SHORT COMMUNICATION

Isolation, Characterization, and Chromosomal Mapping of Mouse P450 17α-Hydroxylase/C₁₇₋₂₀ Lyase

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Cytochrome P450 17α -hydroxylase/C₁₇₋₂₀ lyase (P450_{17a}) catalyzes the conversion of C-21 steroids to C-19 steroids in gonads. A full-length mouse cDNA encoding $P450_{17a}$ was isolated from a mouse Leydig cell library and characterized by restriction mapping and sequencing. The predicted amino acid sequence has 83% homology to rat, 66% homology to human, and 62% homology to bovine $P450_{17a}$ amino acid sequences. The protein is 507 amino acids in length, which is 1 amino acid shorter than the human protein and 2 amino acids shorter than the bovine protein. The structural gene encoding $P450_{17a}$ (Cyp17) was localized utilizing an interspecific testcross to mouse chromosome 19, distal to Got-1. Another cytochrome P450, P4502c (Cyp2c), also is located at the distal end of chromosome 19. CYP17, CYP2c, and GOT1 have been mapped to human chromosome 10, with CYP2C and GOT1 mapped to the distal region, q24.3 and q25.3, respectively. The data in the present study indicate conserved syntenic loci on mouse chromosome 19 and human chromosome 10 and predict that the structural gene encoding $P450_{17a}$ will be found distal to GOT1 on human chromosome 10. © 1991 Academic Press, Inc.

The biosynthesis of testosterone in Leydig cells of the testis involves the action of two cytochrome P450 enzymes, cholesterol side-chain cleavage (P450_{scc}) and 17α -hydroxylase/C₁₇₋₂₀ lyase (P450_{17a}), (Payne, 1990). The initial and rate-limiting step in the biosynthesis of steroid hormones is catalyzed by P450_{scc}, an inner mitochondrial enzyme that cleaves the side chain of cholesterol to yield the C-21 steroid, pregnenolone. Synthesis of androgens from C-21 precursors requires the activities of P450_{17a}, which is associated with the smooth endoplasmic reticulum. P450_{17a} is a single protein that catalyzes two distinct reactions, the hydroxylation of the C-21 steroid progesterone or pregnenolone (17 α -hydroxylase activ-

ity), followed by cleavage of the two-carbon side chain $(C_{17-20}$ lyase activity) to yield the C-19 steroid and rostenedione or dehydroepiandrosterone, respectively (Fevold et al., 1989). Androstenedione is the immediate precursor of testosterone. Previous studies from this laboratory demonstrated that the expression of these two P450 enzymes is differentially regulated in mouse Leydig cells (Anakwe and Payne, 1987; Payne, 1990). P450_{scc} is constitutively expressed. Treatment of Leydig cell cultures with cAMP increases steadystate levels of P450_{scc} mRNA and protein synthesis. In contrast, cAMP is obligatory for de novo synthesis of P450_{17 α} (Hales *et al.*, 1987; Anakwe and Payne, 1987) and accumulation of $P450_{17\alpha}$ mRNA (Payne and Sha, unpublished data). We reported previously that the structural gene for $P450_{scc}$ (Cyp11a) is located on mouse chromosome 9, closely linked to two other genes expressing P450 enzymes, Cyp19, the structural gene that encodes P450 aromatase, and Cyp1, the gene that expresses aryl hydrocarbon hydroxylase (Youngblood et al., 1989). In a subsequent study we demonstrated that quantitative differences in the amount of Leydig cell P450_{scc} enzyme protein are regulated by either the structural gene Cyp11a or a closely linked regulatory gene (Nolan and Payne, 1990).

To further our knowledge of the genetic and hormonal regulation of $P450_{17\alpha}$ expression in Leydig cells, a mouse Leydig cell $P450_{17\alpha}$ cDNA was isolated, characterized, and used to map the chromosomal location of the structural gene encoding $P450_{17\alpha}$ (*Cyp17*).

A mouse Leydig cell λ gt11 library (Bain and Payne, unpublished data) was screened with a full-length rat P450_{17 α} cDNA obtained from Dr. Richard Fevold (Fevold *et al.*, 1989). A clone containing a 1.7-kb insert was isolated and subcloned into Bluescript for further analysis. Figure 1 shows the restriction map of the



FIG. 1. Partial restriction map and sequencing strategy of mouse P450_{17a} cDNA. The solid bar represents the coding sequences. The open bars at each end represent the 5' and 3' untranslated regions. Arrows represent regions sequenced using double-stranded dideoxy sequencing of fragments cloned into Bluescript. Sequences represented by the dashed arrow were obtained using a synthetic oligonucleotide as a primer. Restriction endonuclease abbreviations: P, PvuII; K, KpnI; E, EcoRI; B, BamHI; S, SacI; and Bc, BclI.

mouse $P450_{17\alpha}$ and the strategy used for sequencing. The complete nucleotide sequence and the predicted amino acid sequence are given in Fig. 2. The fulllength $P450_{17\alpha}$ clone contains an open reading frame of 1521 nucleotides, 32 5' untranslated nucleotides, and 143 3' untranslated nucleotides. A putative poly(A) addition signal is located 11 nucleotides upstream of a 17-nucleotide-long poly(A) tail. The predicted protein is 507 amino acids in length.

In Fig. 3, the complete amino acid sequence of mouse P450_{17 α} is compared with that of rat (Fevold *et al.*, 1989), human (Chung *et al.*, 1987), and bovine

(Zuber *et al.*, 1986). The mouse and rat amino acid sequences are 83% identical, while the human (66% identical) and bovine (62% identical) amino acid sequences are considerably less homologous to the mouse sequence. The mouse and rat sequences contain one less amino acid than the human and two less amino acids than the bovine. Regions of high homology common to members of the P450 gene family are shown boxed in Fig. 3. They are the putative heme binding region (aa 434-454) (Gotoh *et al.*, 1983); the Ozols tridecapetide sequence (aa 343-372) (Ozols *et al.*, 1985), which may play a role in substrate specific-

	L	Locus									
Emv-22ª		Got-1*		Cyp17	Nu						
Emv-22 scored											
C ^{<i>b</i>}		С		С		28					
M		Μ		Μ		26					
С	x ^c	Μ		Μ		9					
М	x	С		С		6					
С		С	x	М		2					
М		Μ	x	С		3					
С	x	М	X	С		0					
Μ	x	С	x	Μ		1					
					Total	75					
<i>Emv-22</i> not scored											
		С		C		9					
		Μ		Μ		10					
		С	x	Μ		0					
		Μ	x	С		0					
					Total	19					
Emv-22	-	Got-1	-	Cyp17							
	16/75		6/94	(Recombinants/total)							
	0.213 ± 0.047		0.064 ± 0.025	(Recombination frequen	$cy \pm standar$	rd error)					

TABLE 1

Linkage of Cyp17 to Emv-22 and Got-1 on Chromosome 19 in CAST/Ei × MEV Testcross

^a Segregation data for *Emv-22* and *Got-1* were reported previously (15).

^b Alleles inherited from the CAST/Ei and MEV strains are denoted by the letters C and M, respectively.

^c An x is used to denote regions of recombination.

(32)

