

Letter to the Editor

Prokaryotic and Eukaryotic Pyridoxal-Dependent Decarboxylases are Homologous

F. Rob Jackson

Neurobiology Division, The Worcester Foundation For Experimental Biology, 222 Maple Avenue, Shrewsbury, Massachusetts 01545, USA

Summary. A database search has revealed significant and extensive sequence similarities among prokaryotic and eukaryotic pyridoxal phosphate (PLP)-dependent decarboxylases, including Drosophila glutamic acid decarboxylase (GAD) and bacterial histidine decarboxylase (HDC). Based on these findings, the sequences of seven PLP-dependent decarboxylases from five different organisms have been aligned to derive a consensus sequence for this family of enzymes. In addition, quantitative methods have been employed to calculate the relative evolutionary distances between pairs of the decarboxylases comprising this family. The multiple sequence analysis together with the quantitative results strongly suggest an ancient and common origin for all PLP-dependent decarboxylases. This analysis ^{also} indicates that prokaryotic and eukaryotic HDC activities evolved independently. Finally, a sensitive search algorithm (PROFILE) was unable to detect additional members of this decarboxylase family in protein sequence databases.

Key words: PLP-dependent decarboxylase – Evolution – Profile analysis

Introduction

In vertebrates and invertebrates, several pyridoxal (PLP)-dependent decarboxylases, including dopa

decarboxylase (DDC), glutamic acid decarboxylase (GAD), and histidine decarboxylase (HDC), catalyze the synthesis of neurotransmitters and neuromodulatory compounds (reviewed in Siegel et al. 1989). Although these and other PLP-dependent decarboxylases have quite distinct substrate-binding specificities, significant sequence similarities have been shown to exist among some of the enzymes (Kobayashi et al. 1987; De Luca et al. 1989; Jackson et al. 1990). These sequence similarities and the results of stereochemical studies (Dunathan and Voet 1974) have been interpreted as evidence for a common origin of PLP-dependent decarboxylases. Extensive sequence comparisons, however, have been reported only for eukaryotic decarboxylases (mammals, insects, and plants), although similarities have been documented for short peptides encompassing the PLP-binding domains of decarboxylases from Escherichia coli and pig kidney (Bossa et al. 1977). In addition, multiple sequence alignments, which might be useful for identifying functional domains, have not been performed for this family of enzymes. During the course of studying Drosophila glutamic acid decarboxylase (GAD), it came to my attention that bacterial histidine decarboxylase (HDC) has significant and extensive similarity to the other members of this decarboxylase family. This observation suggests that PLP-dependent decarboxylases have a very ancient evolutionary origin, a conclusion supported by the multiple sequence alignment and quantitative sequence comparisons reported in the present paper.

Offprint requests to: F.R. Jackson

Materials and Methods

All sequence comparisons and database searches including "Profile" analyses (Gribskov et al. 1987) were performed using the software of the Genetics Computer Group (Devereux et al. 1984) implemented on a VAX 11/750 running VMS 4.7. A derivative of the Dayhoff evolutionary distances matrix was used for the database searches of the profile analysis. The analyzed sequences were obtained from published reports or from release 22.0 of the NBRF:NEW protein sequence database (National Biomedical Research Foundation).

Results and Discussion

My laboratory recently deduced the amino acid sequence of Drosophila GAD (Jackson et al. 1990). A search of the NBRF:NEW protein database (release 22.0), using the FASTA program (Pearson and Lipman 1988), revealed that Drosophila GAD (fGAD) shares significant similarities with other eukaryotic PLP-dependent decarboxylases. Surprisingly, this database search also revealed an extensive similarity between fGAD and bacterial (Morganella morganii) histidine decarboxylase (bHDC; Vaaler et al. 1986). The two sequences are approximately 24% identical within a common 366-residue domain that includes the putative PLP-binding site of decarboxylases (Fig. 1). This is a striking degree of similarity, given the evolutionary distance between prokaryotes and eukaryotes. It supports the idea that prokaryotic and eukaryotic PLP-dependent decarboxylases originated from a common ancestral protein.

Other members of the PLP-dependent decarboxylase family, including dopa decarboxylase (DDC). show a comparable similarity to bHDC. This is worth mentioning, because it has recently been reported that rat DDC (rDDC) is not similar to bHDC (Tanaka et al. 1989). Figure 2 shows a multiple sequence alignment for seven different PLP-dependent decarboxylases, including bHDC, rat HDC (rHDC; Joseph et al. 1990), and rDDC, for which extensive primary sequence has been reported. This alignment includes plant tryptophan decarboxylase (pTDC; De Luca et al. 1989) as well as the Drosophila alphamethyldopa hypersensitive protein (fAMD), which is evolutionarily related to DDCs (Eveleth and Marsh 1986; Marsh et al. 1986), although its precise function is unknown. The multiple sequence alignment was constructed after pairwise comparisons of the different sequences. It was then used to derive a consensus sequence for pyridoxal-dependent decarboxylases (Fig. 2). This consensus shows the extensive similarities that exist among all of these decarboxylases, in particular in a 90-residue segment (arrows, Fig. 2) encompassing the PLP-binding domain (rectangle, Fig. 2). Indeed, the putative PLPbinding residue (K) and the adjacent histidine (H)

bHDC	1	MTLSINDONKLDAFWAYCVKNQYFNIGYPESADFDYTNLERFLRFSIN	48
fgad	90		128
bHDC	49	NCGDWGEYCNYLLNSFDFEKEVMEYFADLFKIPFEQSWGYVTNGGTEGNM	98
fGAD	129	NMFTYEIAPVFILMENVVLTKMREIIGWSGGDSILAPGGSISNL	172
bhdc	99	FGCYLGRE.IFPDGTLYYSKDTHYSVAKIVKLLRI	132
fgad	173	YAFLAARHKMFPNYKEHGSVGLPGTLVMLTSDQCHYSIKSCAAVCGLGTD	222
BHDC	133	KSQVVESQPNGEIDYDDLMKKIADDKEAHPIIFANIGTTVRGAIDDI	179
fGAD	223	HCIVVPSDEHCKMITSELERLILERKAKGDIPFFVNATAGTTVLGAPDDI	272
PHDC	180	AEIQKRLKAAGIKREDYYLHADAAL.SGMILPFVDDAQPFTFADGIDSIG	228
fgad	273	NTIADICOKYNCWMHIDAAWGGGLLMSRTHRHPRFTGVERADSVT	317
PHDC	229	VSGHKMIGSPIPCGIVVAKKENVDRISVEIDYISAHD	265
fGAD	318	WNPHKLMGALLQCSTIHFKEDGLLISCNQMSAEYLFMTDKQYDISYDTGD	367
bhdc	266	KTITGSRNGHTPLMLWEAIRSHSTEEWKRRITRSLDMAQYAVDRMQKA	313
fGAD	368	KVIOCGRENDI.FKLWLOWRAKGTEGFEQQQDRLMELVQYQLKRIREQSD	416
PHDC	314	GINAWRNKNSITVVFPCPSERVWREHCLATSGDVAHLITTA	354
£GAD	417	RFHLILEPECVNVSFWYVPKRLRGVPHDAKKEVELGKICPIIKGRMMOKG	466
bHDC	355	HHLDTVQIDKLIDDVIADFNLHAA : :	378
IGAD	467	TLMVGYQPDDRRPNFFRSIISSAAVNEADVDFMLDEIHRLGDDL	510

Fig. 1. Sequence alignment of *Drosophila* glutamic acid decarboxylase (fGAD) and bacterial histidine decarboxylase (bHDC). The numbering is, respectively, according to Jackson et al. (1990) and Vaaler et al. (1986). Vertical lines represent identities, whereas dots indicate similarities between residues. The box encompasses the putative pyridoxal phosphate-binding domain of fGAD.

are conserved in every one of these decarboxylases. Also of interest are the conserved Cys (C) residues at positions 385, 461, and 578, in light of evidence for disulfide linkage of decarboxylase subunits (Legay et al. 1987). Additional noteworthy identities are indicated by stars. The obvious similarities among these sequences strongly suggest that PLPdependent decarboxylases have a common evolutionary origin. In addition to evolutionary considerations, these sequence alignments will be useful for identifying the regions that determine the diverse substrate specificities of PLP-dependent decarboxylases.

