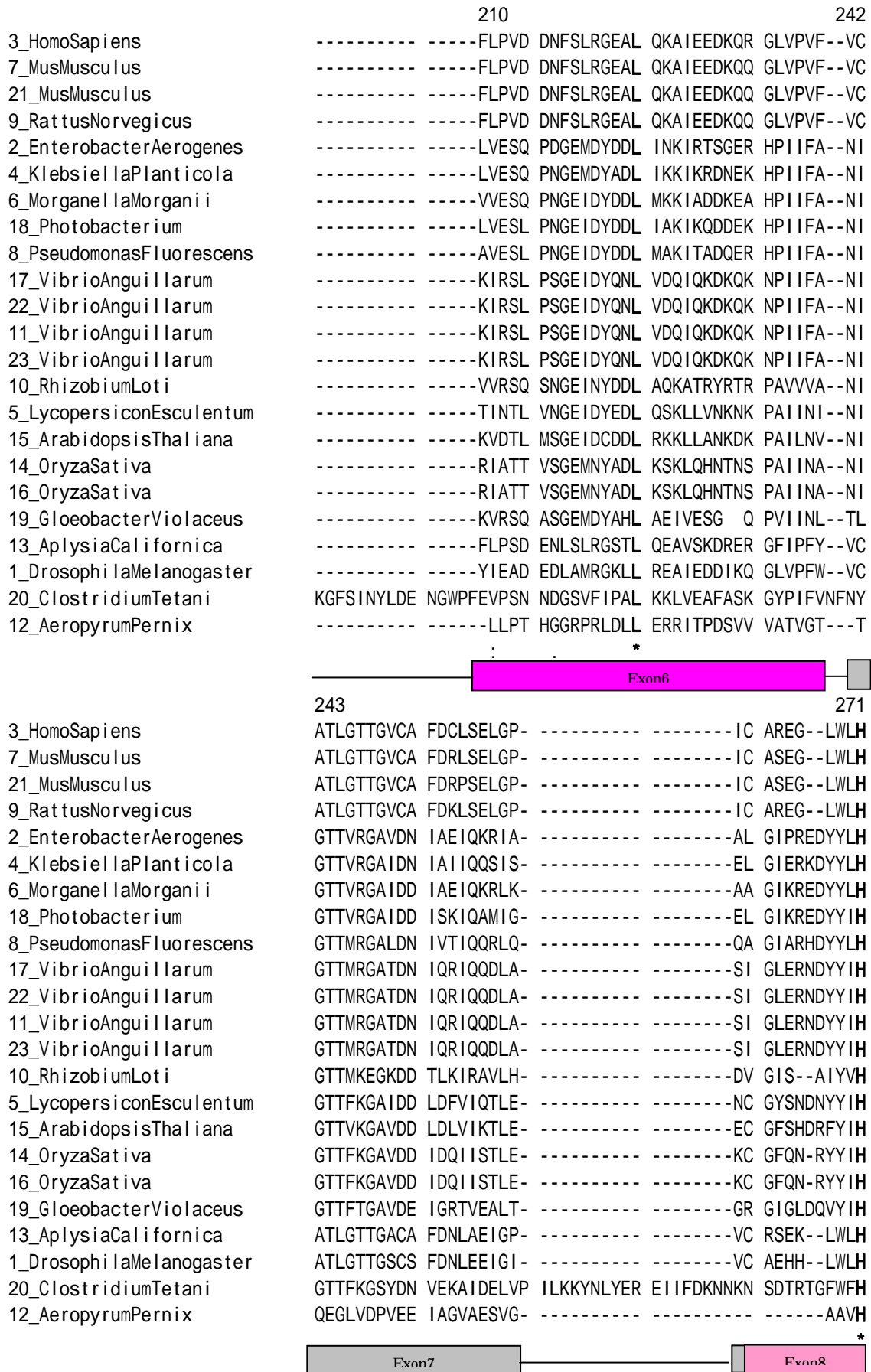


Fig. 2 (continued)