ATG TGG GAA CTT GTG GTG CTT TTG TTT T									ccagctggccatctgcctacacctggctgcc											tgcc					
ATG TGG GAA CTT GTG GGT CTC TTG GTG GTC ATG CTG GTC ATG CTG GCG TAT TTG TTT TGG GCC AAG TGC AAA CCC AAT GCC AAT FTT GC CCC AGG AAC CTT CCA TTC CTG CTG CTG GTG GGT GT CTA CGC GTT GTC GCC AAG GTG GT GAT ATG GAT Ja TTC CCC AGG GAC CTT CCA TTC CTG CTG CTG GTG AGT CTT CTC TC CCC CAG GTG GT GAT ATG GAT Ja TTC CCC AGG GAC CTT CAG TTG CTG GTG ATG GT CGT TA TTC TTT CGC GTG GT ACC ACA ACT GCC GTG GT ATA AAA Phe Phe Jys Jeu Cln Clu Jys Tyr Cly Pro 11e Tyr Ser Leu Arg Leu Cly ThT ThT ThT Ala Val 11e (237) GTC GGT CAC TTG CAG GTG GCC AGA GAA GTG CTC GTG TAG TG TT CTT CGC GTG GT ACC ACA ACT GCA GTG Val Cly His YTY Cln Jeu Ala Arg Clu Val Leu Val Jyg Jys Gly Phe Gu Phe Ser Ser Gly ATg Pro GLM Met Val (321) GTC GGT CAC TTG TG GG GAC AAA GTG CTC GTG TAA GAG GG GAA GAA TTC TT GTG GTG CAG GTG CAC GTG GTG GTG GT CAC TTG TG GG GAC CAA GAA ATG CTC GTG TAA GAG GG AAA GAA TTC TTC GTG CAG GTG CAC GTG CAC GTG GGT ACT TTC CAC GTC TTT TCC GTT CAG GAT CAC CAC AAA GTG ATT ATT AGC TCC TG GTG CAG GTG CAC GTG GT ACT TTC CAC ACCC TTT TCC GTT CAG GAT CAC CAC AAA GTG ATT ATT AGC TCC TTG GAG GTG AAT AGG GG ATA ATG CAC ACCC TTT TCC GTG TAC ACC AGA CAC CAC AAA GTG GTG AAT ATG TAG GTG TAA GTG CAA GTG CAC ATG Leu Val Phe Ser Thr Phe Ser Leu Phe Arg App App Cln Lys Leu Clu Lys Met 11e Cys Gln Clu Ala Aan (627) TTA ACT GT CAC ACTC TG TT CGC GTC TC AGC ATG CTT TTG AGA ATG TGT TGT AGG TCA ATG CAC ATA (627) ATA ATG AGT GTA ATG TAA CT TAC ATA CAC GAC GG CAC TCC GG AAA CTA TTG CGC ATA CTG ACT ACC ATA CAG ACC (627) ATA ATG ATT GG CAT TG GAT ACT TAC ATA CAC CGC CTG TTG TG ATA TTG CAC ATA CGA ACC ACC ACA AGG ATT GG ATT GG ATG CTG CG CGC CCC CTG CTG ATA TTG CCC ATA CGA ACC ACA (627) ATA ATG ATT GTG ATT GCC TG CC CGC CCC CTG CCC ATA CTG ATA ATG CCC ATA CGA AGA ATC ATA ACT TG GAA TTG GAA ATG TAC ACC ACC ACC ACT ACA ACA ACT AAA ATT CGC GTG GAA AGA ATA TTT CCC ATA ATA ACT GTG AATT GGA ATG ATA AGG ACA CAC ATA AAAT GGC TG GT GAA AAA AGC CTG ATG AAA TTT TTG CAA ACT TTT GGA AAA ACT GAA ATG GAA ATG ATA AGG AACA ACT AGC TTA ATG CG CTG GT GAA AGA ATT																									(107)
Net Trp Glu Lu Val Luy Lu	ATG	TGG	GAA	CTT	GTG	GGT	CTC	TTG	CTG	CTC	ATC	CTG	GCC	TAT	TTC	TTT	TGG	CCC	AAG	TCA	AAG	ACA	CCT	AAT	GCC
ALG TC CCC CCC <thccc< th=""> <thccc< th=""> <thccc< th=""></thccc<></thccc<></thccc<>	Met	Тгр	GIU	Leu	vai	GLÀ	Leu	Leu	Leu	Leu	ITe	Leu	AIa	TÀL	rne	rne	пр	PIO	гуз	Ser	гуз	1111	FIO	ASII	(182)
Lys Phe Pro Arg Ser Leu Pro Phe Leu Pro Neu Val Gly Ser Leu Pro Phe Leu Pro Arg Arg Gly His Met His C257 CCC AAC TTC TTC AAG CTG CAG GAA AMG TAT GGT CCC ATC TAT TCT CTT GGC CTG GGT ACC ACA ACT OCA GTG ATT AL Asn Phe Phe Lys Leu Gln Glu Lys Tyr Gly Pro Tle Tyr Set Leu Arg Leu Arg Leu Gly Thr Thr Thr Ala Val His Si GTC GT CAC TAT CAG CTG CCC AGG GAA GTG CTC GTG AMG AMG GGU AAA GAA TTC TCT GGT CGG CCC CG Met GTG (132) TCT CTA GC CTC TG CGC GAC CAA GAA AMG CCT GTG TAA AMG GGU AAA GAA TTC TCT GGT CGG CCC CGG CC CG TTr Leu Gly Leu Leu Ser Asp Gln Gly Lys Gly Val Ala Phe Ala Asp Ser Ser Ser Ser Trp Gln Leu His Arg (482) ANG GTG GTA TTC ACC ACC TTT TCC CTG TTC AGG GAT GAC CAA GAA TTG TACT CTC TGG GAG GCC ACC TTC Leu Cys Leu Leu Ser Asp Gln Gly Lys Gly Val Ala Phe Ala Asp Ser Ser Ser Ser Trp Gln Leu His Arg (482) TCC CTG TG CC TTG TAC CTT ACC ACC GTT TT GGA GAA GTG CC CGA GT ATT ATC TCC GG GAT GT ATA TTC ATC GT GAC TTG ATA CTT ACA TAC GAC GGG GAA GT CCC GAG ATA CTT ATG TGC GTA GT ATA TC ATC GTG GAC TTG GAT GT TA CTT ACA ACT CTC TTT GGA GAA GAA GAT GTAC GTC ACG CTC ATC TC GAG ATC ATG ATT ACC ATC ATC GTG GAC TTG GAT GT CTG GG CAC AGC GAT CTG GTG GAA ATA TTC CCG TG TACA CTA ACC ATA CGG ACC TT TAC ATC GTG GAT GT GTG GGT GT CTG GG CAC AGC GAT CTG GTG GAA ATA TTC CCG ATG TTG GAA GTT TTT CCC ATT TTG GL GLY TL FU LAU ASP Val Leu Gly His Ser Asp Leu Val Asp Pie Pie Trp Leu Lys Hie Phe Po Asn (782) ANA CTTG GAA TG CTG GG GU GAC CAC ATA ATT CGG GAA AAA CAC GTG GTG GAA ATT TTT CCC ATG TTT GLA GAA TG CTA GT AG GT CT CTG GGC CAC AGC GTG GG AGA CT CTT GTG AAA GTG GLA ATA GT GT AAA CTTG GAA TG CTA GT AG CTT CTG GGC CAC AGC GT GTG CAC ATA CTG GAA ATG TTT GAA AAA TGC CAG (792) ANA CTTG GAA TG CTG GG GA GAC CCA AGT GTG TTC TCA GA GAA ACC ATG CTT GAA ATG TTT GAA AAA TGC CAG (457) TTG GLA AAA TGG GAA GGC CGA GAC CCA AGT GTG TTC TCA GAA ACC AGA GGT GGA GAC ATC TTT GG ATT CTG GG GAA GGC CGA GAC CCA ATT GTG TG CTG GGA CTG ACC ATA CTG GTG GCA CAA CTT TTC GGA ATT TG AAA ATG GAA GGC CGA GAC CCA ATG TG GTA CTG ACG GGT T	AAG	TTC	ccc	AGG	AGC	CTT	CCA	TTC	CTG	ccc	CTG	GTG	GGT	AGT	СТА	CCG	TTT	стс	ccc	AGA	CGT	GGT	CAT	ATG	CAT
26 CC ALC TTC TTC AAG CTG CAG GAA AAG TAT GGT CCC ATC TAT TCT CTT CGC TG GGT ACC ACA ACT GCA TT ATT ATT TAT TAT TAT TTC TTC TT CTT CTT CGC CTG GGT ACC ACA ACT TATT ATT TATT AAA TTT CAC TTT CG CG CC AGA GAA GAA TTT TTT TTT TTT TTT TATT ATT TATT ATT TATT ATT TATT CAG CCC AGA GAA GAA GAA TTT CG TT GG GG AAA GAA TTC TTT GG GG CC GC GG TTT GG GG CC AGA GG AAG GAT ATT TTT CG TT GG CG CC CG AGA GG CG CG CTT GTG GG CGC AGA GG CG CG CTT TTT GG AG CGC CTG TG CG CTT TTT CG CG CG CTG CG CTT TTT CG	Lys	Phe	Pro	Arg	Ser	Leu	Pro	Phe	Leu	Pro	Leu	Val	Gly	Ser	Leu	Pro	Phe	Leu	Pro	Arg	Arg	Gly	His	Met	His
GCC MC TTC TTC MA CTG CAG GAM ANG TAT GGT LCC ATC ATA TAT LC CTT GGC LGC WA AN ATC ATA ATC ATG CTG CAG CTG GAC GAG ATG GTG CT CAC TAT CAG CTG GCC CAG ATG GTG CT CAC TAT CAG CTG CCC ATG GTG CCC CAG ATG GTG CT CAC TAT CAG CTG CCC ATG GTG CCC CTG TG CG GCC ATG GTG CAC CGG CT CTG CG GCC CAG ATG GTG CAC CGG CTT GT GG GC CTT GT GG GCC ATG GTG CCC TTT GCG CCC TTG GCG CCC CTG GTG G	26						~ ~ ~	~ • • •								CTT	~~~	ama	CCT	200	202	NOT	CC A	CTC	(257) NTT
(12) All ABA FID	GCC	AAC	TTC	TTC	AAG	CTG	CAG	GAA	AAG	TAT	GGT	Dro	ATC	TAT	TCT	Leu	Ara	LTG	GUT	Thr	Thr	Thr	Ala	Val	Ile
TC GCT CAC TAT CAC TC GCT CACA GAA GTA GTC CTG TC AAA AAG GGG AAA GAA TTC TCT GTG CAG CCC CAG ATG GTG TC AGC CTC TTG TCG CAC CAA GGA AAA GGC GTC GCC TTT GGG CAT AGT AGT AGT AGT AGT AGT AGT TC AGC CTC TTG TCG CAC CAA GGA AAA GGC GTC GCC TTT GGG CAT AGT AGT AGT AGT CTG CG CAC CTG CCC TTC AGC ACC TTT TCC CTG TC AGG GAT GAC CAG AAA TGG GAA AAA GAC TC CTC TGG CAA GCC CAC AGG GT TTG AGC ACC TTT TCC CTG TTC AGG GAT GAC CAG AAA CTG GAG AAG ATA GT AGT CAG CAG CAG CAA AGT GG GTA TTC AGC ACC TTT TCC CTG TC AGG GAG GAC CCC GA GAT CTG GAG AAA GAA TTG CAG GAA GAG CAA AAA TG GAC TTG AAC TTA CA TAC GAC GGG GAG TCC GA GAT CTG TC AGG CTC ATA TTG CAG GAA GAT ATA TTC AGC ATC TG TATA CTT ACA TAC GAC GGG GAG TCC GAG ATT CTG AGC CTA CTT TTG AAA TAC Ser Leu Cys Aps Leu 11e Leu ThT TYT App GJY GLY Ser Agy App Leu Ser Thr Leu LL P PL Lys Ser V1 LL GAT ATT GTC GAT GTC TTC AAC TCT CTT TTT GAA AAC GAT CCG ATA CTG ATT CTG AAC ATA CAG ACC TTT TAT GTC GAT GTC GAT GTC TG GGC CAC AGC GAT CTG GTG GAC ATA TTC CCG TG TG AAA ATT TTT CCC AAA TTT GG GAA TTG ATA ATA AGG GAA CAC ATA GAA AAA ACA CCG TT GAA AAA TTT TT CCC AAA ACT TG GAA ATG ATA AGG GAA CAC ATA ATA GAA AAA ACA CTG GTT GAA ATG TTT GAA AAA TGC TTT GUI GLY LL APP VAL APP VAL APP LLE VAL APP LLE LYS LL APP LLE LYS LLP FLE LYS LLP CAA ATA CCA CTG GAA ATG ATA AAG GAA CAC ATT GTG GTG CTG AGA AAA ACA CTG GTT GAA AAA TT TTT CCC AAA ACT TG GAA ATG ATA AAG GAA CAC ATT ACT CGA GAA AAA ACA CTG GTT GAA ATT GTT GAA AAA TT TTT GUI GLY FLA APP VAL APP SLE APP LEW VAL APP LLE LYA LL APP LLE LYS LLE APP LEW LYS LLP S LLP	A14 51	ASI	Pne	rne	цүз	Leu	orn	GIU	DAP	TÄT	GLÀ	110	116	1 9 1	Der	neu	my	Deu	011	11	****				(332)