The similarity among rHDC and the other decarboxylases is also noteworthy. The rHDC enzyme is more closely related to members of the DDC/ TDC subfamily of PLP-dependent decarboxylases, than to bHDC. The rHDC sequence, for example, is approximately 45% identical to either rDDC or fDDC (Joseph et al. 1990), but is only 15% identical to bHDC, the bacterial enzyme having the same substrate specificity. Thus, it appears that the prokaryotic and eukaryotic HDC activities evolved independently.

The multiple sequence alignment of Fig. 2 has been used with the Genetics Computer Group (GCG) "Distances" program (Devereux et al. 1984) to derive quantitative estimates of sequence relatedness for the PLP-dependent decarboxylase family. Table 1 shows a matrix displaying the pairwise genetic

	1		60		361		
CGAD	asstpsssatssnagadpht	tnlrpttydtwcgvahgetr	klglkicgflqrtnsleeks	cGAD	kIlEaKqkgyVPLYVnATaG	TIVYgAFDDIQLIAD	TO-VID - IDURADA ABGGIL
fgad			· · · · · · · · · · · · · · · · · · ·	f GAD	111ErKakgdIPFFVnATaG	TTV1gAFDDInt1AD	ICQKINCVMHIDAAVgGGIL
t DDC				£DDC	DVAEGLIPFYaVvTLG	TTnsCAFDy1DEcGP	VENCINEVIEVDAATAGSAP
TDDC				r DDC	DkAaGLIPFFVVvTLG	TTscCsFDnllEVGP	ICNGEGVULHIDAAYAGSAF
rHDC				rHDC	DkggGLVPvFVcATLG	TTgvCAFDklsElGP	ICareGLVLHVDAAYAGtAF
pTDC				DTDC	DVAaGyVPLF1cATLG	TTsttAtDpVDslsE	IaNeFGIViHVDAAYAGsAc
EAND				FAND	DVAnGET PVICVATLG	TTgtCAYDDIEs1sa	VCeeFkVVLHVDAAYAGGAF
bHDC				hand	kTADdKeshnTiFAniG	TTVrgAiDDIaEIokrlkAa	gikredvYLHaDAAl.sG.H
Conserve	•••••	• • • • • • • • • • • • • • • • • • • •		6 BADC	DIALCHI IDEEVVATIC	TTV_CAEDDIDELAD	TONKYNLUL HUDAAYAGGAF
10011303				consensus	DIRECKIIFFFVVALLO	CP	FCV
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	61		120		421 *	The second second	+ + 460
CGAD	rivsafkerqssknllscen S	SdrdgrfrrtetdfsnLfAr	DLlpak.ngeEqtvqFLleV	cGAD	msrkhRH.klsG	IERANSVTWNPERMAGVILG	CSAILVKEKg1LdgendmeA
tGAD	·····	51Npngyklsert.gkLtAy	DLmpttvtagpetrEFLlkV	fgad	msrthRHprftG	VERADSVTVNPHRLMgalLq	CStihtKEdgiLischqmsA
fDDC	<pre>.mshipisntiptkqtdgng)</pre>	kaNispdkldpkvsidMEAp	EFkdfaKtHVDFIAEYLENI	fDDC	ICPEYRHLMKG	IESADSFNFNPHRWKLVNFD	CSANV1KDpsvvVnA
rDDC		MDsr	EFRIrGKeMVDYIADYLOgI	rDDC	ICPEFRyLLnG	VEEADSENENPERVLLVNFD	CSAHWVKkrtdLteA
rHDC		mmepsEyh	EYgarGKeHVDYIcgYLstV	THDC	lrPE1RgFLKG	IEyADSFTFNPsKWMHVhFD	CtgFVVKDkykLqqt
PTDC	mesid 9	StNvansnsnvæfknl.EAe	EFRKnahrHVDFTADYvkNV	nTDC	ICPEFRHYLdG	IERvDSLsLsPHKWLLayLD	CtcLVVKqphlLlrA
EAMD		KDAK	EFRefCKaaTDYTADYLENT	FAND	aleECsdLrKG	1DRvDSLNFN18KFHLVNFD	CSAMV1rDankvVds
bBDC			brace and a print in a second s	54DC	TIP FyddannftfadG	I., DSigvsg8Kmigspip	CgivvaKkenvdrisv
Consensur		E N 1 FA	FFR CY NUDVI ADVI FNU	Conconcius	ICPFFRHUKG	TERADSETENPHKUHLVNFD	CSAMVVKDLVA
-senaus		5-NLEA-	ELK GV-HADITADI PENA	consensus	ICFEF MILLIN-SSE	N	, , , , , , , , , , , , , , , , , , ,
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	121		180		481		Jeu
CGAD	vDillnyvrKtfdrs	tKvldFhhp.hqllegm	egfnlelsdhpesLeqiLvD	cGAD	gyLFopd.Kdydvsydt	g. DKalqcGRnvd1FKFV	LawkakGTVGFengInkCLE
IGAD	iDvlldfvkatndrn	EKvldFhhp.eDmk	RildldVpdRalPLqqiieD	EGAD	eyLFmtd.Kqydisydt	g.DkvlqcGRhndiFKLV	LANKAKGTEGFEGGGGGKINE
1DDC	RERrVLPEVKPGYLkpLIPd a	APEKFERVqDVHqDIE	RVIKPGVTHVhSPkFhAY.	fDDC	FNVDP1YLKHdmqGsapD	Yr SVOIPLGRRFRa. LKLV	FVLRIYGVEnLQAHIRKBen
rDDC	egRpVyPDVEPGYLRaLIPt t	tAPqEPEtYEDIirDIE	kIIMPGVTHVhSPyffAY	rDDC	FNMDPVYLrHshqdsglItD	YrEVOIPLGRRFRS. LKMV	FVFRmYGVkGLQAyIRKHVk
rHDC	REROVIPRVKPGYLRagIPs s	SAPEEPDSVDsIFgDIE	gIIMPGVvHVgSPhmhAY	rHDC	FsVnPIYLrHansGvatD	FmHVQIPLsRRFRS1KLV	FVIRSFGVknLQAHVRhgtD
PTDC	atynVLSEVEPGYLRkrTPe I	rAPv1PEnLDDTMkDTmkd.	. I i PGmTnVmSPnFvAF.	DTDC	Lt taPeYLKnkgsdldkVvD	FknWQIatGRkFRSLKLW	LILRSYGVvnLQsHIRsdVa
ÉAND	RDAAU PAVEPOVI 141.1Pt	emPEEPEaWkDVLgDTs	BVTkPG1THseSPhmhAYv.	FAND	FNVDrIYLKHkheGasaIpr	LoslanPLGRRFRa. LKvW	itFRtLeaEGLrnHVaKHIE
bHDC		Car Dor Darnor Dgord	MrleinD	6HDC	eidYisah	DktIt.GsRnghtpLmLV	eaiRShstEeWkrrItRsLD
Consensue	POP ULPEVERCYLE-LTP-	AREVER UDDIN DIE	RUTHPOUTHU-SPI F-AY-D	Consensus	ENVERTYLKHGI-D	Y-DV0IPLGRRFRSLKLV	LVVRSYGVEGLOAHIRKHLE
	E E E E E E E E E E E E E E E E E E E	P	T	consenses	10	FR	FL RV
	÷	5	+				
			740		5/1	***	600
-540	181		240		541	***	600 viPo.slRgipdSherrekL
cGAD	181 crdtlkYgvrTghPrFFNq	LStgLdiiglagEVLtSt	240 AnTNmftYEiapVFv1	cGAD	541 LAeYlYakiknr	*+* eeFEmVfdgE.pehtnVCFV	600 yiPq.slRgipdSperrekL wyPk_rlBgypbdakkEvel
¢GAD ÍGAD	181 crdtlkYgvrTghPrFFNq. cattlkYgvkTghPhFFNq.	LStgLdliglagEWLtSt LSngLdLismagEWLtat	240 AnTNmftYEiapVFv1 AnTNmftYEiapVFi1	eGAD fGAD	541 LAeYlYakiknr LvqYQLkrireQsD	*+* eeFEmVfdgE.pehtnVCFV rfhlIlE.pecvnVsFV CDPFLE.phClVcFP	600 yiPq.slRgipdSperrekL yvPk.rlRgvphdakkEveL urcs NErNEell
CGAD fgad fddc	181 crdtlkYgvrTghPrFFNq cattlkYqvkTghPhFFNq FPTanSYPAYvaD	LStgLdiiglagEVLtSt LSngLdLismagEVLtat .MLSgAiacIGFtViaSP	240 AnTNmftYEiapVFv1 AnTNmftYEiapVFi1 ACTELEvVMMD	eGAD fGAD fDDC	541 LAeYlYakiknr LvqYQLkrireQsD FAK.QFgdLcvaD	*+* eeFEmVfdgE.pehtnVCFV rfhlllE.pecvnVsFV SRFELAE.InMGLVSFR	600 yiPq.slRgipdsperreki yvPk.rlRgvphdakkEvel LKGSNErNEaLL