	272					314
3_HomoSapiens	IDAAYAGTAF	LCPEFRGFLK	-----GIE	YADSFTFNPS	KWMMVHFDCT	
7_MusMusculus	VDAAYAGTAF	LCPELRGFLE	-----GIE	YADSFTFNPS	KWMMVHFDCT	
21_MusMusculus	VDAAYAGTAF	LCPELRGFLE	-----GIE	YADSSTFNPS	KWMMVHFDCT	
9_RattusNorvegicus	VDAAYAGTAF	LRPELRGFLK	-----GIE	YADSFTFNPS	KWMMVHFDCT	
2_EnterobacterAerogenes	ADAALSGMIL	PFVEDPQPFT	-----FAD	GIDSIGVSGH	KMIGSPIPCG	
4_KlebsiellaPlanticola	ADAALSGMIL	PFVDNPQPFN	-----FAD	GIDSIGVSGH	KMIGSPIPCG	
6_MorganelLaMorganii	ADAALSGMIL	PFVDDAQPFT	-----FAD	GIDSIGVSGH	KMIGSPIPCG	
18_Photobacterium	ADAALSGMIL	PFVDEPQGFN	-----FAD	GIDSIGVSGH	KMIGSPIPCG	
8_PseudomonasFluorescens	ADAALSGMIL	PFVDHPQFVS	-----FAD	GIDSI CVS GH	KMIGSPIPCG	
17_VibrioAnguillarum	ADAALSGMIM	PFVEQHPYS	-----FED	GIDSISVSGH	KMIGSPIPCG	
22_VibrioAnguillarum	ADAALSGMIM	PFVEQHPYS	-----FED	GIDSISVSGH	KMIGSPIPCG	
11_VibrioAnguillarum	ADAALSGMIM	PFVEQHPYS	-----FED	GIDSISVSGH	KMIGSPIPCG	
23_VibrioAnguillarum	ADAALSGMIM	PFVEQHPYS	-----FED	GIDSISVSGH	KMIGSPIPCG	
10_RhizobiumLoti	SDAALCGPYA	PLLNPKPAFD	-----FAD	GADSI T L S GH	KFLGAPMPCG	
5_LycopersiconEsculentum	CDRALCGLIL	PFIKHAKKIT	-----FKK	PIGSISISGH	KFLGCPMSCG	
15_ArabidopsisThaliana	CDGALFGLMM	PFVKRAPKVT	-----FNK	PIGSVSVSGH	KFVGCPMPCG	
14_OryzaSativa	CDSALSGMMT	PFMKQAPKVS	-----FKK	PIGSISVSGH	KFLGCPMPCG	
16_OryzaSativa	CDSALSGMMT	PFMKQAPKVS	-----FKK	PIGSISVSGH	KFLGCPMPCG	
19_GloeobacterViolaceus	VDAALGGMIA	CYIR-PELIS	-----FDW	PIGLAISGH	KFIGCPHPCG	
13_AplysiaCalifornica	LDAAYAGSAF	ICPEFRSWMA	-----GIE	FSDSFAFNPS	KWLMVHFDCS	
1_DrosophilaMelanogaster	VDAAYAGSAF	ICPEFRTWLR	-----GIE	RADSI AFNPS	KWLMVHFDAT	
20_ClostridiumTetani	VDGALGAAYM	PFLEMTT DNE	DFPVDFRLK	DVHSISMSGH	KWIGVPWPCG	
12_AeropyrumPernix	VDAAYGGYIA	RFLTGKARFR	-----LEP	PVMTVVVD AH	KIPEAPPAG	
	* * .			:	. . *	.
	Exon8					
	315					361