Val Gly His Tyr Cin Lau Ala Arg Glu Val Lau Val Lys Lys Gly Lys Glu Phe Ser Gly Arg Pro Gln Met Val (407) ACT CTA GGC CTC TTG TCG GAC CAA GGA AAA GGC GTG GCC TTT GGG AA AGT AGT AGT AGT CTC TGG CAG CTG CAC GGG GA AGT GLU Lau Leu Ser Sap Gln Gly Lys Gly Val Ala Phe Ala Ang Ser Ser Ser Ser Ser Trp Gln Leu His Arg (487) AGT GTA TTC AGC ACC TTT TCC CTG TTC AGG GAT GAC CGA AAA TTG GAG AAA ATT G GAG AAA AT TT G AGA ACC ATT TA AGT ACC TTA ACA TAC GAC GGG GAG TCC GG AT GT GTG TA CTG ATA CTT AAA TACT ACA TAC GAC GGG GAG TC CG GA AT GTG TT Lau Hie Phe Lys Ser Val Hie (557) TCA CTG TA TCC ATA ACT ACA TAC GAC GGG GAG TCT GTG GG GAA T GTG ACT ACT GTG ACC ATT A CGA CAC ATT ACG GAC ATT TT GAA AAA CCA TT TT GAG AAA CAA GA GAT TTT GAA ATA CCA TA ACC TTT AAA GG GAC CTT TT GAG AAC AAG GAT CTG GTA ACT ATA CGA ACC TTT AAA TT CGA GAA ATA TTC GG GAT ATT GTG GAT ATT CGG GAT ATT GTG GAT ATT CGA GAA ATA CTG GTG GAC ATT TT GAA AAA CCA TT GAA ATT TTT CCA AAA TTT CGA GAA ATA CTG GTA AAA TTT GAA AAA CAA CTG GTT GAA ATT TT GAA AAA CAA CTG GTT GAA ATT TT GAA AAA CAA CTG GTT GAA ATT TT GAA AAA TA CAA GTG GAT AAA ATA TT GAA AAA TT GAA AAA CAA CTG GTT GAA ATT TA AAA GAA CAA GAA CAA GTA TTT GAA AAA TTT GAA AAA CTA GTG GAA ATA TT GAA AAA TTT GAA AAA CTA GAA CAAA ATA CTA GAA GAA TTT GAA AAA TTT GAA AAA CAA CTG GTT GAA ATA TT GAA AAA TAA TAA TAA GAA ATT GAA CAA CAC ACA ACT AAA ATT CGA GAA AAA ACA CTG GTT GAA ATA TT GAA AAA TAA TAA TAA GAA ATT GAA AAA TGA GAA AAA TTT GAA AAA TTT GAA AAA CCA TT GAA AAA TAA TAA TAA ATA GAA GAA GAA	GTC	GGT	CAC	TAT	CAG	CTG	GCC	AGA	GAA	GTG	стс	GTG	AAG	AAG	GGG	AAA	GAA	TTC	тст	GGT	CGG	ccc	CAG	ATG	GTG
The ACT CTA GGC CTC TTG TCG GAC CAA GGA AAA GGC GTG GCC TTT GCG GAT ACT ACT AGT AGT AGT AGT AGT AGT AGT AGT AGT AG	Val	Gly	His	Tyr	Gln	Leu	Ala	Arg	Glu	Val	Leu	Val	Lys	Lys	Gly	Lys	Glu	Phe	Ser	Gly	Arg	Pro	Gln	Met	Val
AT CIM GLU CIC ING IGG GAR CAR GGM ANG GUE GIG GUT IT GLG ANG AND AGE CAR GGM ANG GUT IT GLG GAR CIA GGM ANG GUT ANG GUT IT CLG GAR GAM ANG GUT IT GLG GAR CIA TT CLG AGE ANG CAR GAT ATT CLG GAR GAR CAR CIT TT CAR TAR CIT ACC TAR CAR GAR GAR GAR CAR GAR CIG GAR GAR CIG TA TT AGE AAR CIT ACA TAR CAR CAR GAG GAR GAR CIG TA TC ACT ACC ATA CIT ACA TAR CIT CAR GAR GAR GAR CIG TA TC ATC ATC TAR AAR CIT CAR TAR CIT ACA TAR CIT CAR GAR GAR CIG GAR CIG TCT AGG CIT ACC ATA CAR GAR CIT TAR AND GAR AND TAR CIT ACT ACC ATA CIT ACA TAR CAR CAR CIT TI GAR AND GAR CIG TAR CIT ACC ATA CAR ACC ATT TAR AND GAR AND TAR AND GAR GAR CIG TAR CAR ACC ATA CAR ACC ATT TAR AND GAR GAR CIG TAR CIT ACC ATA CAR ACC ATT TAR AND GAR AND TAR TT CIT GAR AND TAR TAR CIT ACC ATA CAR ACC ATT TAR AND GAR AND TAR CIT GAR AND TAR TAR CIT GAR AND TAR A	76				-		~ ~	~~~	~~~		~~~	CTC	<i></i>	ጥጥጥ	ccc	CAT	ACT	ACT	ACC	TCC	TCC	CAG	CTG	CAC	(407) CGG
(42) AG CTG GTA TTC AGC ACC TTT CCC CTG TC AGG AG CAC CAG AAA CTG GAG AAA CTG GAG AAA CTG GAG GAA ATG GT GAC TTG AG AAA ATG CTG TTC AGG AAA ATG ATA TGT CAG GAA ATG GTG GAC ATG TTC AGG CAA CTG GTG GAC TTG ATA CTT ACA TAC ATA CAAC GAG GAG CTG CTG TCT ACG CTC ATC ATG ATA CTT ACA TAC ATA CAAC GAG GAG CGG GAG TCC CGA GAT CTG TCT ACG CTC TTC AGT CAA GTA ATC TAC CTG TG AC TTG ATA CTT ACA TAC GAC GGG GAG TCC CGA GAT CTG TCT ACG CTC ATC ATC AGTA ATC Ser Leu Cys Asp Leu 11e Leu Thr Tyr Asp GLY GLU Ser Arg Asp Leu Ser Thr Leu 11e Phe Lys Ser Val 11e (527) ATA TAC TC TGT ACC ATC TG CTG ACA CAC CTC TTT GAG AAC GAG CGC CGC ATA CTG ATC ACC ATT AGA CC ATT ATA TIC ATC TGT ACC ATC GG CTG AC ATC CT TTT GAG AAA GAG GAT CCG GTT GA ATG ATT TTT I CCC AAT ATT GLU GLY 11e Val Asp Val Leu GLY HIS Ser Asp Leu Val Asp 11e Phe Pro Trp Leu Lys 11e Phe Pro AnT 116 10 AAA ATT G GAA ATG ATA AAG GAA CCA CT AAA ATT CGA GAA AAA CAC CTG GTT GAA ATG TTT GAA AAA ACT TG GAA ATG ATA AAG GAA CCA CT AAA ATT CGA GAA AAA CAC CTG GTT GAA ATG TTT GAA AAA ATG 112 AAA AAC TTG GAA ATG ATA AAG GAA CCA CC TTA AAA TT CGA GAA AAA ACA CTG GTT GAA ATG TTT GAA AAA GT 112 ATTC AAT AGT GAA TCT CTC TCC CACC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG ATT GAA AAAA ATT 112 ATC AAT AGT GAA TCT CTC TCC CACC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG ATT GCA GAA ATT AAT 112 ALY PHA ASS SET GLU SET LEU SET SET LEU THT ASP 11e LAU 11e GLI ALI LYS MET ASS ALI CUA GAA ATT AAT 112 ALY PHA ASS SET GLU SET LEU SET SET LEU THT ASP 11e LAU VAI CLA GG GG GAG ACA CT CTT TTG GG 113 ATT AAC GAG GAC ACA CAC ATT GTG GTG TCA CAT AAA CTC GTG GTG TCA CAT ATT CTG GTG GAG ACA CT TTT GGG 114 ATT ATT ASS SET GLU SET LEU SET SET LAU THT ASP 11E LAU VAI THT VAI GAG GGA ACA CT TTT GGG 115 ATT AAA GG GAA ACT AGC TCT GTG CTG AAC TGG ATT CTG GTG TCA CAT ATT GAG GGA ACA CT TTT GGG 114 AT ATT TAT SET SET VAI LAU ASS TTP I LEU VAI THT VAI AST GTG GAA CAC TTT TGG GA ACA CT TTT GGG GAA GGC AAC ACT TTT GTG GAA GGC CAA GTA TTT GG GC TTA TGT GGG ACA ACC ATT GTG GTG CAC ATT GGG GAA GGC ACT ACT ATT G	ACT	Lou	GGC	Len	Leu	Ser	Asn	Gln	Glv	Lvs	Glv	Val	Ala	Phe	Ala	Asp	Ser	Ser	Ser	Ser	Trp	Gln	Leu	His	Ara
AGG CTG CTA TTC AGC ACC TTT TCC CTG TTC AGG GAT GAC CAG AMA CTG GAG AMA MTG TAT ATG TAG GAA GCC AAC AAC Arg Lau Val Phe Ser Thr Phe Ser Lau Phe Arg App GD Lys Leu GLU Lys Met IIe Cys GLD GLU ALA Am Can GL TGT GAC TTG CAT ATT ACA TAC CAC GG GAG TCT GTC TTC AGG CAC CAC GAG ATT CTT ACA TT ACA TAC CAC GG GAT CTT CA GC CAC GAG CTC CGA GAT CTG TT AGG CAC CAT CTG AGT ACC GTA ATC Ser Leu Cys App Leu IIe Leu Thr Tyr App GLY GLU Ser Arg App Leu Ser Thr Leu IIe Phe Lys Ser Val IIe (537) GTA ATC TAC ATC TTC AGT CAC TAC ATC TTT TTG AGT CAC TAC ATC TTT TTG AGT CAC GTA CT TTT TTG AGT CAC TAC ATC TTT TTG AGT CAC TAC ATT TTG GGT CAC TAC ATC TTT AGT CAC TAC ATC ATC TTT TTG AGT CAC TAC ATT TTT TTG AGT CAC TAC ATT TTT TTT TTT TTT TTT TTT TTT TTT	101	Dea	ULY	Dea	Dea	Det	лэр	0111	019	710	011														(482)