CGAD fgad fDDC rDDC	181 crdtlkYgvrTghPrFFNq. cattlkYqvkTghPhFFNq. FPTanSYPATvaD. FPTasSYPAmLaD.	LStgLdiiglagEWLtSt LSngLdLismagEVLtat .MLSgAiacIGFtViaSP .MLcgAigcIGFsVaaSP	240 AnTNmftYEiapVFvl AnTNmftYEiapVFvl ACTELEVVMMD ACTELEtVMMD	eGAD fGAD fDDC rDDC	541 LAeYlYakiknr LvqYQLkrireQsD FAK.QFgdLcvaD Lsh.eFEsLVRQD	*** eeFEmVfdgE.pehtnVCFV rfhIIE.pecvnVSFV SRFELaAE.InMGLVSFR pRFELctEvIl.GLVCFR	600 yiPq.slRgipdsperrekL yvPk.rlRgvphdakkEveL LKGSNErNEaLL IXGSNqlNEtL IXCSNqlNEtL
CGAD fgad fDDC rDDC rDDC rHDC	181 crdtlkYgvrTghPrFFNq. FPTanSYPAYvaD. FPTanSYPAMLaD. YFAITSYPSILGD.	LStgLdiiglagEVLtSt LSngLdLismagEVLtat .MLSgAiacIGFtViaSP .MLcgAigcIGFsVaaSP .MLadAstavGsrgLpa.	240 AnTNmftYEiapVFvl AnTNmftYEiapVFil ACTELEvVMMD ACTELENIMHD	eGAD fGAD fDDC rDDC rHDC	541 LAeYlYakiknr LvqYQLkrireQsD FAK.OFgdLcvaD Lsh.eFESLVRQD MAK.yPEsLVRsD	*** eeFEmVfdgE.pehtnVCFV rfhllE.pecvnVsFV SRFELaAE.InMGLVSFR pRFELct.EvIl.GLVCFR pvFEIpAErhl.GLVVFR	600 yiPq.slRgipdsperrekL yvPk.rlRgvphdakkEveL LKGSNglNEtLL LKGSNglNEtLL LKGSNglNEtLL LKGSNglNEtLL
cGAD fGAD fDDC rDDC rHDC pTDC	181 crdtlkYgvrTghPrFFNq. FPTanSYPAYvaD. FPTasSYPAmLaD. YPAITSVPsLLGD. PFAtvSsaAFLGE.	LStgLdiiglagEVLtSt LSngLdLismagEVLtat .HLSgAiacIGFtViaSP .HLcgAigcIGFsVaSP .HLadAstavGsrgLpa .HLStALnsVGFtVvsSP	240 AnTNmftYEiapVFv1 AnTNmftYEiapVFi1 ACTELEvVMMD ACTELEmVMMD ACTELEmIMD	cGAD fGAD fDDC rDDC rHDC rHDC pTDC	541 LAeYIYakiknr LvqYQLkrireQsD FAK.OFgdLcvaD Lsh.eFEsLVRQD MAK.yFEsLVRSD MgK.mFEevVRsD	*** eeFEmVfdgE.pehtnVCFV rfhllE.pecvnVsFV SRFELA.E.InNGLVSFR pRFEIct.EvIl.GLVCFR prFEIA.Erhl.GLVCFR SRFEIVvp.rnFsLVCFR	600 yiPq.slRgipdSperrekL yvPk.rlRgvphdakkEveL LKGSNerNEaLL LKGSNqlNEtL LKGpNcltEsvL LKPd.vsslhv.eEvNkkLL
cGAD fgAD rDDC rDDC rHDC pTDC fAMD	181 crdtlkYgvrTghPrFFNq. cattlkYgvkTghPhFFNq. FPTanSYPATwaD. YPAITSVPsLLGD. PAITSVPsLLGD. PAITSVPsLLGD. FPAITSSYPSIVGE.	LStgLdiiglagEVLtSt LSngLdLismagEVLtat .MLSgAiacIGFtViaSP .MLcgAigcIGFsVaaSP .MLadAstavGsrgLpa .MLS1ALnsVGFtVvSP .MLasgFyVGFSVicSP	240 AnTNmftYEiapVFv1 AnTNmftYEiapVFv1 ACTELEVVMMD ACTELEVIMD ACTELEWIMD ATELEMIVMD ACTELEWIVMD	eGAD fGAD fDDC rDDC rHDC pTDC fAMD	541 LA@TlYakiknr LvqYQLkrireQSD FAK.QFgdLvaD Lsh.eF8sLVRQD MAK.yFEsLVRSD MgK.mFEevVRSD LaK.QFEqLV1kD	*** eeFEmVfdgE.pehtnVCFV rfhllE.pecvnVsFV SRFELAA.E.InMGLVsFR prFEIct.EvIl.GLVCFR pvFEIpA.Erhl.GLVFR SRFEIVp.rnFsLVCFR SRFEIVAp.raLGLVCFR	600 yiPq.slRgipdsperrekL yvPk.rlRgvphdakkEvel LKGSNETNEAL LKGSNqlNEtL LKGPNcltEsvL LKPd.vsslhv.eEvNkkLL pKGdNEittqLL
cGAD fGAD fDDC rDDC rHDC pTDC fAND bHDC	181 crdtlkYgvrTghPrFFNq 	LStgLdiiglagEVLtSt LSngLdLismagEVLtat LSgAiacIGFtViaSP HLagAigcIGFsVaaSP HLadAstavGsrgLpa HLstALnsVGFtVvSSP HLasgFgvIGFsVicSP 	240 AnTNmftYEiapVFv1 AnTNmftYEiapVFi1 ACTELEvVNMD ACTELEtVHMD ACTELEnIIKD ACTELENIYMD ACTELEVVMD SinNegdyegvcnyLlasfd	eGAD fGAD rDDC rDDC rHDC pTDC fAMD bHDC	541 LAeTlYakiknr LvqYQLkrireQsD Lsh.ePEsLVRQD HaK.yPEsLVRSD HgK.mFEevVRsD LAK.QPEqLV1KD HAqTavDrH.JQkaginavr	*** eeFEmVfdgE.pehtNVCFW SRFElaA.E.InMGLVsFR pRFElat.EvILGLVFR prFElat.Ethl.GLVFR SRFEIVp.rnFsLVCFR SRFEIVA.p.raLGLVFR sRFEIVA.p.raLGLVFR	600 yvPk.slRgipdsperrekL LKGSNErNEALL LKGSNEINEALL LKGSNcltEsvL LKPd.vsslhv.ebvNkkLL pKGdNEittqLL C-PerrvVrEhcL
cGAD fGAD fDDC rDDC rHDC pTDC fAMD bHDC Consensus	181 crdtlkYgvrTghPrFFNq. FPTanSYPATvaD. FPTanSYPATvaD. YPATvSTPALGD. PATvSTPALGD. PAtvSsaAFLGE. FTSTPsivGE. qnkldaFvAycvknqYFNg y FPT-TSYPAFFND.	LStgLdiiglagEVLtSt LSngLdLismagEVLtat .MLSgAiacIGFtViaSP .MLsgAigcIGFSVaSP .MLstALnsVGFtVsSP .MLstALnsVGFtVsSP .MLssgFyIGFSVicSP .MLssgFlrf	240 AnTNmftYEispVF1 AnTNmftYEispVF1 ACTELEVVMMD ACTELEVVMMD ACTELENIIMD AATELENIYMD SinNcgdYgeycnyLlnsfd ACT	cGAD fGAD fDDC rDDC rHDC fAMD bHDC Consensus	541 Lac1174kiknD Lvq70Lkrire05D FAK.0PgdLevaD Lsh.eFEsLVR0D MaK.yFEsLVR5D MgK.mFEeVVR5D MaqTavDrH0Kaginav LAK.0FEQLV1kD	*.* eePEmVfdgE.pehtnVCFU rfhllE.pecvNvFV SRFlatE.InMCUVSFR SRFlatEvll.GLVCFR SRFLVp.rfsLVCFR SRFLVp.rfsLUVCFR nknsltVVPS SRFLVAelGLVCFR	600 yiPq.slRgipdsperrekL kGSNqlNetL LKGSNqlNetL LKGSNqlNetL LKGANcltEsvL LKPd.vsslhv.eBvNkkLL pKGdNEittqLL C.FServWrEhcL LKPSNE-NE-L
cGAD fGAD fDDC rDDC rHDC pTDC fAND bHDC Consensus	181 ctd1lkYgvrTghPrFFNq. PTanSYPAvaD. PTanSYPAvaD. PTarSYPALAD. PAtvSsaAFLGE. PTATvSsaAFLGE. PTATvSTPSILOD. PTATvSTPFILOD. ALGAFVAvcNnqTNNg. ALGAFVANTYNG.	LStgLdiiglagEVLtSt LSngLdLismagEVLtat MLSgAigCIGFV4aSP .MLcgAigCIGFV4aSP .MLStALnsVGPtVvSP .MLasgFgvIGFV1cSP ye5adFdY11ERFIT MLS-LAL-IGFEVL-SP	240 AnTNmftYEiapVFv1 AnTNmftYEiapVFi1 ACTELEvVMMD ACTELEtVMMD ACTELENVMD ATELEmIIHD ATELEMIYMD ACTELEVVMD SinNegdyegvnyLlnsfd ACTNYELE-VFMD V	cGAD fGAD fDDC rDDC pTDC fAMD bHDC Consensus	541 LA&IYakiknr LvqYQLkrireQsD FAX.QFgdLcvaD HAX.yFgsLVRQD HAX.yFgsLVRQD HAX.yFgsLVRSD LAX.QFgQLV1kD HAQTavDHLAkginawr LAXYQFE_LVRQD	*.* eeFEmVfdgE.pehtnVCFV rfhl1E.pecvnVsFV SRFElaA.E.InHGLVSFR pRFELA.E.InHGLVSFR pRFELA.E.Th.GLVCFR SRFELVA.p.rnFsLVCFR SRFELVA.p.raLGLVCFR SRFELVA-E.I-GLVCFR	600 yvPk.rlRgvphdkLEvel LKCSNErNBaLL LKCSNelNErLL LKGpNelYEsUL LKPd.vsslhv.eEVNkkLL PKCdNElttqLL C.PServWFEhcL LKPSRNE-NE-LL G