3_HomoSapiens	GFWVKDKYKL	QQ TFSVNP	IYLRH-ANSG	VATDFMHWQI	PLSRRFRSVK	
7_MusMusculus	GFWVKDKYKL	QQ TFSVNP	IYLRH-ANSG	AATDFMHWQI	PLSRRFRSIK	
21_MusMusculus	GFWVKDKYKL	QQ TFSVNP	IYLRH-ANSG	AATDFMHWQI	PLSRCFRSIK	
9_RattusNorvegicus	GFWVKDKYKL	QQ TFSVNP	IYLRH-ANSG	VATDFMHWQI	PLSRRFRSIK	
2_EnterobacterAerogenes	IVVAKKANVD	R----ISVEI	DYISA-HDKT	ISGSRN----	----GHTPLM	
4_KlebsiellaPlanticola	IVVAKKKNVD	R----ISVEI	DYISA-HDKT	ISGSRN----	----GHTPLM	
6_MorganelLaMorganii	IVVAKKENVD	R----ISVEI	DYISA-HDKT	ITGSRN----	----GHTPLM	
18_Photobacterium	IVVAKKRNV D	A----ISVEI	DYISA-HDKT	ITGSRN----	----GHTPLM	
8_PseudomonasFluorescens	IVVAKRNNVA	R----ISVEV	DYIRA-HDKT	ISGSRN----	----GHTPLM	
17_VibrioAnguillarum	IVLAKRHMVD	Q----ISVEV	DYISS-RDQT	ISGSRN----	----GHSALF	
22_VibrioAnguillarum	IVLAKRHMVD	Q----ISVEV	DYISS-RDQT	ISGSRN----	----GHSALF	
11_VibrioAnguillarum	IVLAKRHMVD	Q----ISVEV	DYISS-RDQT	ISGSRN----	----GHSALF	
23_VibrioAnguillarum	IVLAKRHMVD	Q----ISVEV	DYISS-RDQT	ISGSRN----	----GHSALF	
10_RhizobiumLoti	VVLSHKLHVQ	R----VMRNI	DYIGS-SDTT	LSGSRN----	----AFTPII	
5_LycopersiconEsculentum	VQITRRSYVS	----TLS-KI	EYINS-ADAT	ISGSRN----	----GFTPIF	
15_ArabidopsisThaliana	VQITRMEHIK	----VLSSNV	EYIAS-RDAT	IMGSRN----	----GHAPLF	
14_OryzaSativa	VVITRLEHAE	----VLSTDI	EYIAS-RDST	ITGSRN----	----GHAPIF	
16_OryzaSativa	VVITRLEHAE	----VLSTDI	EYIAS-RDST	ITGSRN----	----GHAPIF	
19_GloeobacterViolaceus	VVLT YKETAD	RFSSEISA EV	EYIGS-TDLT	IMGSRN----	----GHTPLY	
13_AplysiaCalifornica	AMWVKDARAL	HR TFNVEP	LYLQH-ENSG	AAIDYMHWQI	ALSRRFRALK	
1_DrosophilaMelanogaster	ALWVRDSTAV	HR TFNVEP	LYLQH-ENSG	VAVDFMHWQI	PLSRRFRALK	
20_ClostridiumTetani	IYMSKIKYQL	LP----PDNP	NYIGS-PDST	FAGSRN----	----AFSSLI	
12_AeropyrumPernix	VILASKQKLL	DN---LWFES	PYIPTGRQFG	ILGTRP----	----GGPIVA	
			*	.		.
	Exon9		Exon10			