Arg Leu Val Phe Ser Thr Phe Ser Leu Phe Arg Aap Asp Gin Lys Leu Glu Lys Met Ile Cys Gin Glu Ala Asn (557) TCA CTG TGT GAC TTG ATA CTT ACA TAG GAC GGG GAG TCC CGA GAT CTG TCT AGG CTC ATC TTC TAG CTG ATA ATC (557) TCA CTG TGT GAC ATG TGT ATA CTA CAC GAC GGG GAG TCC CGA GAT CTG TCT AGG CTC ATC TTC TAG AGT CTG ATA ATC (557) TAT CTG TGT ACC ATC TGT ACA CAT CTG TTT GAG AC AAG GAT CTG TTT LEU IL PHE Lys Ser Val Ile (612) ATA TCT GTG ACT GTG CAT GTC TTC AAC ATC TCT TTT GAG ACA AAG GAT CCG ATA CTG ACT ACC ATA CGG ATA CTG ATA CTG GG ATT GTG GAT GTC CTG GGC CAC ACG GAT CTG GTG GGA CATA TTG CAC TG ATA CGG AGA ATT TTT CCC AT TTT GLU Gly Ile Val Asp Val Leu Gly His Ser Asp Leu Val Asp Ile Phe Pro Trp Leu Lys Ile Phe Pro Asn (787) ATT GG GAA TGT ATA AG GAA CAC ACT ATA ATT CCA GAC AAA ATA CCG GTG GTG AAC ATG TTT GAA ATA TCC AGA ATA ATT GAA ATT CTA CAC ACC ATG ATA CTG ATA CAA GCG AGG AAA ATA CA CTG GAA ATG ATA AGG GAA CAC ACT ATC TCT CCA CAC GAC AATT CTG ATA CAA CCA ACG AAG AATA ATA Glu Lys Phe Asn Ser Glu Ser Leu Ser Ser Leu Thr Asp Ile Leu Ile Gln Ala Lys Met Asn Ala Glu Asn Asn (932) ACT GGG GAA GGC CAG GAC CCA AGT GTG TTC TCA GAT ATC CTG GTG CAC AAT CTC GAG GAC ATC TTT GAG ATT ATG GGG GAA GGC CAG GAC CCA GTG GTG TTC CAG GAT CTG GG CTT TC CTG GTG GAC ACC ATT TTG GA ATT GGG GAA GGC CAG GAC CCA GAG TT GTG TTC CAG ATC CTG GG CTT TC CTG GTG GAC ACC ATT TTG GG ATT AGG AAG ACA ACT AGC TCT GTG GTG AAC GGG TT CAG ACA CCG TTT CAG ATA AGG ACT ACC TTT GAG ATT AGG ATG GAA GGA ATT GAC CAC TAT GTG GTG TAC GGA ACC CGT TTC CAG AAT AGC GGG AGG ACC ACA TTT GG ATA ATG GAA GGA ATT GAC CAG TAT GGC TTT GAT ACG GG GTG GCC CCT TTC CTG GTG GAC GAC ACT CTC CGC CAC AGG GGA GGC CAC ACT ACC CAG TAT GGC TTC GGT ATC GGA GAC CAC CTT TTC AAT GAC CAA CCG GA GC CAC CAC CCC CAC ACA GCA G	AAG	CTG	GTA	TTC	AGC	ACC	TTT	TCC	CTG	TTC	AGG	GAT	GAC	CAG	AAA	CTG	GAG	AAG	ATG	ATA	TGT	CAG	GAA	GCC	AAC
126 TGT GAC TGT GAC TG ATA CTT ACA TAC GAC GGG GAG TCC CGA GAT CTG TCT ACG CTC ATC TTC AAG TCA GTA ATC Ser Leu Cys Asp Leu II e Leu Thr Tyr Asp Gly Glu Ser Arg Asp Leu Ser Thr Leu ILe Phe Lys Ser Val ILe (632) AAT ATC ATC TGT ACC ATC TGC TTC AAG ATC TCT TTT GAG AAC AAG GAT CTG TCT ACG TCA CTA ACG ATC TTT GAG AAC TAG GAA CC AAG GAT CTG CTA CTA CT ACG ATC TTT CAG GAC TT (782) AAT ATC ATC TGT GAC TAT GTG GAT CTC TGT GG GC CA CA GAT CTG GTG GAC ATA TTC CGG TG GAA GAT TTT CCA ATT TTT CUC ATT (782) AAA ATC TG GAA ATG ATA AAG GAA CAC ACT AAA ATT CGA GAA AAA AAC CTG GTT GAA ATG TTT GAA AAA CC AGG (AA ATT TTT CAG AAT CCA GAA AAT AAT (782) AAA ATC TAG GAA ATG ATA AAG GAA CAC ACT AAA ATT CGA GAC ATA TTC CAA GCA AAC AAG ATG AAT CCA GAA AAT AAT (782) Ya haa Leu Glu Met Tle Lys Glu His Thr Lys IIe Arg Glu Lys Thr Leu Val Glu Met Phe Glu Lys Cys Lys (18) (782) GGG GAA GGC CAG GAC CCA AGT GTG TTC TCA GAT AGC ATA TTC CTG GAC AAA ATA AT (782) GAA ATT AAT GAG GAA CCT CTC TGC CG GAC GAT AAG CAT ATTC CTG GTG TG CAC GG GG GA GAC ATC TTT GAG (782) AAA TTC AAT AGT GAA ACT CTC TCC CAC CG ACA GAC ATA TTC CAA GAA AAT CCA GAA ATA AT (782) GAA ATC AAT AAG GAA CCA ACT TAA ATT TTC CAG GTA TAT TTC GAG GAG AAT CTT TG GAG AAT ATTC GAG GAA ATA TTC GA GA ATA TTC GAA GAG GAA ATA TTC GA GA ATA TTC GA GA ATA TTC GAA GAG GAA ATA TTC GAA GAG GAC ACA CAT GAT GAA ATA CCA GAA ATA ATA TT GAG GAA GAG CAT GAT GAA ATA GAA GAG CAC ACA TA GAG AACA ACA ACA ACA ACA ACA ACA ACA A	Arg	Leu	Val	Phe	Ser	Thr	Phe	Ser	Leu	Phe	Arg	Asp	Asp	Gln	Lys	Leu	Glu	Lys	Met	Ile	Cys	Gln	Glu	Ala	Asn
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151151161161161161161163ATT CT GT AC TGT CT AC TG CT TT GAC AC TT TT GAG AC AAG GAT CGG ATA CGG ACT AC CA ACA CT TTAsn Tie Ser Phe Glu Asn Lys Asp Pro IIe Leu Thr Thr IIe Gln Thr Phe(701)176GAG GGT ATT GTG GAT GTC CTG GGC CAC AGC GAT CTG GTG GAC ATA TTC CCG TGG TTG AAG ATT TTT CCC AATTTT GTG GAA ATG ATA AAG GAA CAC AAA AG CAT CTG ATT GG GAA ATG TT GAA AAA TCC AAG(782)176GUI GUI Leu GLU MET IIE Lys GLU HIS TH LyS IIE ATG GLU LYS TH LEU VAI GUI MET Phe Pro Trp Leu LyS IIEPhe Pro Asn(782)178GAA ATG ATA AAG GAA CAC ACT AAA ATT CGA GAA AAA ACA CTG GAT GAA ATG TTT GAA AAA TGC AAG(782)Yas178GUI US STH LEU SG IU HIS TH LYS IIE ATG GLU LYS TH LEU VAI GLU MET Phe GLU LYS CYS LyS(857)179GAA ATG ATA AAG GAA CTC TC TCC CC CCC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG AAT ATT(932)170GAA GGC CAG GAC CAC AACT GTG TTC TCA CA GAT AAG CAT ACC CTG GTG CAC AAT ATT GG(932)171GAA GGA CAC AACT AGC TCT GTG CTG GAA CTG ATC CTG GAT CTG GTG CAC AAT CTT GGG(1082)172GGA GAA AGA AAA ACT AGC CTG GTG TTC TCA GAT AAG CAT ACC CG GGA GAC ACT CTT GGG(1082)176GGG GAA AGA GAC AACT AGC TGT GTG CTG GAAC CGG GTG CCC GTG TTC CAA GAA GAA GAG(1082)176GAA GAA CAA AACT AGC TCT GTG CTG GTG CTG ATC AGG CTC AGT CGG ACA CAC CG TG CTC TTC AAT GAA GAA CTT GA GAA GAA ATT GAA GAA ATT GAA GAA CTT TT GGA GAA ATA CTG ATT CCA GAA AAG GAA ATT GAA GAA ATT GAA GAA CAC ATT CTC GAG GAA CTT TT GGA GAA GAG CTT CTG GTG CAC CAA AAG GAA CTT CTT GGA GAA GAG TTT GCA ATC CGA AAA GGA CTT GAA TGC GTG GTG CCC CTG TTC CAA GAA GAA CTT GGA GAA GAT GAA CTT GTT GGA GAA GAC CTT TTA GAA GCC GAA GAG CTT CAC GAA	Ser	Leu	Cvs	Asp	Leu	Ile	Leu	Thr	Tvr	Asp	Glv	Glu	Ser	Arg	Asp	Leu	Ser	Thr	Leu	Ile	Phe	Lys	Ser	Val	Ile
AAT ATC ATC TOT ACC ATC TOT CTT CTT TT GAG AAG AAG GAT CCG ATA CTG ACC ATA CCG CCG CTG CCC CTG CCC CCG CCG CTG CCC CCC	151	Deu	010		200				-1-	F	1											-			(632)
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The Glu Gly Tle Val Asp Val Leu Gly His Ser Asp Leu Val Asp Tle Phe Pro Trp Leu Lys Ile Phe Pro Asn (782) AAA AAC TTG GAA ATG ATA AAG GAA CAC ACT AAA ATT CGA GAA AAA ACA CTG GTT GAA ATG TT GAA AAA TGC AAG Lys Asn Leu Glu Met Ile Lys Glu His Thr Lys Ile Arg Glu Lys Thr Leu Val Glu Met Phe Glu Lys Cys Lys (857) GAC AAA TTC AAT AGT GAA CTC CTC TC CACC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG CAT GCA GAA AAA ATA Glu Lys Phe Asn Ser Glu Ser Leu Ser Ser Leu Thr Asp Ile Leu Ile Gln Ala Lys Met Asn Ala Glu Asn Asn Glu Clys He Asn Ser Glu Ger Leu Ser Ser Leu Thr Asp Ile Leu Ile Gln Ala Lys Met Asn Ala Glu Asn Asn Glu Clys Glu Glu Glu Gln Asp Pro Ser Val Phe Ser Asp Lys His Ile Leu Val Thr Val Gly Asp Ile Phe Gly (1921) ACA CAT GGG GAA GAC ACT ACT CTG TG CTG TG TG TG CAG ATA GCA TTC CTT GTG CAG GGA GAC ATC TTT GGG Anan Thr Gly Glu Gly Gln Asp Pro Ser Val Phe Ser Asp Lys His Ile Leu Val Thr Val Gly Asp Ile Phe Gly (1007) CGG GGC ATA GAG ACA ACT AGC TTT GTG GTG GTG GGG TTC AGT CGG ACA CCG TTT CC TG GAG GAC ATC CTC GAG Ala Gly Ile Glu Thr Thr Ser Ser Val Leu Asn Trp Ile Leu Ala Phe Leu Val His Asn Pro Glu Val Lys Arg 301 AGG ATC CAA AAG GAG ATT GAC CAG TAT GTA GGC TTC AGT CGA ACA CCG TCT TTC AAT GAC CGG ACT CAC CTC CTC Lys Ile Gln Lys Glu Ile Asp Gln Tyr Val Gly Phe Ser Arg Thr Pro Ser Phe Asn Asp Arg Thr His Leu Leu (1157) ATG CTG GAG GCC ATT GGG GAG TTT GCG ATC CGA AGG CG GTG GCC CC TTG CTA ATC CAA CAG GGA CTA CAC (1157) ATT GAC TCC AGC ATT GG GAG TTT GCC ATC CGA AGG GCT GGA CCG TTC TTA GAT CCA ACA GGA CAC CAT CAC ASA AAA AT GAA TGG GAC CAG CCA GAT CGG TTT ATG CTG GAG CAC TT GGA GAA CAC CAT TCC ATT CCA ASP Lys Asn Glu Trp Asp Gln Pro Asp Arg Phe Met Pro Glu Arg Phe Leu Asp Pro Thr Gly Ser His Leu His His (1307) ATA AAA ATG GA CCC AGG CTA GCC CTG CGG GGT CGC GGT CCC GG TCT GGA GAG AGC CAT CTC ATT Asp Lys Asn Glu Trp Asp Gln Pro Asp Arg Phe Met Pro Glu Arg Phe Leu Asp Pro Thr Gly Ser His Leu His His (1457) CTC TTT ATC TTC ATG GCC TTG CTG CAG CGG GTT GAG CCC TTG GGA CTA GAC AAA CAG CTG CGC CGG CAG GAG Thr Pro Thr Pro Ser Tyr	1/6	GAG	сст	АТТ	GTG	GAT	GTC	CTG	GGC	CAC	AGC	GAT	CTG	GTG	GAC	АТА	ттс	CCG	TGG	TTG	AAG	ATT	TTT	ccc	AAT