cGAD fGAD fDDC rDDC rHDC pTDC fAND bHDC Consensus	181 crdtikYgvrTghPrFPNq. PrlanSTPATvaD. PrlanSTPATvaD. PrlanSTPATvaD. PratsSrPALGE. PratsSrsivGe. qnkldaFvAycvknqtYNig y PrStPSivGe. A LG	LStgLdiiglagEVLtSt LSngLdiimmagEVLtat .KLSgAiacIGFtViaSP .HLcgAigcIGF3VaASP .HLadAstarGStgLpa. .HLStALnSVGFUVSSP .HLSsgFgVGF3V1CSP ypeSadFdYtnlERF1rf .HLSLALIGFEVL-SP	240 AnTNm ftYEispVP1 ACTELEVVMD ACTELEVVMD ACTELEIVMD ACTELENIIMD ATELENIIMD ATELENIYMD SinNegdYgeycnyLlnsfd ACTNYELE-VFMD Y	cGAD fCAD fDDC rDDC rHDC pTDC fAMD bHDC Consensus	541 LAETIYakiknr LvqTQLkrireOsD FAK.OPgdLevaD Lsh.ePEsLVRSD MaK.yFEsLVRSD MgK.aFZevVRsD LAK.OFELVIXD NAQTavDrHOkaginavr LAK.OFELVIXD	e+FEnVfdgE.pthtVCFV rfhllE.pecvNv5VV SRFELAA.E.InMGLVsFR pvFEItA.Ethl.GLVvFR pvFEItA.Ethl.GLVvFR SRFEIVV.p.rnFsLVCFR sKREIVA.p.raLGLVCFR skrEIVA-E-I-GLVCFR	000 yiPq.slRgipdsperrekL yvPk.rlRgvphdakkEvel LKGSNETNEaLL LKGSNQINELL LKGPNQIKELL LKPd.vsSlhv.eEvNkkLL C.PServWFEhcL LKPS-RNB-NE-LL G
CGAD fGAD fDDC rDDC PTDC fAND bHDC Consensus	18] crdtlkYgvrTghPrFPNq. PrasSYPAvaD. PrasSYPAvaD. PrasSYPALGD. PAtvSsaAFLGE. PrsTSYPSivGE. gakldaFvAyevknqYNig y PrT-TSYPAPND. A LG	LStgLdiiglagEVLtSt .LSngLdLismagEVLtat MLSgAigclGFV4aSP .MLGAigclGFV4aSP .MLdstwCSrgLpa. .MLStALnsVGFUVsSP .MLasgFgvIGFSVicSP ypeSadPdYtnl.SRPITF .MLSLALIGFEVL-SP	240 AnTNmftYEiapVFv1 AnTNmftYEiapVFv1 ACTELEVVNHD ACTELEVVNHD ACTELENTIHD AATELEMIIHD ACTELEMIYHD SinNegdYgeycnyLinsid ACTNYELE-VFHD V 300	CGAD fGAD fDDC rDDC rTDC pTDC fAND bBDC Consensus	541 LASTIYakiknr LvqYQLkrireQsD FAX.OPgdLcvaD Lsh.eFZsLVRQD MAX.yFZSLVRQD MAX.yFZSLVRSD MAX.YZSLVRSD MAQYAVDTHQkaginavr LAKYQFZ-LVRQD 601	*.* eeFEmVfdgE.pehtruCFU rfhl1E.pecvnVsFV SRFElaAE.InHGLVSFR pRFEIAE.Ih.GLVCFR SRFEIVp.rnFsLVCFR SRFEIVp.raLGLVCFR nknsltVvPp SRFEIVA-E-I-GLVCFR	600 yvPk.rlRgipdsperrekL yvPk.rlRgvphdakLEvel LKGSNETNEaLL LKGSNeTNEaLL LKGNeTtegL LKPd.vsslhv.eEvMkkLL pKddNEIttgL C.PServWFEhcL LKPS-RNE-NE-LL G 660
cGAD fGAD fDDC rDDC rDDC rHDC pTDC fAHD bHDC Consensus	181 crdtikYgvrTghPrFPNq crtikYgvrTghPhFNq PrasSYFAHLaD PrasSYFAHLaD PratSSTALGE anklafvAycvknqiYnkg y FYTSYFSVGE A LG 241	LStgLdiiglagEVLtSt LSngLdiimmagEVLtat .KLSgAiacIGFtViaSP .HLcgAigcIGFsVaaSP .HLadAstevSorgLpa. .MLStAlnsVGFVVsSP .MLasgEVJGFSViSSP ypeSadPdYtn1ERFIrf .HLSLALIGFEVL-SP .SeLdCdCIfenGGaiSNW*	240 AnTNm ft YE is pVF1 ACTELEVVMD ACTELEVVMD ACTELENTIMD ACTELENTIMD ATELENTIMD SinNegdVgeycnyLlnsfd ACTNYELEVVMD y 300 THAAR.VEFFFEVKtemaa	CGAD ÉCAD ÉDDC TDDC TDDC FTDC ÉAND BUDC Consensus	541 LA&TIYakiknr LvqTQLkrireOsD FAK.OFgdLevaD Lsh.erZeLVRGD MAK.yFESLVRSD MAK.JFESLVRSD MAGTavDrHOkaginavr LAK.OFGLVILD MAGTavDrHOkaginavr LAK.OFGLVILD 601 hvrankiKalaMesgTtMvG	*** eFEnVfdgE.pehtwCFV rfhllE.pecvWsFV SRFELAA.E.InMCLVsFR pVFEIDAEthl.GLVvFR pVFEIDAEthl.GLVvFR SRFEIVASILVVFP SRFEIVASILVVFP SRFEIVAE.I-GLVCFR YOprgtrptfsgv5	600 yyPq.slRgipdsperrekL yyPk.rlRgyphdakLEvel LKGSNETNEaLL LKGSNelNELL LKGPNelKEsvL LKPd.vsBiv.eEvNkkLL pKd.dNElttqLL C.PServVTEhcL LKPSRNB-NE-LL G SRtqlih.spiltsspr
cGAD fGAD fDDC rDDC rDDC fAND bDDC Consensus	18] crdtlkYgvrTghPrFPNq. PrasSYPAvaD. PrasSYPAvaD. PrasSYPALGE. PrsTSYPSiCE. PrsTSYPSiCE. PrsTSPsivCE. ALGETVS:vaPND- A LG 241 meqltUCkmrEiVGV.	LStgLdiiglagEVLtSt LSngLdLismagEVLtat MLSgAigclGFVVaSF MLGAigclGFVVaSF .MLSAigcVGFVVsSF .MLSJLnSVGFUVSSF .MLSgFgvIGFSViCSF ymeSaFd7Vthl.ERF1rf .MLSLALIGFEVL-SF SskdGdGIfspGGaiSNMYS datlacGSSNMYS	240 AnTNmftYEiapVFv1 AnTNmftYEiapVFv1 ACTELEVVNMD ACTELEVVMD ACTELENTYMD AGTELEMIYMD AGTELEMIYMD SinNegdYgeycnyLlnsid ACTNYELE-VFMD V 300 IHAAR.yKPFPEvkkgmaa FLAD.PYPUykH	CGAD fCAD fDDC rDDC rTDC fTDC fLAD bHDC Consensus	541 LASIYakiknr LvqYQLkrireQsD FAX.OPgdLcvaD Lsh.eFZsLVRQD MAX.yFZSLVRQD MAX.yFZSLVRZD MAX.9FZQLVRSD MAQTavDrHQkaginavr LAX:QFZQLVRQD 601 hrvapkiKalmMesgTtMvG	*.* eeFEnVfdgE.pehtnVCFV rfhllE.pecvNv5VV SRFElaAE.InHGLVsFR pRFELAE.InHGLVsFR SRFELVp.rnFsLVCFR SRFELVp.rnFsLVCFR sRFLVAp.raLGLVCFR nknsltVvPp SRFELVAE-I-GLVCFR YOprgtrptfsgVs	600 yvPk.rlRgipdsperrekL yvPk.rlRgvphdakLEvel LKGSNETNEaLL LKGSNeltBsvL LKPd.vsslhv.eEvNkkLL pKddNEittqL C.PServWFEhcL LKPS-RNE-NE-LL G SRtqlih.spiltssrr. Saavnea.dvdfMLdeihrl
CGAD fGAD fDDC rHDC pTDC fAND bHDC Consensus cGAD	181 crditkygvrTghPrFPNq. 	LStgLdiiglagEVLtSt LSngLdiimmagEVLtat .KLSgAiacIGFtViaSP .HLcgAigcIGFSVaaSP .HLadAstwSorgLpa. .MLStAlnsVGFVVsSP ypeSadPdYtn1ERFIrf .HLSLAL-IGFEVL-SP SskdGdGIfspGGaiSNMYS SGGdz1apGSiSNLXA	240 AnTNm ft YE is pVF1 AnTNm ft YE is pVF1 ACTELEVVMHD ACTELENTIHD ACTELENTIHD AATELENTIHD SinNegdVgeycnyLlnsfd ACTNYELEVVMD y 300 IHAAR.yKFFFEVKtkgmaa FLAAR.bKHFPnykeHgøyg	cGAD fGAD fDC rDC rDC fADC fAMD bBDC Consensus cGAD fGAD	541 LAETIYakiknr LvqTQLkrireOsD FAK.OPgdLevaD Lsh.erZetURGD MAK.yFEsLVRSD MAK.yFEsLVRSD MAGTAVD:HOkaginavr LAK.OPGLVIXD MAGTAVD:HOkaginavr LAK.OFGLVIXD 601 hrvapkiRalaMesgT1WoG gKicpiiKgramAkgT1WoG	*** eFEmVfdgE.pehtwCFV rfhllE.pecvwSvFV SRFELAE.inMCLVsFR pvFEIfAEthl.GLVvFR pvFEIfAEthl.GLVvFR SRFEIVAp.raLGLVCFR nknsitVvFp SRFEIVAE.IGLVCFR YOprgtrptfsgvs YOpdgrpnffsgis YOpdgrpnffsslis J.g.LRMAIGSFTGseDmeV	000 yiPq.slRgipdsperrekL yvPk.rlRgvphdakLEveL LKGSNETNEaLL LKGSNelNELL LKGPNelVEkLL LKGVNEIttqLL C.PServWPBcL LKPSRNB-NE-LL G SRtqlih.spitsspr Saavnea.dvdfMLdeihrl SKevSdaaEHeq.Eq.