Fig. 2 (continued)

	362		405
3_HomoSapiens	LWFVIRSGV	KNLQAHVRHG	TEMAKYFESL VRND----- PSFEIPAKRH
7_MusMusculus	LWFVIRSGV	KNLQAHVRHG	TEMAKYFESL VRSD----- PSFEIPAKRH
21_MusMusculus	LWFVIRSGV	KNLQAHVRHG	TEMAKYFESL VRSD----- PSFEIPAKRH
9_RattusNorvegicus	LWFVIRSGV	KNLQAHVRHG	TDMAKYFESL VRSD----- PVFEIPAERH
2_EnterobacterAerogenes	MWAAVRSHD	AEWRRRIGHS	LNMAKYAVDR FKAA----- GIDALCHKNS
4_KlebsiellaPlanticola	MWEAIRSHSW	EEWRRRIERS	LNMAQYAVDR FQSA----- GIDAWRNKNS
6_MorganelLaMorganii	LWEAIRSHST	EEWKRRITRS	LDMAQYAVDR MQKA----- GINAWRNKNS
18_Photobacterium	MWCAVKSHTH	EDFKRRINRS	LDLAQHAVQR LQSA----- GINAWCNKNS
8_PseudomonasFluorescens	MWAALRSYSW	AEWRRRIKHS	LDTAQYAVDR FQAS----- GIDAWRNENS
17_VibrioAnguillarum	MWTAIKSHSF	VDWQGVNQC	LNMAEYTVQR FQEV----- GINAWRNKNS
22_VibrioAnguillarum	MWTAIKSHSF	VDWQGVNQC	LNMAEYTVQR FQEV----- GINAWRNKNS
11_VibrioAnguillarum	MWTAIKSHSF	VDWQGVNQC	LNMAEYTVQR FQEV----- GINAWRNKNS
23_VibrioAnguillarum	MWTAIKSHSF	VDWQGVNQC	LNMAEYTVQR FQEV----- GINAWRNKNS
10_RhizobiumLoti	LWYAIRSLGI	EGIKQTFQQC	ERLAAYTAD E LNVR----- GVSAWRPNNA
5_LycopersiconEsculentum	LWYCLSKKGH	ARLQQDSITC	IENARYLKDR LLEA----- GISVMLNDFS
15_ArabidopsisThaliana	LWYTLNRKGY	KGFQKEVQKC	LRNAHYLKDR LREA----- GISAMLNELS
14_OryzaSativa	LWYTLNRRGY	KGLLKEVHIC	MGNARYLEVL LKQV----- GISASCNTLS
16_OryzaSativa	LWYTLNRRGY	KGLLKEVHIC	MGNARYLEVL LKQV----- GISASCNTLS
19_GloeobacterViolaceus	LWAEIQRR-K	STFHLEAEAI	VDKARFLHQK LSDQ----- GLPALLNPLS
13_AplysiaCalifornica	LWFVLRSGV	SGLQRHIRRG	VELAQMFENL VQAD----- LRFVETAPRW
1_DrosophilaMelanogaster	VWFVLRSYGI	KGLQRHIREG	VRLAQKFEAL VLAD----- HRFELPAKRH
20_ClostridiumTetani	LWYYIATHSY	EDCKNMILDC	QDTAKYVEK LNELSKLGI DLWVEYSSKS
12_AeropyrumPernix	AWRRVEDLER	NPGFPRLASI	LMRRLRKTLC ALER-----L GYETPVTPDL
	*	.	
	Exon10		Exon11
	406		448
3_HomoSapiens	LGLVVFRLKG	PNCLTE----	---NVLKEIA KAGRLFLIPA TIQDKLIIRF
7_MusMusculus	LGLVVFRLKG	PNCLTE----	---SVLKEIA KAGQLFLIPA TIQDKLIIRF
21_MusMusculus	LGLVVFRLKG	PNCLTE----	---SVLKEIA KAGQLFLIPA TIQDKLIIRF
9_RattusNorvegicus	LGLVVFRLKG	PNCLTE----	---SVLKEIA KTGQVFLIPA TIQDKLIIRF
2_EnterobacterAerogenes	ITVVFPCP-S	EWVWKK----	---HCLATSG NVAHLITTAH HLDSSRIDAL
4_KlebsiellaPlanticola	ITVVFPCP-S	EAVWKK----	---HCLATSG DIAHLIATAH HLDSSKIDAL
6_MorganelLaMorganii	ITVVFPCP-S	ERVVRE----	---HCLATSG DVAHLITTAH HLDTVQIDKL
18_Photobacterium	ITVVFPCP-S	EAVWKK----	---HCLATSG GQAHLITTAH HLDASKVDAL
8_PseudomonasFluorescens	ITVVFPCP-S	ERIATK----	---YCLATSG NSAHLITTPH HHDCSMIDAL
17_VibrioAnguillarum	NTVVFPCP-S	EPVWRK----	---HSLANSG SVAHIITMPH LDGPDKLDPL
22_VibrioAnguillarum	NTVVFPCP-S	EPVWRK----	---HSLANSG SVAHIITMPH LDGPDKLDPL
11_VibrioAnguillarum	NTVVFPCP-S	EPVWRK----	---HSLANSG SVAHIITMPH LDGPDKLDPL
23_VibrioAnguillarum	NTVVFPCP-S	EPVWRK----	---HSLANSG SVAHIITMPH LDGPDKLDPL
10_RhizobiumLoti	LTVVLPPV-E	DSIKTK----	---WQIAT-Q DVSHLVVTPG TT-KQQADAL
5_LycopersiconEsculentum	ITVVFERPCD	HKFIRR----	---WNLCLLR GMAHVVIMPG ITRETIDSFF
15_ArabidopsisThaliana	STVVFERPKD	EEFVRR----	---WQLACQG DIAHVVMPS VTIEKLDNFL
14_OryzaSativa	NIVVFERPKD	ERIVCR----	---WQLACEG NLAHIVVMPN VTFEKLTVFV
16_OryzaSativa	NIVVFERPKD	ERIVCR----	---WQLACEG NLAHIVVMPN VTFEKLTVFV
19_GloeobacterViolaceus	STVVFPRP-P	QPVIK----	---YQLAVQV DQAHAVIMQQ HSYELLEEFA
13_AplysiaCalifornica	LGMVVFRLVG	PNELTE----	---ALLKRLN KEGKVHMVPA SLKGKYVIRF
1_DrosophilaMelanogaster	LGLVVFRIIRG	DNEITE----	---KLLKRLN HRGNLHCIPS SLKGQYVIRF
20_ClostridiumTetani	LTIRFKEANP	DIVFKYLSLG	EILYVNGEKR AYSHIYIMPH VTKDLIDKFI
12_AeropyrumPernix	PVACATHPRL	GEVLER----	---LKASGVR VYRCRSPKPC LHVNTYGRCL
	Exon11		Exon12

Fig. 2 (continued)