(782) ARA ARC TIG GAA ATG ATA ARG GAA CAC ACT ARA ATT CGA GAA ARA ACA CTG GTT GAA ATG TTT GAA ARA TGC ATA (857) 226 226 226 226 226 226 226 22	Thr	Glu	Gly	Ile	Val	Asp	Val	Leu	Gly	His	Ser	Asp	Leu	Val	Asp	Ile	Phe	Pro	Trp	Leu	Lys	Ile	Phe	Pro	Asn
AAA AAC TTG GAA ATG ATA AAG GAA CAC ACT AAA ATT CGA GAA AAA ACC TG GTT GAA ATG TTT GAA AAT TC CAAG GU Met ILe Lys Glu His Thr Lys ILe Arg Glu Lys Thr Leu Val Glu Met Phe Glu Lys Cys Lys (857) GAG AAA TTC AAT AGT GAA TCT CTC TCC CAGC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG ATA GCA GAA AAT AAT GAT TC AAT AGT GAA TCT CTC TCC CAGC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG ATA GCA GAA AAT AAT S10 Lys Phe Asn Ser Glu Ser Leu Ser Ser Leu Thr Asp ILe Leu ILe Gln ALA Lys Met Asn ALA GLU ASN ANT (932) (1007) ACC ATG GGG GAA GCC CAG GAC CCA AGT GTG TTC TCA GAT AAG CAT ATC CTG GTG CAC AAT CCT GAG GAC ACT TTT GGG AAA AAG AGG AAT AGT GGG GAA GCC CAG GAC CCA AGT GTG TTC TCA GAT AAG CTG GTT TCC TG GTG CAC AAT CCT GAG GAG AGG AAG AGG AAA TT AGC CAG TAT GTG GTG CTG AAC TGG ATC CTG GTT TCC AGA CAA CCT GTT GGA GAG AGG AAG AGG AAA TT AGC CAG TAT GTA GGC TTC AGT AGA CAA CCT G GTT TCC AAT GAC CAC TTC CTG GTG CAC AAT CCT GGA GAC ACT CCC TC CTC Lys ILe GLu Thr Thr Ser Ser Val Leu Asn Trp ILE Leu ALA Phe Leu Val His Asn Pro Glu Val Lys Arg (1082) AGA CT CAA AAG GAG ATT GAC CAG TAT GTA GGC TT CAT AGT CGG GTG GCC CCT TTC AAT GAC CAG ACT CAC CTC CTC CTC Lys ILe GLu FLU TLE ATG GLU AST ILE ATG TLC CGA GAG GTG GTT CCT AGT GAC CAC CTG CTT CAT ACC CAC ACA GGA GCC ACT ATC CGA AGA GTG CTT CAT AGT CAC CAC GTG GTG CCC CTG CTG CTC CAC CAC ACA CAC CAC CAC CAC CAC CAC	201		1			•			-			-			-										(782)
Lys Asn Leu Glu Met Tie Lys Glu His Thr Lys Tie Arg Glu Lys Thr Leu Val Glu Met Phe Glu Lys Cys Lys (857) GAG AAA TTC AAT AGT GAA TCT CTC TC CA GC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG AAT GCA GAA AAT AAT Glu Lys Phe Asn Ser Glu Ser Leu Ser Ser Leu Thr Asp Ile Leu Ile Gln Ala Lys Met Asn Ala Glu Asn Asn Glu Gly Glu Gly Gln Asp Pro Ser Val Phe Ser Asp Lys His Tile Leu Val Thr Val Gly Asp Tile Phe Gly (1007) GCA GGC AA GAC ACT AGC TCT GTG TC TCA GAT AAG CAT ATC CTT GTC ACG GTG GAC AAT CTT GGG GAA ACT AGG GAA ACT AGC TCT GTG TG TG TG TA TAG ATC CTG GCT TTC CTG GTG CAC AAT CCT GAG GTG AAG Asn Thr Gly Glu Gly Gln Asp Pro Ser Val Phe Ser Asp Lys His Tile Leu Val Thr Val Gly Asp Tile Phe Gly (1007) GCA GGC ATA GAG ACA ACT AGC TCT GTG TG GTG TTC AGT GGA TTC CTG GTG GAC AAT CCT GAG GTG AAG AGA GAC AAT GAA GAG ATT GAC CAG TAT GTA GGC TTC AGT GAA ACC GG TCT TTC AAT GAC CGG ACT CAC CTC CTC Lys Tile Glu Thr Thr Ser Ser Val Leu Asn Trp Tile Leu Ala Phe Leu Val His Asn Pro Glu Val Lys Arg (1082) AGA ACT CAA AAG GAG ATT GAC CAG TAT GTA GGC TTC AGT GAA ACA CGG TCT TTC AAT GAC CGG ACT CAC CTC CTC Lys Tile Glu Lys Glu Te Asp Gln Tyr Val Gly Phe Ser Arg Thr Pro Ser Phe Asn Asp Arg Thr His Leu Leu 126 ATT GAC CCC ACT ATC CGA GAA GTG CTT CGT ATC AGG CGG GTG GCC CCC TTG CTC ATC CAC CAC CAC CAC CAC (1157) ATT GAC TCC AGC ATT GGA GAG TTT GCC ATC CGG AGG GAC ACA CAT GTG ATC ATC ATC TT GG GCA CTG CAT CAC 116 Asp Ser Ser TIE GLY GLU Phe ALT TE Pro Lys Asp Thr His Val TIE TE Asn Leu Trp ALa Leu His His 116 ATT AAA AAT GAA TGA GAC CAG CCA GAT CGG TTT ATG CCT GAG CGC TTC TTA GAT CCA ACA GGA GCC CAG CCA GT CTG TTC GGA GCT GTC CCC GA TCG TG ATC GGA GGA GCT CTG GCC CGA GAG CCC ACA CCA GCA GCA GAG CAG C	AAA	AAC	TTG	GAA	ATG	ATA	AAG	GAA	CAC	ACT	AAA	ATT	CGA	GAA	AAA -	ACA	CTG	GTT	GAA	ATG	TTT	GAA	AAA	TGC	AAG
226 AAA TTC AAT AGT GAA TCT CTC TCC AGC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG AAT GCA GAA AAT AAT GAA ATT CAT GAG GAA AGT GAA TTC CTC TCC AGC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG ATA GCA GAA AAT AAT GU Lys Phe Asn Ser Glu Ser Leu Ser Ser Leu Thr Asp Ile Leu Ile GIn Ala Lys Met Asn Ala GLu Asn Asn (332) AAC ACT GGG GAA GCC CAG GAC CCA AGT GTG TTC TCA GAT AAG CAT ATC CTT GTC ACG GTG GGA GAC ATT TTT GGG GGA ATT TTT Val Gly Glu Gly Gln Asp Pro Ser Val Phe Ser Asp Lys His Ile Leu Val Thr Val Gly Asp Ile Phe Gly (1007) GCA GCC ATA GAG ACA ACT AGC TCT GTG CTG AAC TGG ATC GTG GAT CTG GTG TTC TCG GTG CAC AAT CCT GAG GTG AAG AGG AAT AGT GAC CAG TAT GAC CAG TAT GTA GGA GCT TA GGA ACA CCG GTT TTC TA AT GAC CGG ACT CAC CTC CTC Jala Gly Ile Glu Thr Thr Ser Ser Val Leu Asn Trp Ile Leu Ala Phe Leu Val His Asn Pro Glu Val Lys Arg (1082) JAG ATT GAC CAG ATA GGT GTT GGT ATG GGA ACA CCG GTG GCC CCC TTG CTC ATT GAC CAC CTC CTC JATC CTG GAG GCC ACT ATC CGA GAA GTG GTT CGT ATC AGG CCG GTG GCC CCC TTG CTC ATC CCA CAC AAG GCT AAC JAG GTT ATT ILe Arg Glu Val Leu Arg Ile Arg Pro Val Ala Pro Leu Leu Ile Pro His Lys Ala Asn (1157) JATT GAC TCC AGC ATT GGA GAG TTT GCC ATC CCG AAG GAC ACA CAT GTG ATC GAT CAC CTC GG AC CTC CAT CAC CAC AGT CAC CTC ATT CAG GAA CAC CTC GAG GAC CAT GTG ATT GAA GAG GAC CAT GTG ATT GAC CCG GAG GCT GAT CAC CTC GAG GAC CAT CTC ATT GAG CCC ACA CAC CCA GAC GAG TTT AGC CTC GAG GCT GCC CCC TTG CTC ATT CAG GAC CAT CTC ATT GAG GAC CCC AC AC TTG GAG GAG TTT AGC CT GGA GCC GTT CTA GAG GAC CTT CTA GGA GAC CTT CTA TAG CCC ACA CCC AGT GAC CAG GAC CAT GTG ATT GGA GCC TTG GAG CCC TG GCC CGG CGG CTG CTG GCC CGG CAG CAT CTC ATT AGA CCCA ACA CCC AGT GAC TAT TTA CCC TC GCG GGA CCG GGT CCC CTG CTG CTG CTG CTG CTG CTG	Lys	Asn	Leu	Glu	Met	Ile	Lys	Glu	His	Thr	Lys	11e	Arg	GIU	Lys	Thr	Leu	Val	GIU	Met	rne	GIU	Lys	cys	Lys (857)
Giu Lys Phe Asn Ser Giu Ser Leu Ser Ser Leu Thr Asp IIe Leu IIe Gin Ala Lys Met Asn Ala Giu Asn Asn (932) AC ACT GGG GAA GGC CAG GAC CCA AGT GTG TTC TCA GAT AAG CAT ATC CTT GTC ACG GTG GGA GAC ATC TTT GGG Asn Thr Gly Giu Gip Gin Asp Pro Ser Val Phe Ser Asp Lys His IIe Leu Val Thr Val Gip Asp IIe Phe Gly (1007) GCA GGC ATA GAG ACA ACT AGC TCT GTG CTG AAC TGG ATC CTG GCT TTC CTG GTG CAC AAT CCT GAG GTG AAG AG Ala Giy IIe Glu Thr Thr Ser Ser Val Leu Asn Trp IIe Leu Ala Phe Leu Val His Asn Pro Glu Val Lys Arg (1082) AAG ATC CAA AAG GAG ATT GAC CAG TAT GTA GGC TTC AGT CGA ACA CCG TCT TTC AAT GAC CGG ACT CAC CTC CTC Lys IIe Gin Lys Giu 11e Asp Gin Tyr Val Giy Phe Ser Arg Thr Pro Ser Phe Asn Asp Arg Thr His Leu Lau (1157) ATG CTG GAG GCC ACT ATC CGA GAA GTG CTT CGT ATC AGG CGG GTG GCC CCC TTG CTA ATC CAC AGA GGC AAA Met Leu Giu Ala Thr IIe Arg Giu Val Leu Arg IIe Arg Pro Val Ala Pro Leu Leu IIe Pro His Lys Ala Asn (1222) ATT GAC TCC AGC ATT GGA GAG ATT GCC ATC CCG AAG GAC ACA CAC ACA GTG GTC ATC ATC AGA GCA TAC AAA AAT GAA TGG GAC CAG CAT GC CTT CCT ATG CGA ACA CCC GT TT TA AAT CTC TG GGA AGC CAT CAC IIe Asp Ser Ser IIe Giy Giu Phe Ala IIe Pro Lys Asp Thr His Val IIe IIe Asn Leu Trp Ala Leu His His (1307) GAT AAA AAT GAA TGG GAC CAG CTA GTC GGA GGT CGC GGG CCC CGA TG GAT GAC CAC GGA AGC CAT CTC ATT ASP Lys Asn Glu Trp Asp Gin Pro Asp Arg Phe Met Pro Glu Arg Phe Leu Asp Pro Thr Gly Ser His Leu IIe (1382) ACA CCC ACA CCC AGT TAT CA GCA GAG CGG GGT CCC GGA TGG GCC CGG ATT GAC GCC GG CAG GAC ACC CAT CAC CCG AGT TAT TTA CCC TTC GGA GGT GGT CCC GGA TGA GAC GAT GAC ATG GAC ACA CACA GAA GCA TG GCC CGG CAG GAG ACT CTT TATC TTC ATG GCC TTG CTG CTG GGA GCT GGT CCC GGA TGA GAT GAC CAA GCA TGC CC GG GG CCC GG GAC CCC AGG TAT TTA CCC TTC GAG AGC TTT GAC TTT GAT GGT GAA AAT CACA GTG GCC CGG CAG GAG ATT Fro Thr Pro Ser Tyr Leu Pro Phe Gly Ala GIP Pro Asp Phe Asp Pha Asp Lys Gin Leu Pro Cys Leu (1382) ACA CCC ACA CCC AG GTT GTG CTG CTG GAC CAC CTT TTC AAA GTG GAA AATC ACA GTG GCA CAA GCA TGG AGG AGC CTT GTG	GAG	AAA	ттс	ААТ	AGT	GAA	TCT	стс	тсс	AGC	CTG	ACA	GAC	ATT	CTG	АТА	CAA	GCC	AAG	ATG	ААТ	GCA	GAA	AAT	AAT