CGAD fGDD fDDC rDDC rHDC pTDC fAND bHDC Consensus cGAD	18] crd1kYgvrTghPrFPNq. PTasSYPAtDaD. PTasSYPAtDaD. PAtVSsaFLGE. PAtVSsaFLGE. qnkldaFVAycvknqYFNig y FYT-TSYFsiVGE. 4 LG 241 meqtULKknrE1Vgv. menVVLIkgE1Vgv.	LStgLdiiglagEVLtSt LSngLdLismagEVLtat .HLSgAigclGFVVaaSP .HLcgAigclGFVVaaSP .HLcdAstwStgLpa. .HLStALnsVGFUVsSP .HLSFUGFSV1SP ypeSadFdYtnlERFlrf .HLS-LALIGFEVL-SP SskdCdGIfspGGaiSNHYS SGGdFIlapGGSISNLY gch.GGGVIGTASESTLVA	240 AnTNmftYEiapVF1 AnTNmftYEiapVF1 ACTELEVVMHD ACTELEVVMHD ACTELENIYHD ATELEMIYHD SinNegdVgeycnyLlnsfd ACTYELE-VFMD V 300 IHAAR.yKFPFEvk(tgmas sagsagaeveggegApsgvg sagsagaeveggegApsgvg ILabs TWVIFIDAcres	CGAD fCAD fDDC rDDC rTDC fAND bHDC Consensus cGAD fDDC rDCC	541 LASIYakiknr LvqTQLkrireQsD FAK.QFgdLcva.D HAK.yFg2LVRQ.D NAK.yFg2LVRQ.D NaK.aFZeVVRSD LAK.QFgLVRSD NAQTavDrH.Okaginavr LAKTQFP-LVRQD 601 hrvapkiKalmHesgTtHVG gKicpiiKgrmMqkgTlHVG .KRIMgrghTLVFrlTvK	*** eeFEmVidgE.pehtwVCFV rfhl11E.pecvWJsFV SRFELAE.InHCLVJSFR prFEIC4Evhl.GLVCFR prFEID4Evhl.GLVCFR SRFEIV4p.rnFsLVCFR sKRFLV4p.raLGLVCFR nknsitVvPp SRFEIV4E.IGLVCFR YOprgtrptfsgVs YOpddrtpnffsiis f.gLRMAICSrfTqseDmeY f.VLRFAVCSrtvesbhoel	600 yvPk.rlRgvphdakLEvel LKGSNETNEALL LKGSNelNELL LKGFNelNELL LKGPNeltEsvL LKPdNEIttqL C.PSErvWFEhcL LKPSNE-NE-NE-LL G 660 SRtqllh.spl1f3ssrr. Saavnea.dvdfMLdeihrl SVkeVsAaadEMeq.Eq. 30ehrD13ssvLraekE.
CGAD fGAD fDDC rDDC pTDC fAND bBDC Consensus CGAD fGAD fDDC rDDC	181 crdtikYgvrTghPrFPNq. PPTanSYPATVaD. PTanSYPATVaD. PTanSYPATUAD. PTATSYPALGD. PATVSsaAFLGE. PATVSsaAFLGE. akLdaFVAycvknqYTNig y PTTSYPSVGE. A LG 241 meqtVLtkmrEiygv. meqtVLtkmrEigv. ULgKHLEIPAEFlacS ULgKHLEIPAEFlacS	LStgLdiiglagEVLtSt LSngLdiimmagEVLtat .KLSgAigcIGFsVaaSP .KLadAstavSargLpa .KLstAinsVGFVVxSP .KLsgEVIGFsViSSP ypeSadPdYtnlERFlrf .KLSLALIGFEVLSP SskdCdGIfspGGaiSMLM gck.cGGVIGGASSETLW asdGGGVIGGASSETLW	240 AnTNm ft YE is pVF1 AnTNm ft YE is pVF1 ACT ELEVVMD ACT ELEVVMD ACT ELEMIIHD AAT ELEMIIHD AT ELEMIYMD SinNegdVgeycnyLlnsfd ACTNYELEVVMD y 300 IHAAR.yKPFPEvktkgmaa FLAAR.JKNFPnykelgsvg LLAAR.tKNiclonaspel LLAAR.tKNiclonaspel LLAAR.tKNiclonaspel	cGAD fCDC rDDC rDDC rDDC rADC fAND bBDC Consensus cGAD fGAD fCAD fDDC rDDC	541 LAETIYakiknr LvqTQLKrireOsD FAK.OFgdLevaD Lsh.eFZELVRSD MAK.JFZELVRSD MAGTANDEHDKAGINAV LAK.OFZELVRSD MAGTANDEHLKAGINAV AKAGFGLIVIKD MAGTANDEHDKAGINAV MAGTANDEHDKAGINAV GOI hrvapkiKalmMesgTIMvG gKicpiiKgramMqkgTIMvG gKicpiiKgramMqkgTIMvG gKicpiiKgramMqkgTIMvG gKikpiiKgkLVPciirbk KalakrenVILPATTON	*** eFEnVfdgE.pehtwCFV rfhllE.pecvNv5VV SRFELA.E.InMCLVsFR pvFEITA.Etl.GLVvFR SRFEIVAp.raLGLVvFR SRFEIVAp.raLGLVCFR nknsitVvPp SRFEIVA.e.I.GLVCFR vOprgtrptfsgvs YOpdgrpnffsls r,gLRMiCSErTqseDmeY f.VLRFAVCSrtvesahVqL LIRFVtvSrtvesAtVqL	000 yiPq.slRgipdsperrekL yvPk.rlRgvphdakEvel LKGSNETNBaLL LKGSNelNELL LKGPNelVEkLL LKGVNEITtqLL C.FServWNEITtqL C.FServWNENE-LL G 660 SRtqlih.spitcssrr Sasvnea.dvdfMLdeihrl SKeVs.AadEMeq.8q. dVnlrEahnJu-saphtss
CGAD fGDC rDDC rDDC rHDC fAND bHDC Consensus CGAD fDDC rDDC rDDC rHDC	181 crdtlkYgvrTghPrFPNq. PTanSYPArUaD. PTanSYPArUaD. PArUSSAPLGE. PArUSSAPLGE. PSTYPSiVGE. qnkldaFvkycvknqYPNig y PTTSYPSiVGE. 4 LG 241 meqitlKKnrEivgv. menvVLikerEi.j.g.gv. VLgKMLELPAEPLaS VLgKMLELPAEPLaS VLgKMLELPAEPLaS	LStgLdiiglagEVLtSt LSngLdlismagEVLtat .HLSgAigclGFVVaSP .HLgAigclGFVVaSP .HLsFgVGFVVsSP .HLsFgVGFVvSP ypeSadFdYtnlERFlrf .HLSLALIGFEVL-SP SskdCdGIfspGGaiSNMYS SGCdsJlapGGSiSNIYS aGe.GGGVIGGASERIVA aGe.GGGVIGGASERIVA	240 AnTNmftYEiapVF1 AnTNmftYEiapVF1 ACTELEVVMHD ACTELEVVMHD ACTELEmIIHD ATELEmIIHD ATELEMIIHD SinNcgdVgeycnyLlnsfd ACTYELE-VFND Y 300 IHAAR.yKFFFEvktkgmaa FLAAR.JKHFPTykkelgayg sagsagqeveggegApagvg LLAAR.tkiriqlaAnspel LLAAR.tkiriqlaKAHepna LAAR.thilEmKAHepna	CGAD fGAD fDDC rDDC rTDC fAND bHDC Consensus cGAD fDDC rDDC rDDC	541 LASIYakiknr LvqTQLKreOSD FAK.OFgdLcvaD Lsh.eFZsLVRQD MAK.yFZsLVRQD MAK.yFZsLVRZD LAK.OFZQLVRZD MAQTavDrH.Okaginavr LAKIOFZ-LVRQD 601 hrvapkiKalmMesgTtMvG gKicpiiKgrmMqkgTlMvG .KRIMgrghThLVFAtIKDv QRIMSAKLNUVFctTvA	*** eFEmVidgE.pehtwCFV rfhll E.pecwUsFV SRFELAE.InHCUVSFR prFEIAEthlGUVFR SRFEIVp.rnFsLCPR SRFEIVp.rnFsLCPR sknsitVvPp SRFEIVAE.IGLVCPR YOprgtrptfsgVs YOpddrepnffsis f.gLRMAICSrTqseDmeY L.URFVVSGTrveshVqL L.IRFVVSGTrveshVqL	600 yvPk.rlRgvphdakLEvel LKGSNETNEALL LKGSNelNEtALL LKGSNelNEtALL LKGNelYESVL LKPd.vsslhv.eEvNkkLL pKGdNEIttqLL C.PSErvVFEhcL LKPSRNB-NE-LL G 660 SRtqllh.spilt3ssr Sasvnea.dvdfMLdeihrl SVkeVsAaadEMeq.Eq. dvhlThEAnlyLsphctsq V.dip.kltdDLLF.as.
CGAD fGAD fDDC rDDC fAND bBDC Consensus CGAD fGAD fGAD fDDC rDDC rDDC rDDC gTDC	181 crdtikYgvrTghPrFPNq PPTanSYPATVaD PTanSYPATVaD PTATSYFALGD PTATSYFALGD PATVSsaAFLGE qnklabrWycvknqYfNig y PTTSYFSVGE A LG 241 meqrtLCkmrEivgv. meqrVLtkmrEi.i.gv. ULgKHLEIPAeFlacS VLASHLgL7dfVLhhh VLASHLgL7dfVLhh	LStgLdiiglagEVLtSt LSngLdiimagEVLtat .KLSgAigcIGFViaSP .KLgAigcIGFViaSP .KLsAinsVGFVVSSP .KLsgEVIGFViSP ypeSadPdYtnlERFIrf .KLSLALIGFEVLSP SskdCdGIfspGGaiSMIM gGk.GGGVIGGASETLVA pssqGGVIGFXSETLA Sot.GGGVIGGASETLVA pssqGGVIGFTSESTLA	240 AnTNm ft YE is pVF1 ACTELEVVMD ACTELEVVMD ACTELENTIMD ACTELENTIMD ATELENTIMD StnNegdVgeycnyLlnsfd ACTNYELEVVMD y 300 IHAAR.yKPFPEVKtkgmaa FLAAR.JKMFPnykelgsvg LLAAR.tKnilemAATepna LLAAR.knilemAATepna IIAARE.eLek	cGAD fDDC rDDC rDDC rDDC rADC fAND bBDC Consensus cGAD fGAD fDDC rDDC rDDC rDDC	541 LAETIYakiknr LvqTQLkrireOsD FAK.OFgdLevaD Lsh.eFZELVRGD MAK.yFZELVRGD MAGTARDYRD MAGTARDY	*** eFEmVfdgE.pehtnVCFV rfhllE.pecvnVsFV SRFELA.E.InMCLVsFR pvFEITA.Etl.GLVvFR SRFEIVA.p.raLGLVvFR SRFEIVA.p.raLGLVCFR nknsit.VVPp SRFEIVA.p.raLGLVCFR vppgtrptfsgvs YOpdgrpnffsgvs YOpdgrpnffssls f.JLRAVCScrTqsebmey j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCScrTqsberg j.vLRAVCS	000 yiPq.slRgipdsperrekL yvPk.rlRgvphdakEvel LKGSNETNBaLL LKGSNelNELL LKGPNelVEkLL LKGV.eEvNekLL pKd.dsNEittqLL pKd.dsNEittqL C.FServWNENE-LL G 660 SRtqlih.spitcssrr Sasvnea.dvdfMLdeihrl SKevS.AadEMeq.8q. dvhlrEahulsaghctsg v.diq.kltdpLlk.Ea. v.net.fl.dpl.asv. Sk.ps.