	449	478		
3_HomoSapiens	TVTSQFTTRD	DILRDWNLIR	DAATLILSQH	-----
7_MusMusculus	TVTSQFTTKE	DILRDWHLIQ	EAANLVLSQH	-----
21_MusMusculus	TVTSQFTTKE	DILRDWHLIQ	EAANLVLSQH	-----
9_RattusNorvegicus	TVTSQFTTKD	DILRDWNLIR	EAANLVLSQH	-----
2_EnterobacterAerogenes	IDDDIADLAQ	RAA-----	-----	-----
4_KlebsiellaPlanticola	IDDDIADLKK	QAA-----	-----	-----
6_Morganel laMorganii	IDDDIADFNL	HAA-----	-----	-----
18_Photobacterium	IDDDVIKDANG	ETIAA----	-----	-----
8_PseudomonasFluorescens	IDEVVAEAQL	NTLRSKRAFT	EQTVVERLPA	ASFNLRTHY-
17_VibrioAnguillarum	IEDVIYDLLP	NYNILNVSGQ	N-----	-----
22_VibrioAnguillarum	IEDVIYDLLP	NYNILNVSGQ	N-----	-----
11_VibrioAnguillarum	IEDVIYDLLP	NYNILNVSGQ	N-----	-----
23_VibrioAnguillarum	IEDVIYDLLP	NYNILNVSGQ	N-----	-----
10_RhizobiumLoti	IETISNRNR-	-----	-----	-----
5_LycopersiconEsculentum	KDLMQERNYK	WYQDVKALPP	CLADDLALNC	MCSNKKMHN-
15_ArabidopsisThaliana	KDLVKHR-LI	WYEDGSQPPC	LASEVGTNNC	ICPAHK----
14_OryzaSativa	EELAERKRDW	YQDKGFDIPC	LAVDIGKENC	YCNLHAKKLR
16_OryzaSativa	EELAERKRDW	YQDKGFDIPC	LAVDIGKENC	YCNLHAKKLR
19_GloeobacterViolaceus	GVLGTCLG--	-----	-----	-----
13_AplysiaCalifornica	TVTSQFTLES	DIEKDWITIT	DMASKILIEA	GEQADESIEE
1_DrosophilaMelanogaster	TITSTHTTLD	DIVKDWEIR	QVASTVLEEM	NITISNRVYL
20_ClostridiumTetani	KDLSKPGAFP	EQVSHLEKDG	VNFNSNSHKG	IYVPQIGRGF
12_AeropyrumPernix	RARLGSSRSP	RGCLRKPLGA	SLGNPGVTGL	GL-----

Exon12

3_HomoSapiens	-----	-----	-----	-----
7_MusMusculus	-----	-----	-----	-----
21_MusMusculus	-----	-----	-----	-----
9_RattusNorvegicus	-----	-----	-----	-----
2_EnterobacterAerogenes	-----	-----	-----	-----
4_KlebsiellaPlanticola	-----	-----	-----	-----
6_Morganel laMorganii	-----	-----	-----	-----
18_Photobacterium	-----	-----	-----	-----
8_PseudomonasFluorescens	-----	-----	-----	-----
17_VibrioAnguillarum	-----	-----	-----	-----
22_VibrioAnguillarum	-----	-----	-----	-----
11_VibrioAnguillarum	-----	-----	-----	-----
23_VibrioAnguillarum	-----	-----	-----	-----
10_RhizobiumLoti	-----	-----	-----	-----
5_LycopersiconEsculentum	-----	-----	-----	-----
15_ArabidopsisThaliana	-----	-----	-----	-----
14_OryzaSativa	-----	-----	-----	-----
16_OryzaSativa	-----	-----	-----	-----
19_GloeobacterViolaceus	-----	-----	-----	-----
13_AplysiaCalifornica	AETTQMSTNS	NKEEPPTLQR	VPRKNAARSN	GLTNGEAHLC
1_DrosophilaMelanogaster	GSSLLLSNSP	LSPKVVNGSF	AAIFDADEFL	AKTYAG----
20_ClostridiumTetani	-----	-----	-----	-----
12_AeropyrumPernix	-----	-----	-----	-----

Fig. 2 (continued)

3_HomoSapiens	-----	-----	-----	-----	-----
7_MusMusculus	-----	-----	-----	-----	-----
21_MusMusculus	-----	-----	-----	-----	-----
9_RattusNorvegicus	-----	-----	-----	-----	-----
2_EnterobacterAerogenes	-----	-----	-----	-----	-----
4_KlebsiellaPlanticola	-----	-----	-----	-----	-----
6_MorganeliaMorganii	-----	-----	-----	-----	-----
18_Photobacterium	-----	-----	-----	-----	-----
8_PseudomonasFluorescens	-----	-----	-----	-----	-----
17_VibrioAnguillarum	-----	-----	-----	-----	-----
22_VibrioAnguillarum	-----	-----	-----	-----	-----
11_VibrioAnguillarum	-----	-----	-----	-----	-----
23_VibrioAnguillarum	-----	-----	-----	-----	-----
10_RhizobiumLoti	-----	-----	-----	-----	-----
5_LycopersiconEsculentum	-----	-----	-----	-----	-----
15_ArabidopsisThaliana	-----	-----	-----	-----	-----
14_OryzaSativa	-----	-----	-----	-----	-----
16_OryzaSativa	-----	-----	-----	-----	-----
19_GloeobacterViolaceus	-----	-----	-----	-----	-----
13_AplysiaCalifornica	HAKTASLRRK	EFGISLLLSN	VPMSPKVVNG	SFAALYDDND	VGLEQLAGQL
1_DrosophilaMelanogaster	-----	-----	-----	-----	----VRIAHQ
20_ClostridiumTetani	-----	-----	-----	-----	-----
12_AeropyrumPernix	-----	-----	-----	-----	-----