(32) AC ACT GG GAA GGC CAG GAC CCA AGT GTG TTC TCA GAT AAG CAT ATC CTT GTC ACG GTG GGA GAC ATC TTT GGG Asn Thr Gly Glu Gly Gln Asp Pro Ser Val Phe Ser Asp Lys His Ile Leu Val Thr Val Gly Asp Ile Phe Gly (1007) GCA GGC ATA GAG ACA ACT AGC TCT GTG CTG AAC TGG ATC CTG GCT TTC CTG GTG CAC AAT CCT GAG GTG AAG AGG Ala Gly Ile Glu Thr Thr Ser Ser Val Leu Asn Trp Ile Leu Ala Phe Leu Val His Asn Pro Glu Val Lys Arg (1027) AGA ACT CAA AAG GAG ATT GAC CAG TAT GTA GGC TTC AGT CGA ACA CCG TCT TTC AAT GAC CGG ACT CAC CTC CTC (1027) AGA ATC CAA AAG GAG ATT GAC CAG TAT GTA GGC TTC AGT CGA ACA CCG TCT TTC AAT GAC CGG ACT CAC CCC CTC (1027) AGG ATC CAA AAG GAG ATT I GAC CAG TAT GTA GGC TTC AGT CGA ACA CCG TCT TTC AAT ASA ASP Arg Thr His Leu Leu (1157) ATG CTG GAG GCC ACT ATC CGA GAA GTG CTT CGT ATC AGG CCG GTG GCC CCC TTG CTA ATC ACA CAC ACA AG GCT AAC Met Leu Glu Ala Thr Ile Arg Glu Val Leu Arg Ile Arg Pro Val Ala Pro Leu Leu Ile Pro His Lys Ala Asn (1232) ATT GAC TCC AGC AAT GGA GAT TTG CCA ATC CCG AAG GAC ACA CAT GTG ATC ATC AAT CTC TG G GAC CTG CAC CAC (1237) ATT AAA AAT GAA TGG GAC CAG CCA GAT CGG TTT ATG CCT GAG CCC TTC TTA GAT CAA CAC GGA ACC CAT CTC ATT Asp Lys Asn Glu TTP Asp Gln Pro Asp Arg Phe Met Pro Glu Arg Phe Leu Asp Pro Thr Gly Ser His Leu Ile (1382) ACA CCC ACA CCC AGT TAT GTG CTG CGC GGA CGG TCC GGA CGC TTC TTA GAT CAA CAG GA ACC CTG CCC GG CAC GAC Thr Pro Thr Pro Ser Tyr Leu Pro Phe Gly Ala Gly Pro Arg Ser Cys Ile Gly Glu Ala Leu Ala Arg Gln Glu (1457) CTC TTT ATC TTC ATG GCC TTG CTG CTG GAC GAG GTT GAC TTT GAT GTG TCA GAT GAC AAA CAG CTG CCC TG TC TC Leu Phe Ile Phe Met Ala Leu Leu Leu Glu Arg Phe Asp Phe Asp Val Ser Asp Asp Lys Gln Leu Pro Cys Leu (1532) GTG GAT GAC CCC AAG GTG GTC TTT CTG ATC GAC CTT TTC AAA GTG AAA ATC ACA GTG GCA CAA GCA TGG AAA GAC TTG CAT CTT TTA ATC TTC ATG GGC TTG CTG CTG GAC CAC CTT TTC AAA GTG AAA ATC ACA GTG CGA CAA GCA TGG AAA GAC TGG CTG TC CTG GGT GAC CCC AAG GTG	Glu	Lys	Phe	Asn	Ser	Glu	Ser	Leu	Ser	Ser	Leu	Thr	Asp	Ile	Leu	Ile	Gln	Ala	Lys	Met	Asn	Ala	Glu	Asn	Asn
AAC ACT GGG GAA GGC CAG GAC CCA AGT GTG TTC TCA GAT AG CAT ATC CTT GTC ACG GTG GGA GAC ATC TTT GGG Asn Thr Gly Glu Gly Gln Asp Pro Ser Val Phe Ser Asp Lys His Ile Leu Val Thr Val Gly Asp Ile Phe Gly (1007) GGG GAC ACA ACT AGC TCT GTG CTG AAC TGG ATC GGA TTC CTG GCT TTC CAG GTG CAC ATT CCT GAG GAG ATC AGC (1082) Ala Gly Ile Glu Thr Thr Ser Ser Val Leu Asn Trp Ile Leu Ala Phe Leu Val His Asn Pro Glu Val Lys Arg (1082) Ala ATC CAA AAG GAG ATT GAC CAG TAT GTA GGC TTC AGT GGA ACA CCG TCT TTC AAT GAC CGG ACT CCT CTC TL Ala Glu Si Lie Glu Thr Thr Ser Ser Val Leu Asn Trp Ile Leu Ala Phe Leu Val His Asn Pro Glu Val Lys Arg (1082) Ala ATC CAA AAG GAG ATT GAC CAG TAT GTA GGC TTC AGT GGA ACA CCG TCT TTC AAT GAC CGG ACT CCT CTC TC Ala GLU Si Lieu Ash GAG GAG ATT GAC CAG TAT GTA GGC TTC ATT GGT ACG GA ACA CCT TTC AAT GAC CGG ACT CCT CTC TTC AAT ASP Arg Thr His Leu Leu Lau Glu Ala Thr Ile Arg GLU Val Leu Arg Ile Arg Pro Val Ala Pro Leu Leu TI Lev AIG ACA CAC ATT GGA CAC ATC AAT CTC ACC ACC CAC CAC CAC CA	251	-																							(932)
As in the Gly Glu Gly Glu Gly Glu Gly Glu Asp Pro Ser Val Pre Val Gly Val Glu Val Gly Val	AAC	ACT	GGG	GAA	GGC	CAG	GAC	CCA	AGT	GTG	TTC	TCA	GAT	AAG	CAT	ATC	CTT	GTC	ACG	GTG	GGA	GAC	ATC	TTT	GGG
ACAGGCATAGAGACAACTAGCTCTGTGCTGAACTGGATCCTGGTTCTGGTGCTGGTGCTGGAGAAGAlaGluIhThrThrThrSerSerValLeuAsnTrpIleLeuAlaPheLeuValHisAsnProGluValLysArgArgArgAndAAGACCCAGATTGACGAGTTTGTAGGCGGCTTTATGAAGACCCGTTTTTCAATGAAGACCCGTTTCAAAAGAAGAGCCACCTCATCCAACAACTC <td>Asn 276</td> <td>Thr</td> <td>GIY</td> <td>GIU</td> <td>GIY</td> <td>GIN</td> <td>Asp</td> <td>Pro</td> <td>Ser</td> <td>Val</td> <td>Phe</td> <td>ser</td> <td>Asp</td> <td>Lys</td> <td>HIS</td> <td>116</td> <td>Leu</td> <td>Vai</td> <td>Inr</td> <td>vai</td> <td>GIY</td> <td>Asp</td> <td>116</td> <td>rne</td> <td>(1007)</td>	Asn 276	Thr	GIY	GIU	GIY	GIN	Asp	Pro	Ser	Val	Phe	ser	Asp	Lys	HIS	116	Leu	Vai	Inr	vai	GIY	Asp	116	rne	(1007)
Ala Gly Ile Glu Thr Thr Ser Ser Val Leu Asn Trp Ile Leu Ala Phe Leu Val His Asn Pro Glu Val Lys Arg 301 AGA ATC CAA AAG GAG ATT GAC CAC TT CAC CA	GCA	GGC	ATA	GAG	ACA	ACT	AGC	тст	GTG	CTG	AAC	TGG	ATC	CTG	GCT	TTC	CTG	GTG	CAC	AAT	CCT	GAG	GTG	AAG	AGG
301 (1082) AAG ATC CAA AAG GGA ATT GAC CAG TT GTC TT AAT GAC CGG ACT CAC CTC TT TT TT AAT GAC CGG ACT CAC CTC AAC CTC TT TT TT GAC CCG AAG GTC CTC CTC ATT GAC CTC AAG GTC TT CTC AAG TT TT TT CT GTC ATT GAC CTC ATT GAC GTC ATT GAC GTC ATT GTC ATT GTC ATT GTC ATT AAG GTC ATT GTC GTC GTC ATT GTC	Ala	Gly	Ile	Glu	Thr	Thr	Ser	Ser	Val	Leu	Asn	Trp	Ile	Leu	Ala	Phe	Leu	Val	His	Asn	Pro	Glu	Val	Lys	Arg
AAG ATC CAA ARG GAC ATT GAC CAG TAT GTA GGA GTG CTT CAT GTA GGC TTC CTT CAT GAC CCG TTG CTC ATC CGG ACT CCC CCC TTG CTC ATC CGG ACT CCC CGA AGG GTG GCC CCC TTG CTC ATC CCA CAC AAG GCC TACCCAC CCC CTG CTG CTC ATC CCA CAC AAG GCC TACC326326326326327328 <td>301</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>a a</td> <td>~ ~ ~</td> <td>m m</td> <td></td> <td></td> <td>mmo</td> <td>3 C III</td> <td>661</td> <td>101</td> <td></td> <td>mem</td> <td></td> <td></td> <td>C 2 C</td> <td></td> <td>ACT</td> <td>CAC</td> <td>CTC</td> <td>(1082)</td>	301						a a	~ ~ ~	m m			mmo	3 C III	66 1	101		mem			C 2 C		ACT	CA C	CTC	(1082)
Jy Tre off Try off off Try off off try the off try try the off try try try the off try try try try try try try off off try	AAG	ATC	CAA	AAG	GAG	ATT	GAC Agn	Gln	TAT	GTA Val	GGC	Phe	Ser	Ara	Thr	Pro	Ser	Phe	AAI	Asp	Aro	Thr	His	Leu	Leu
ATG CTG GAG GCC ATC ATC CGA GAA GTG CTT CGT ATC AGG CCG GTG GCC TTG CTC ATC CAC CAA GGC AAC Met Leu Alu Alu Trr ILe Arg Glu Ala Pro Leu Leu ILe AA ILe ILe AI ILe Ar CCG AA CA C	326	110	01	2,5	010	110	1155	01	-1-	vur	01]														(1157)
Met Leu Glu Ala Thr The Arg Glu Val Leu Arg Pro Val Ala Pro Leu Leu Ile Pro His Lys Ala Asn (1232) ATT GAC TCC AGC ATT GGA GTT GCC ATC CCG AAC CAT GTG ATC AAT CTC TGG GCA CTG CAC CAC CAT GTC AAT GCA CTT GCC ATC CCG AAT GTC CAC AAA AAT TAT TAC CCC TAT TAT ATA CCC TTC	ATG	CTG	GAG	GCC	ACT	ATC	CGA	GAA	GTG	CTT	CGT	ATC	AGG	CCG	GTG	GCC	ccc	TTG	CTC	ATC	CCA	CAC	AAG	GCT	AAC