cGAD fGAD fDDC rHDC rHDC fAND bHDC Consensus cGAD fGAD fDDC rHDC rHDC fAND	 181 crdtikYgvrTghPrFPNq. crdtikYgvrTghPrFPNq. PPTasSYPAnLaD. PPTasSYPALAD. PPTarSYPsiJCD. PPAtVSsaAFLGE. qnkldaFvAycvknqYrNig y PPT-TSYPAFPND- A LG 241 meqitiKknrEivgv. nenvULKknrEivgv. ULgYMLEIPAEFlacs VLaKHLGIPAEFlacs VLAKHLGIPAEFlacs VLAKHLGIPAEFlacs VLAKHLGIPAEFlacs 	LStgLdiiglagEVLtSt LSngLdLismagEVLtat .KLSgAiaclGFtViaSP .HLGAigclGFtViaSP .HLGAigclGFtViaSP .HLGAINSVGFUVSSP .HLGJEVGFVUSSP ypeSadFdYtnlERFIrf .HLSLALIGFEVL-SP SS.CGGVIGFASESTLVA gGC.GGGVIGFASESTLVA psqGGGVIOTVSESTLA SGC.GGGVIOTVSESTLA GGD.GGGVIOTSSESTLA	240 AnTNmftYEispVF1 AnTNmftYEispVF1 ACTELEVVMHD ACTELEVVMHD ACTELEMIIHD ATELEMIIHD ATELEMIYHD SINNCgdVgeycnyllnsfd ACTNYELE-VFMD Y 300 IHAAR.yKFFFEVKtKgmaa FLAAR.JKMFFnyKelgavg sagsugqeveggegApsgvg LLAAR.KhiTqlqAspel LLAAR.khiTqlAspel LLAAR.khiTqlAspel LLAAR.khiTglAspel LLAAR.khiTglavgspis	CGAD fCAD fDDC rDDC rTDC fAND bHDC Consensus CGAD fCAD fCAD fDDC rHDC rHDC rTDC fAMD	541 LASIYakiknr LvqTQLkrireOsD Lsh.eF2sLVRQD MAK.yF2sLVRQD MAK.yF2sLVRSD LAK.OF2GLVIXD MAGTAVDHOkaginavr LAK.OF2GLVIXD MAGTAVDHOkaginavr LAK.OF2GLVIXD MAGTAVDHOkaginavr GO1 hrvapkiKalmMesgTtMvG gKicpiiKgrmMqkgTlMvG .KRINgrghIhLVFAtLKDv .KEIaktgqVPLIPATIqOk delmksgtVPLIPATIqOk delmksgtVPLIPATIqOk	*** eFEmVfdgE.pehtwCFV rfhll E.pecvWsFV SRFELAA.E.inHGLVSFR pRFEIA.E.I.HGLVSFR SRFEIVAp.rnFsLVCFR SKFEIVAp.rnFsLVCFR sKRFIVAp.raLGLVCFR nknSILVVFP SRFEIVAE.IGLVCFR YOprgtrptfsgVs YOpdgrpnffsils Y.gLRMAICSFTqseDmeY f.VLRFAVCSFTvesBhVgL L.IISPTVVSgFTk4Dllr igMRLAVgSFTvesBhVgL	600 yvPk.rlRgvphdakL&vel LKGSNETNEALL LKGSNelNELL LKGSNelNELL LKG4.vslhv.eEvNkkLL pKd4NEltEsvL LKPd.vslhv.eEvNkkLL pKd4NEltest C.PServVPehc LKPSRenK-NE-NE-LL G 660 SRtqlih.spiltsspr Sasvnea.dvdfMLdeihrl SVkeVskaadEMeq.Eq. 3VehtPilssvIraekE. dvnlirEanlvLsqhctsq v.diq.kldDlk.Ea. aV.qeiz.sqliDLqadEsl dTnlhas
CGAD fGAD fDDC rHDC pTDC tAND Consensus cGAD fGDD fDDC rHDC rHDC fConsensus	181 crdtikYgvrTghPrFPNq crtikYgvrTghPrFNq PPTaSYPATVaD PrtaSYPALGD PrtsSYPALGD PrtSYPsiVGL qnkldafvAycvknqYfNig y PrtSYPSiVGL A LG 241 meq1tLKurE1vgv. meq1tLKurE1Ygv. meq1tLKurE1Ygv. MigWILEIPeaPlagr VLKYLGLP6Plagr VLKYLGLP6Plagr	LStgLdiiglagEVLtSt LSngLdiimagEVLtat .KLSgAigcIGFSVaaSP .KLadstavSrgLpa. .KLSiAinsVGFUVXSP .KLSgEVIGFSViSS ypeSadFdYthlERFIrf .KLS-LAL-IGFEVLSP SskdCdGIfspGGaiSNMYA sGGGVIGCTASSFILM aGe.GGGVIGGASSETIM psaqGGGVIGGASEATIVA psaqGGGVIGGASEATIVA psaqGGGVIGGASEATIVA ysqCGGVIGGASEATIVA ysqCGGVIGGASEATIVA ysqCGGVIGGASEATIVA ysqCGGVIGGASEATIVA cGGGVIGGASEATIVA cGGGVIGGASEATIVA cGGVIGGASEATIVA .GGGVIGGASEATIVA	240 AnTNm ft YE is pVF1 ACTELEVVMD ACTELEVVMD ACTELENIIMD ACTELEMIIMD ATELEMIIMD ATELENIYMD SinNegdYgeycnyLlnsfd ACTNYELE-VYMD y 300 IHAAR.yKPFPEVKtkgmaa FLAAR.hKNFPnykeHgsvg LLAR.khkiBmKAHepna ILAAR.tkhiglm(Anspel LLAR.tkhiglm(Anspel LLAR.tkhiglm(Anspel LLAR.tkjm(BMR) ILARR.khiglm(Anspel LLAR.tkjm(BMR) JARCSALS	cGAD fCDC rDDC rDDC rDDC rDDC rDDC tAND bBDC Consensus cGAD fCAD fCAD fDDC rDDC rDDC rDDC rDDC rDDC rDDC rDD	541 LAETIYakiknr LvqTQLKrireOsD FAK.OPgdLevaD Lsh.eFZELVRSD MaK.yFZELVRSD MaKTAPCHVID MAGTAVDTHQkaginavr LAKOPFGLVIkD MAGTAVDTHQkaginavr LAKTOPFE_LVROD 601 hrvapkiKalaMesgTIMvG KRINgrghiLVPALIKDV QRINSAKLINLVPC:IrDk KelaktgQVPIIPATIQb dalMs;grVYHthtVg.G QRIdgrKvFNLIPATIQb	*** eFEnVfdgE.pehtNCFV rfhllE.pecvNv5VV SRFELA.E.InNGLVsFR pVFEITA.EV1.GLVcFR SRFEIVA.p.rsLGLVcFR SRFEIVA.p.rsLGLVcFR SRFEIVA.p.rsLGLVcFR SRFEIVA.eE-1-GLVCFR YOpdgtrpffsgVs YOpdgtrpffsgVs YOpdgtrpffsgVs TyREAVCSrtVesBNQL LIRPEVtScTfqseDmey fofLRFVCgGTtkdDlT jwRLRLVgSsLTeehNVrr fofLRFVCgmTkabldf vOId klidDVia	000 yiPq.slRgipdsperrekL yyPk.rlRgyphdakEvel LKGSNETNBaLL LKGSNelNELL LKGSNelNELL LKGV.selVikkL pKd.dsNEIttqLL CG. C.PServWFEhcL LKPSRNE-NE-LL G 6600 SRtqlih.spiltssrr. Saavnea.dvdfMLdeihrl SKeVs.AadEMeq.8q. dvlitplasvLraekE. dvlitplas
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Fig. 2. Multiple sequence alignment of the pyridoxal phosphate (PLP)-dependent decarboxylase family. The indicated alignments are based upon pairwise comparisons of the PLP-dependent decarboxylases. Dots indicate pads that were inserted to optimize alignments. Uppercase letters indicate functional similarities or identities. Consensus residues represent at least three (out of eight) identities or three similarities (with at least two being identical). The rectangle encompasses the putative PLPbinding domain of these decarboxylases (the K residue of DDC is known to bind PLP; Bossa et al. 1977). Residues that are identical in all eight proteins are indicated with stars. Three conserved Cys (C) residues at positions 385, 461, and 578 are identified by a plus (+). The lengths of the various proteins, excluding