			479		499
3_HomoSapiens	-----	-----	-----CTS	QPSPRVGNLI	SQIRG--ARA
7_MusMusculus	-----	-----	-----CTS	QPSPRAKNVI	PPPPG-----
21_MusMusculus	-----	-----	-----CTS	QPSPRAKNVI	PPPPG-----
9_RattusNorvegicus	-----	-----	-----CTS	QPSPRAKNLI	PPPVTRDSKD
2_EnterobacterAerogenes	-----	-----	-----	-----	-----
4_KlebsiellaPlanticola	-----	-----	-----	-----	-----
6_MorganeliaMorganii	-----	-----	-----	-----	-----
18_Photobacterium	-----	-----	-----	-----	-----
8_PseudomonasFluorescens	-----	-----	-----	-----	-----
17_VibrioAnguillarum	-----	-----	-----	-----	-----
22_VibrioAnguillarum	-----	-----	-----	-----	-----
11_VibrioAnguillarum	-----	-----	-----	-----	-----
23_VibrioAnguillarum	-----	-----	-----	-----	-----
10_RhizobiumLoti	-----	-----	-----	-----	-----
5_LycopersiconEsculentum	-----	-----	-----	-----	-----
15_ArabidopsisThaliana	-----	-----	-----	-----	-----
14_OryzaSativa	-----	-----	-----	-----	-----
16_OryzaSativa	-----	-----	-----	-----	-----
19_GloeobacterViolaceus	-----	-----	-----	-----	-----
13_AplysiaCalifornica	SVGGEFIRLS	PRKRGKLSEK	DRQRSLDLCSF	LAYRRDNPIK	MKMMGSLDSK
1_DrosophilaMelanogaster	ESPSMRRRVR	GILMSGKQFS	LDSHMDVVVQ	TTLDAGNGAT	RTSTTNSYGH
20_ClostridiumTetani	-----	-----	-----	-----	-----
12_AeropyrumPernix	-----	-----	-----	-----	-----

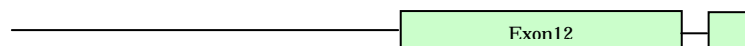


Fig. 2 (continued)

	500	549
3_HomoSapiens	WACGTSLQSV SGAGDDPVQA RKI IKQPQRV GAGPMKRENG LHLETLLDPV	
7_MusMusculus	-TRGLSLESV SEGGDDPAQA RKI IKQPGAS LA---RREGG SDLETMPDPF	
21_MusMusculus	-TRGLSLESV SEGGDDPAQA RKI IKQPGAS LA---RREGG SDLETMPDPF	
9_RattusNorvegicus	LTNGLSLESV NEGGDDPVQV RKI FRLP--- -----G DSLETTMPDPF	
2_EnterobacterAerogenes	-----	-----
4_KlebsiellaPlanticola	-----	-----
6_MorganellaMorganii	-----	-----
18_Photobacterium	-----	-----
8_PseudomonasFluorescens	-----	-----
17_VibrioAnguillarum	-----	-----
22_VibrioAnguillarum	-----	-----
11_VibrioAnguillarum	-----	-----
23_VibrioAnguillarum	-----	-----
10_RhizobiumLoti	-----	-----
5_LycopersiconEsculentum	-----	-----
15_ArabidopsisThaliana	-----	-----
14_OryzaSativa	-----	-----
16_OryzaSativa	-----	-----
19_GloeobacterViolaceus	-----	-----
13_AplysiaCalifornica	IDDILEMGSK VAGGGDDSDG ETAEGRKEKD KEEDDRRECK GKVDEEGKEV	
1_DrosophilaMelanogaster	TTSAAQANSE RQASIQEDNE ESPEETELLS LCRTSNVPSP EHAHSLSTPS	
20_ClostridiumTetani	-----	-----
12_AeropyrumPernix	-----	-----