ATT GAC TCC AGC ATT GGA GAG TTT GCC ATC CCG AAG GAA CAT GTG ATC ATC AAT CTC AGC ACT CGG ATC CTC AAT CTC CGG CAC CCG AAG GAA CAT GTG ATC ATC ATC AAT CTC TGG GCA CAT CAT CCC AGC ATT GGA GAG CAT CAT CCC AAA AAT GAA TGG GAC CAG CAG GAG TTT ATT ATT ATT GAG CCA GAC CAG CAG CAT CTC ATT His Val Val Val ATT AAA AAT GAA TGG GAC CAG CAC CAG CAG CAG CAG CAG CAG CAG CAG TTT TTA CCC TTA TTA TTA CCC TTA TTA CCC TTA TTA CCC TTA TTA TTA C	Met	Leu	Glu	Ala	Thr	Ile	Arg	Glu	Val	Leu	Arg	Ile	Arg	Pro	Val	Ala	Pro	Leu	Leu	Ile	Pro	His	Lys	Ala	Asn
All GAC ICC ACC ACT IL GOA GAG THI GCC ALC CCG ALC GAC GAC ACT IL ALC ALL CLC ALC ALC ICC ICC CAL CLC CLL CLC ALC ICC ALC ICC ICC ICC ICC ICC ICC ICC ICC ICC I	351 877	CAC	TCC	ACC	እጥጥ	CON	CNG	ጥጥጥ	ccc	ልጥሮ	ccc	MAG	GAC	ACA	СУД	GTG	ATC	እጥር	דגג	стс	тсс	601	CTG	САТ	(1232)
376(1307)GAT AAA AAT GAA TGG GAC CAG CCA GAT CGG TTT ATG CCT GAG CGC TTC TTA GAT CCA ACA GGA AGC CAT CTC ATTAsp Lys Asn Glu Trp Asp Gln Pro Asp Arg Phe Met Pro Glu Arg Phe Leu Asp Pro Thr Gly Ser His Leu Ile401401ACA CCC ACA CCC AGT TAT TTA CCC TTC GGA GCT GGT CCC CGA TCG TGC ATT GGA GAG GCT CTG GCC CGG CAG GAGACA CCC ACA CCC AGT TAT TTA CCC TTC GGA GCT GGT CCC CGA TCG TGC ATT GGA GAG GCT CTG GCC CGG CAG GAGThe Pro The Pro Ser Tyr Leu Pro Phe Gly Ala Gly Pro Arg Ser Cys Ile Gly Glu Ala Leu Ala Arg Gln Glu426426426426426426426427428429429429420420421421422423424424425426426427428429429429420420421421422423424424425426427428429429420421421421422423424424424425426427428429429429420421421421422423424	Ile	Aso	Ser	Ser	Ile	Glv	Glu	Phe	Ala	Ile	Pro	Lvs	Asp	Thr	His	Val	Ile	Ile	Asn	Leu	Tro	Ala	Leu	His	His
GAT AAA AAT GAA TGG GAC CAG CCA GAT CGG TT ATG CCT GAG CGA TT ATG CT ATG CCA ATT TTA ASP GIn Pro Asp Arg Pro And Arg Pro GIn Pro TT ATG CCC GG TT ATG CCC GG CTT ATG CGA CGC TT ATG CCC ATG Pro Pro TTr GIN Pro Ser TT TT CCC TT GGA GGT CCC CGG CGG CCC CGA CG TT GGA GGA GGT CCC CTG TT TT CCC TT CCC TT CCC TT ATG GGA GGA GGA GGA GGA GGA GGA GGA CTC TT TT </td <td>376</td> <td>F</td> <td></td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>-1</td> <td>····t</td> <td></td> <td>(1307)</td>	376	F				1						-1	···· t												(1307)
Asp Lys Asn Glu Trp Asp Gln Pro Asp Arg Phe Met Pro Glu Arg Pho Leu Asp Pro Thr Gly Ser His Leu Ile 401 4	GAT	AAA	AAT	GAA	TGG	GAC	CAG	CCA	GAT	CGG	TTT	ATG	CCT	GAG	CGC	TŤC	TTA	GAT	CCA	ACA	GGA	AGC	CAT	CTC	ATT
401 11321 ACA CCC ACA CCC AGT TAT TTA CCC TTC GGA GCT GGT CCC CGA TCG TGC ATT GGA GAG GCT CTG GCC CGG CAG GAG Thr Pro Thr Pro Ser Tyr Leu Pro Phe Gly Ala Gly Pro Arg Ser Cys Ile Gly Glu Ala Leu Ala Arg Gln Glu 426 CTC TTT ATC TTC ATG GCC TTG CTG CTG CAG AGG TTT GAC TTT GAT GTG TCA GAT GAC AAA CAG CTG CCC TGT CTG Leu Phe Ile Phe Met Ala Leu Leu Leu Gln Arg Phe Asp Phe Asp Val Ser Asp Asp Lys Gln Leu Pro Cys Leu 451 GTG GGT GAC CCC AAG GTG GTC TTT CTG ATC GAC CCT TTC AAA GTG AAA ATC ACA GTG CGA CAA GCA TGG AAG GAT 451 GTG GGT GAC CCC AAG GTG GTC TTT CTG ATC GAC CCT TTC AAA GTG AAA ATC ACA GTG CGA CAA GCA TGG AAG GAT 451 GTG GGT GAC CCC AAG GTG GTC TTT CTG ATC GAC CCT TTC AAA GTG AAA ATC ACA GTG CGA CAA GCA TGG AAG GAT Val Gly Asp Pro Lys Val Val Phe Leu Ile Asp Pro Phe Lys Val Lys Ile Thr Val Arg Gln Ala Trp Lys Asp 476 GTA GAG GTT GAG GTT AGC ACC TAG Aggecgaatctaacgtccggatcccatgccttgacacccacgccaatcttagaggtgcctccaacatcctc Ala Gln Val Glu Val Ser Thr End	Asp	Lys	Asn	Glu	Τrp	Asp	Gln	Pro	Asp	Arg	Phe	Met	Pro	Glu	Arg	Phe	Leu	Asp	Pro	Thr	Gly	Ser	His	Leu	Ile
The Pro The Pro Ser Tyr Leu Pro Phe Gly Ala Gly Pro Arg Ser Cys Ile Gly Glu Ala Leu Ala Arg Gln Glu (1457) CTC TTT ATC TTC ATG GCC TTG CTG CTG CAG AGG TTT GAC TTT GAT GTG TCA GAT GAC AAA CAG CTG CCC TGT CTG Leu Phe Ile Phe Met Ala Leu Leu Leu Gln Arg Phe Asp Phe Asp Val Ser Asp Asp Lys Gln Leu Pro Cys Leu (1532) GTG GGT GAC CCC AAG GTG GTC TTT CTG ATC GAC CCT TTC AAA GTG AAA ATC ACA GTG CGA CAA GCA TGG AAG GAT Val Gly Asp Pro Lys Val Val Phe Leu Ile Asp Pro Phe Lys Val Lys Ile Thr Val Arg Gln Ala Trp Lys Asp (1631) GCA CAG GTT GAG GTT AGC ACC TAG aggecgaatctaacgtccggatcccatgccttgacacccacagcccaatcttagaggtgcctccaacaatcctcc Ala Gln Val Glu Val Ser Thr End	401 ACA	ccc	202	ccc	ACT	ጥልጥ	ጥጥል	ccc	TTC	663	CCT	CGT	ccc	CGA	TCG	TCC	ልጥጥ	GGA	GAG	CCT	CTG	600	CGG	CAG	(1382) GAG
426 (1457) CTC TTT ATC TTC ATG GCC TTG CTG CTG CAG AGG TTT GAC TTT GAT GTG TCA GAT GAC AAA CAG CTG CCC TGT CTG Leu Phe Ile Phe Met Ala Leu Leu Gln Arg Phe Asp Phe Asp Val Ser Asp Asp Lys Gln Leu Pro Cys Leu 451 GTG GGT GAC CCC AAG GTG GTC TTT CTG ATC GAC CCT TTC AAA GTG AAA ATC ACA GTG CGA CAA GCA TGG AAG GAT Val Gly Asp Pro Lys Val Val Phe Leu Ile Asp Pro Phe Lys Val Lys Ile Thr Val Arg Gln Ala Trp Lys Asp 476 GCA CAG GTT GAG GTT AGC ACC TAG aggccgaatctaacgtccggatcccatgccttgacacccacagcccaatcttagaggtgcctccaacaatcctcc Ala Gln Val Glu Val Ser Thr End	Thr	Pro	Thr	Pro	Ser	Tvr	Leu	Pro	Phe	Glv	Ala	Gly	Pro	Arg	Ser	Cvs	Ile	Glv	Glu	Ala	Leu	Ala	Arg	Gln	Glu
CTC TTC ATG GCC TTG CTG CTG CAG AGG TTT GAC TTT GAT GAC GAT GAC CAG CTG C	426									4		- 4						-4					-		(1457)
Leu Phe Ile Phe Met Ala Leu Leu Con Arg Phe Asp Phe Asp Val Ser Asp Asp Lys Gln Leu Pro Cys Leu (1532) GTG GGT GAC CCC AAG GTG GTC TTT CTG ATC GAC CCT TTC AAA GTG AAA ATC ACA GTG CGA CAA GCA TGG AAG GAT Val Gly Asp Pro Lys Val Val Phe Leu Ile Asp Pro Phe Lys Val Lys Ile Thr Val Arg Gln Ala Trp Lys Asp 476 GCA CAG GTT GAG GTT AGC ACC TAG aggecgaatetaacgtecggateceatgeettgacaceeacageecaatettagaggtgeetecaacateetec Ala Gln Val Glu Val Ser Thr End 501	CTC	TTT	ATC	TTC	ATG	GCC	TTG	CTG	CTG	CAG	AGG	TTT	GAC	TTT	GAT	GTG	TCA	GAT	GAC	AAA	CAG	CTG	ccc	TGT	CTG
(1532) GTG GGT GAC CCC AAG GTG GTC TTT CTG ATC GAC CCT TTC AAA GTG AAA ATC ACA GTG CGA CAA GCA TGG AAG GAT Val Gly Asp Pro Lys Val Val Phe Leu Ile Asp Pro Phe Lys Val Lys Ile Thr Val Arg Gln Ala Trp Lys Asp 476 GCA CAG GTT GAG GTT AGC ACC TAG aggecgaatetaacgtecggateceatgeettgacaceeacageecaatettagaggtgeetecaacaateetee Ala Gln Val Glu Val Ser Thr End 501	Leu	Phe	Ile	Phe	Met	Ala	Leu	Leu	Leu	Gln	Arg	Phe	Asp	Phe	Азр	Val	Ser	Asp	Asp	Lys	Gln	Leu	Pro	Cys	Leu
Val Gly Asp Pro Lys Val Val Phe Leu Ile Asp Pro Phe Lys Val Lys Ile Thr Val Arg Gln Ala Trp Lys Asp 476 (1631) GCA CAG GTT GAG GTT AGC ACC TAG aggecgaatetaacgteeggateceatgeettgacacceacageecaatettagaggtgeetecaacaateetee Ala Gln Val Glu Val Ser Thr End 501	951 GTG	GGT	GAC	ccc	AAG	GTG	GTC	<u> </u>	CTG	ATC	GAC	CCT	TTC	ааа	GTG	AAA	АТС	ACA	GTG	CGA	CAA	GCA	TGG	AAG	(1332) GAT
476 (1631) GCA CAG GTT GAG GTT AGC ACC TAG aggccgaatctaacgtccggatcccatgccttgacacccacagcccaatcttagaggtgcctccaacaatcctcc Ala Gln Val Glu Val Ser Thr End 501	Val	Gly	Asp	Pro	Lys	Val	Val	Phe	Leu	Ile	Asp	Pro	Phe	Lys	Val	Lys	Ile	Thr	Val	Arg	Gln	Ala	Trp	Lys	Азр
GCA CAG GTT GAG GTT AGC ACC TAG aggeogaatetaacgtooggateceatgeettgacaceeacageeeaatettagaggtgeeteeaacaateetee Ala Gln Val Glu Val Ser Thr End 501	476	-	-		-						-			-		-				-			-		(1631)
ALA GIN VAL GIU VAL SER THR ENG 501	GCA	CAG	GTT	GAG	GTT	AGC	ACC	TAG	aggo	cgaai	tctaa	cgtc	cggat	cccai	tgcct	tgac	accca	cage	ccaat	ctta	gaggt	gcct	ccaac	aatc	ctcc
	ALA 501	GIN	Val	GIU	Val	Ser	Thr	End																	