distances among these enzymes (a distance value represents the number of identical matches between a pair, excluding gaps, divided by the shorter se-Quence length; therefore, a value of 1 indicates a perfect match). This quantitative assessment confirms that cGAD (from cat) and fGAD are more closely related to one another than to members of the DDC/TDC subfamily. Likewise, pTDC (from periwinkle), fAMD, and the DDCs are highly related to one another (also see De Luca et al. 1989). Importantly, this analysis also underscores the relatpads, are given in Table 1. Note that the final 141 residues of rHDC are not included in this figure, as they cannot be aligned with any other decarboxylase. The group alignment is numbered beginning with residue 1 of cGAD, cGAD = cat glutamic aciddecarboxylase (GAD) (Kobayashi et al. 1987); fGAD = fly (Drosophila) GAD (Jackson et al. 1990); fDDC = Drosophila dopa decarboxylase (Eveleth et al. 1986); rDDC = rat DDC (Tanaka et al. 1989); pTDC = Catharanthus roseus (periwinkle) tryptophan decarboxylase (De Luca et al. 1989); fAMD = Drosophila alpha-methyldopa hypersensitive protein (Marsh et al. 1986; Marsh, personal communication); bHDC = bacterial (Morganella morganii) histidine decarboxylase (Vaaler et al. 1986); rHDC = rat HDC (Joseph et al. 1990).