Exon12

	550	571
3_HomoSapiens	DDCFSEEAPD ATKHKLSSFL FS-----	-----
7_MusMusculus	DDCFSEEAPN TTKHKLSSFL FS-----	-----
21_MusMusculus	DDCFSEEAPN TTKHKLSSFL FS-----	-----
9_RattusNorvegicus	DDCFSEEASD TTKHKLSSFL FS-----	-----
2_EnterobacterAerogenes	-----	-----
4_KlebsiellaPlanticola	-----	-----
6_MorganellaMorganii	-----	-----
18_Photobacterium	-----	-----
8_PseudomonasFluorescens	-----	-----
17_VibrioAnguillarum	-----	-----
22_VibrioAnguillarum	-----	-----
11_VibrioAnguillarum	-----	-----
23_VibrioAnguillarum	-----	-----
10_RhizobiumLoti	-----	-----
5_LycopersiconEsculentum	-----	-----
15_ArabidopsisThaliana	-----	-----
14_OryzaSativa	-----	-----
16_OryzaSativa	-----	-----
19_GloeobacterViolaceus	-----	-----
13_AplysiaCalifornica	DQAEAEASNE KSFSEKNVVG AKKGRVIEVP AVTKVKVKMS NGGLVKGEGT	
1_DrosophilaMelanogaster	RSCSSSSHSL THSLTQSSAR SSPVNQFRHI TLCAVPSQSH LSMPLAMPLP	
20_ClostridiumTetani	-----	-----
12_AeropyrumPernix	-----	-----

Exon12

Fig. 2 (continued)

	572			610
3_HomoSapiens	----- -YLSVQTKKK	TVRSLSCNSV	PVSAQKPLPT	EASVKNGGSS
7_MusMusculus	----- -YLSVQNRK	TTRSLSCNSV	PMSAQKSLPA	DASLKNGGSF
21_MusMusculus	----- -YLSVQNRK	TTRSLSCNSV	PMSAQKSLPA	DASLKNGGSF
9_RattusNorvegicus	----- -YLSVQNKKK	TMRSLSCNSM	PMSAQKSPPP	DASVKHGGFF
2_EnterobacterAerogenes	-----			
4_KlebsiellaPlanticola	-----			
6_MorganeliaMorganii	-----			
18_Photobacterium	-----			
8_PseudomonasFluorescens	-----			
17_VibrioAnguillarum	-----			
22_VibrioAnguillarum	-----			
11_VibrioAnguillarum	-----			
23_VibrioAnguillarum	-----			
10_RhizobiumLoti	-----			
5_LycopersiconEsculentum	-----			
15_ArabidopsisThaliana	-----			
14_OryzaSativa	-----			
16_OryzaSativa	-----			
19_GloeobacterViolaceus	-----			
13_AplysiaCalifornica	SLEGRVLEQE	RWDTGHRGQK	GKKSQTGQEK	DTGVKNNEIA
1_DrosophilaMelanogaster	NRNVTVSVD	LLNPVTTCNV	YHGKRFLEPL	ENLAQTSASF
20_ClostridiumTetani	-----			
12_AeropyrumPernix	-----			
		Exon12		
	611			649
3_HomoSapiens	RVRIFSRFPE	DMMMLKKSFA	KKLIKFYSP	SFPECSSQC-
7_MusMusculus	RARIFSGFPE	QMMMMKKGAF	KKLIKFYSP	SFPECSSQC-
21_MusMusculus	RARIFSGFPE	QMMMMKKGAF	KKLIKFYSP	SFPECSSQC-
9_RattusNorvegicus	RARIFSGFPE	EMMMMMKGGF	KKLIKFYSP	SFPECSSQCG
2_EnterobacterAerogenes	-----			
4_KlebsiellaPlanticola	-----			
6_MorganeliaMorganii	-----			
18_Photobacterium	-----			
8_PseudomonasFluorescens	-----			
17_VibrioAnguillarum	-----			
22_VibrioAnguillarum	-----			
11_VibrioAnguillarum	-----			
23_VibrioAnguillarum	-----			
10_RhizobiumLoti	-----			
5_LycopersiconEsculentum	-----			
15_ArabidopsisThaliana	-----			
14_OryzaSativa	-----			
16_OryzaSativa	-----			
19_GloeobacterViolaceus	-----			
13_AplysiaCalifornica	QKRDQKSNTA	SENQNSVGDH	KMVLKASKSS	ELPTKSKNSV
1_DrosophilaMelanogaster	MATPTRESPE	DPDWPAKTFS	QLLLERYSSQ	SQSLGNNSST
20_ClostridiumTetani	-----			
12_AeropyrumPernix	-----			
		Exon12		

Fig. 2 (continued)