tcactcctatcccgttttctacttggcagcaatgaagggtgaagacacat<u>attaaa</u>ggttttccaataaaaaaaaaaaaaaaaa

FIG. 2. Nucleotide and predicted amino acid sequence of mouse $P450_{17\alpha}$. The putative poly(A) addition signal is underlined. Numbers on the left and under the line indicate the amino acid position. Numbers on the right, above the line and in parentheses, indicate the nucleotide position.

(1715)

SHORT COMMUNICATION

Mouse:	MWELVGLLLLILAYFFWPKSKTPNAKFPRSLPFLPLVGSLPFLPRRGHMHANFFKLQEKYGPIYSLRLGT	70
Human: Bovine:	HKKV-M 	
Mouse: Rat: Human: Bovine:	$\label{eq:transform} \begin{split} &TTAVIVGHYQLAREVLVKKGKEFSGRPQMVTLGLLSDQGKGVAFADSSSSWQLHRKLVFSTFSLFRD \bullet DQK &-TIIK-G\bulletQSAGHK-G\bulletK-G$	140
Mouse: Rat: Human: Bovine:	LEKMICQEANSLCDLILTYDGESRDLSTLIFKSVINIICTICFNISFENKDPILTTIQTFTEGIVDVLGH LY-KNKA-KIAT-D ISTMLA-HN-Q-I-I-FPV-VA-T-V-SLT-YK-GE-NVNYNI-N-SK I-NFLA-QHAIEPLSLA-TSFF-K-EA-KA-QNVNDLESK	210
Mouse: Rat: Human: Bovine:	SDLVDIFPWLKIFPNKNLEMIKEHTKIREKTLVEMFEKCKEKFNSESLSSLTDILIQAKMNAENNNTGEG RNTGVGYA-V-NEV-TGIRD-Q-ISDSDSC DSLVTKL-S-VNDL-NKIL-NYR-D-ITNML-T-MSD-G-A-PD EV-LVS-AM-KM-GCVQT-NELLN-ILQ-N-S-D-ITN-LHVDA-PD	280
Mouse: Rat: Human: Bovine:	QDPSVFSDKHILVTVGDIFGAGIETTSSVLNWILAFLVHNPEVKRKIQKEIDQYVGFSRTPSFNDRTHLL R-DRA	350
Mouse: Rat: Human: Bovine:	MLEATIREVLRIRPVAPLLIPHKANIDSSIGEFAIPKDTHVIINLWALHHDKNEWDQPDRFMPERFLDPT	420
Mou se: Rat: Human: Bovine:	GSHLITPTPSYLPFGAGPRSCIGEALARQELFIFMALLLQRFDFDVSDDKQLPCLVGDPKVVFLIDPFKV Q	490
Mouse: Rat: Human: Bovine:	KITVRQAWKDAQVEVST 507 MA* KREA-G* EEA-GP*	

FIG. 3. Comparison of the predicted amino acid sequences of mouse, rat, human, and bovine P450_{17a}. Boxed regions indicate conserved sequences common to members of the P450 gene family: the N-terminal hydrophobic region, the unique P450_{17a} sequence (amino acids 296–319); the Ozols tridecapeptide region (343–372), and the heme binding region (434–454). Diamonds (\blacklozenge) indicate sites where comparable amino acids are absent. Dashes (—) indicate identity.

ity (Zuber *et al.*, 1986); and a region specifically conserved among different species of $P450_{17\alpha}$ (aa 296– 319), which may function in catalysis (Ono *et al.*, 1988). The functions of other highly conserved regions seen in Fig. 3 are unknown at present.

To map Cyp17 initially, genomic DNA from A/J and C57BL/6J, the progenitor strains for 43 recombinant inbred strains of mice, was examined for a restriction fragment length variant (RFLV) between the two progenitor strains. An unambiguous RFLV could not be identified after digestion with 19 restriction enzymes and analysis by Southern blotting. Therefore, the DNA from the intersubspecific testcross recently described by Taylor and Rowe (1989) and Warden et al. (1989) was examined. This testcross involved mating the CAST/Ei strain (inbred from Mus musculus castaneus) to the newly established MEV linkage testing stock to produce an F_1 hybrid, which was then mated to either the BXD-32 recombinant inbred strain or the SWR/J inbred strain to produce the testcross generation. The purpose of this testcross was to map several of the endogenous ecotropic murine leukemia virus proviruses present in the MEV stock, utilizing multiple biochemical and DNA variants of CAST/Ei distinguishing it from most laboratory strains. Southern blot analysis of DNA from the four progenitor strains. CAST/Ei, MEV, BXD-32, and SWR/J, identified an RFLV with the restriction enzyme EcoRI for the mouse $P450_{17\alpha}$ cDNA. Fragments of 7.1 and 4.6 kb were detected in CAST/Ei DNA, while 6.4- and 4.6kb fragments were detected in MEV, BXD-32, and SWR/J DNA (Fig. 4). All three bands are present in $(CAST/Ei \times MEV)F_1$ DNA (data not shown). Genomic DNA from 94 interspecific testcross mice was hybridized and scored for the presence or absence of the 7.1-kb EcoRI fragment detected in CAST/Ei. Figure 4 is a representative autoradiograph that illustrates the presence or absence of the CAST/Ei associated fragment. The distribution of alleles in the 94 testcross progeny was compared to previously mapped loci. Cyp17 shows significant linkage with the ecotropic provirus insertion (Emv-22) and glutamate oxaloacetate transaminase-1 (Got-1) loci on chromosome 19 (Table 1). The apparent gene order and estimated recombination frequencies are Emv-22-0.213



FIG. 4. Autoradiogram of a Southern blot of EcoRI-digested genomic DNA hybridized with the full-length mouse P450_{17α} cDNA. The first three lanes show the hybridized fragments of DNA from the progenitor strains indicated (SWR/J not shown). The last three lanes are representative testcross strains showing the presence or the absence of the CAST/Ei allele. Arrows indicate the length of the fragments in kilobases.

 ± 0.047 -Got-1-0.064 ± 0.025 -Cyp17. This gene order requires postulating only a single double crossover. while alternative gene orders require a minimum of five doubles. Thus, Cyp17 maps to the distal end of chromosome 19, presumably close to esterase-18 (Es-18, von Deimling, 1988). Recently, another member of the P450 gene family, Cyp2c, associated with constitutive expression of aryl hydrocarbon hydroxylase, was mapped to the distal end of mouse chromosome 19 using Chinese hamster/mouse somatic cell hybrids and in situ hybridization (Meehan et al., 1988a). The linkage of Cyp2c and Got-1 on chromosome 19 was not determined. The human homologs of Got-1 (Grezschik and Kazaian, 1985) and Cyp2c (Meehan et al., 1988b) have been mapped to chromosome 10g24.3 and 10q25.3, respectively, indicating that these two genes are found in the same region of human chromosome 10, with GOT1 mapping distal to CYP2C. The human gene for $P450_{17\alpha}$, CYP17, has also been mapped to human chromosome 10 (Matteson et al., 1986) but the region of chromosome 10 was not identified. The localization of Cyp17 6.4 cM distal of Got-1 on mouse chromosome 19 predicts that CYP17 will be

found in the homologous region of human chromosome 10 close to GOT1.

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