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edness of bacterial HDC to eukaryotic decarboxylases.

All of the enzymes of Fig. 2, including bHDC, have small segments in common with mouse ornithine decarboxylase (mODC; Kahana and Nathans 1985), another PLP-dependent decarboxylase (data not shown and De Luca et al. 1989). At best, however, mODC has a 10-12% overall identity with any of the other decarboxylases. Although mouse ODC and human ODC sequences are present in the NBRF database, they were not detected by FASTA

* *** 420

328

Table 1. Distance matrix

	l	2	3	4	5	6	7	8
I 2 3 4 5 6 7 8	1.00	0.53 1.00	0.17 0.19 1.00	0.17 0.18 0.58 1.00	0.17 0.17 0.45 0.51 1.00	0.17 0.17 0.40 0.41 0.36 1.00	0.17 0.17 0.45 0.45 0.39 0.37 1.00	0.19 0.24 0.15 0.13 0.15 0.13 0.13 1.00

Key for column and row indices: 1, cGAD, length without gaps: 585; 2, fGAD, length without gaps: 510; 3, fDDC1, length without gaps: 511; 4, rDDC, length without gaps: 480; 5, rHDC, length without gaps: 514; 6, pTDC, length without gaps: 500; 7, fAMD, length without gaps: 510; 8, bHDC, length without gaps: 378. See Fig. 2 for abbreviations

searches with multiple individual decarboxylase sequences. Therefore, among the known PLP-dependent decarboxylases, the ODCs appear to be the most divergent. Figure 3 shows a possible phylogeny of the characterized PLP-dependent decarboxylases, including mODC. This pictorial representation summarizes the relationships among these decarboxylases, but cannot be thought of as quantitative because of likely differences in the rates of evolution among the different enzymes and species.

Profile analysis is possibly the most sensitive method for detecting distantly related members of a family of proteins; it utilizes dynamic programming algorithms to search databases for proteins with similarities to an aligned group of sequences (Gribskov et al. 1987). To perform such searches, the information in the multiple sequence alignment is represented quantitatively in a table of positionspecific symbol comparison values (a profile), which can then be compared to existing protein sequence databases.

This method was used to derive a profile for the decarboxylase alignment shown in Fig. 2. This "decarboxylase profile" was then employed to search the PIR:NEW database for additional sequences with similarity to the group. This search found fDDC, fAMD, and bHDC (already known to be in the database), but did not detect ODCs or any other proteins with significant similarity to the PLP-dependent decarboxylase group (note that the GADs and pTDC are not present in this database). Importantly, the search did not detect numerous non-PLPdependent decarboxylases present in the database. Thus, it appears that the family of PLP-dependent decarboxylases is unrelated to other characterized proteins.

In conclusion, the results of these analyses suggest an ancient evolutionary origin for the gene duplications that gave rise to the PLP-dependent decarboxylase family. Interestingly, the data also imply



Fig. 3. Schematic representation of decarboxylase evolution. Abbreviations are the same as in Fig. 2, excluding mODC which represents mouse ornithine decarboxylase (Kahana and Nathans 1985).

that histidine decarboxylase activity evolved independently within eukaryotic and prokaryotic species.

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