				650	657
3_HomoSapiens	-----	-----	-----	-----	--GLQLPCCP
7_MusMusculus	-----	-----	-----	-----	--ARQLPCCP
21_MusMusculus	-----	-----	-----	-----	--ARQLPCCP
9_RattusNorvegicus	-----	-----	-----	-----	--TLQLPCCP
2_EnterobacterAerogenes	-----	-----	-----	-----	-----
4_KlebsiellaPlanticola	-----	-----	-----	-----	-----
6_MorganelLaMorganii	-----	-----	-----	-----	-----
18_Photobacterium	-----	-----	-----	-----	-----
8_PseudomonasFluorescens	-----	-----	-----	-----	-----
17_VibrioAnguillarum	-----	-----	-----	-----	-----
22_VibrioAnguillarum	-----	-----	-----	-----	-----
11_VibrioAnguillarum	-----	-----	-----	-----	-----
23_VibrioAnguillarum	-----	-----	-----	-----	-----
10_RhizobiumLoti	-----	-----	-----	-----	-----
5_LycopersiconEsculentum	-----	-----	-----	-----	-----
15_ArabidopsisThaliana	-----	-----	-----	-----	-----
14_OryzaSativa	-----	-----	-----	-----	-----
16_OryzaSativa	-----	-----	-----	-----	-----
19_GloeobacterViolaceus	-----	-----	-----	-----	-----
13_AplysiaCalifornica	GGRYMMELSK	AVCSKVKEAL	LTLPGSGGGN	STPAAMAGDG	DGDECCPCCG
1_DrosophilaMelanogaster	PTPTPMSSLD	ELVTPLLLSF	ASPSQPMLSA	HGIGEGQRER	GSDSDATVCS
20_ClostridiumTetani	-----	-----	-----	-----	-----
12_AeropyrumPernix	-----	-----	-----	-----	-----

Exon12

	658
3_HomoSapiens	LQAMV----
7_MusMusculus	LEAMV----
21_MusMusculus	LEAMV----
9_RattusNorvegicus	LQAMV----
2_EnterobacterAerogenes	-----
4_KlebsiellaPlanticola	-----
6_MorganelLaMorganii	-----
18_Photobacterium	-----
8_PseudomonasFluorescens	-----
17_VibrioAnguillarum	-----
22_VibrioAnguillarum	-----
11_VibrioAnguillarum	-----
23_VibrioAnguillarum	-----
10_RhizobiumLoti	-----
5_LycopersiconEsculentum	-----
15_ArabidopsisThaliana	-----
14_OryzaSativa	-----
16_OryzaSativa	-----
19_GloeobacterViolaceus	-----
13_AplysiaCalifornica	RELPSLLS
1_DrosophilaMelanogaster	TTSSMESL-
20_ClostridiumTetani	-----
12_AeropyrumPernix	-----

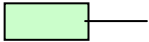


Fig. 2 (continued)

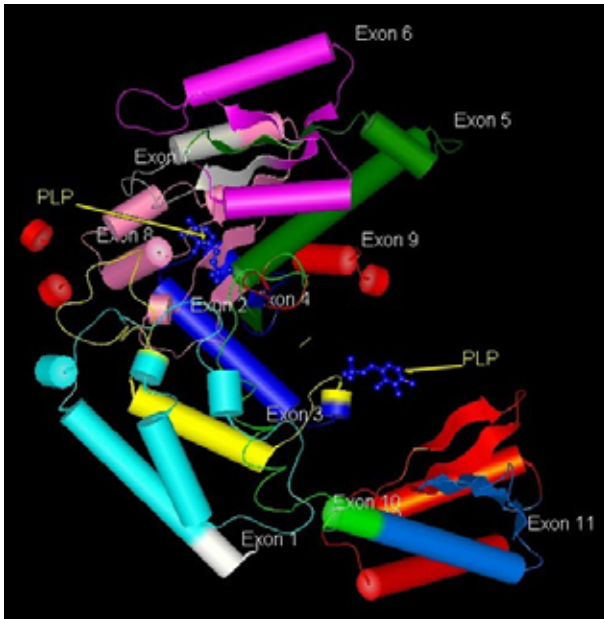


Fig. 3. Three-dimensional orientation of exons in histidine decarboxylase structure predicted from AroDC structure (1JS3.pdb (21)). Exon 1-11 are colored as indicated in Fig. 2. Exon 12 is not shown here because HDC has extra 150 amino acids in its C-terminal region as compared to AroDC and it was not possible to construct the structure for Exon 12.

link (Schiff base) with an aldehyde group of PLP. During the catalysis, the active site Lys residue acts as a base (see page 744 in ref (24)).

We have presented here the convenient way to apply currently available internet tools for the structural study on the protein whose three-dimensional structure is not yet established. We have also demonstrated the relationship between exon/intron boarder on the structure of HDC. We would like to extend our study to explore the roles of exon/intron boarder on the structure of HDC in the future study.

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