



## The Transcriptional Factor PPARαb Positively Regulates *Elovl5* Elongase in Golden Pompano *Trachinotus ovatus* (Linnaeus 1758)

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Zhu K-C, Song L, Zhao C-P, Guo H-Y, Zhang N, Guo L, Liu B-S, Jiang S-G and Zhang D-C (2018) The Transcriptional Factor PPARαb Positively Regulates Elov15 Elongase in Golden Pompano Trachinotus ovatus (Linnaeus 1758). Front. Physiol. 9:1340. doi: 10.3389/fphys.2018.01340 The nuclear peroxisome proliferator-activated receptors (PPARs) regulate the transcription of elongases of very long-chain fatty acids (ElovI), which are involved in polyunsaturated fatty acid (PUFA) biosynthesis in mammals. In the present study, we first characterized the function of ElovI5 elongase in Trachinotus ovatus. The functional study showed that ToElovI5 displayed high elongation activity toward C18 and C20 PUFA. To investigate whether PPAR $\alpha$ b was a regulator of *Elov*/5, we also reported the sequence of T. ovatus PPARab (ToPPARab). The open reading frame (ORF) sequence encoded 469 amino acids possessing four typical characteristic domains, including an N-terminal hypervariable region, a DNA-binding domain (DBD), a flexible hinge domain and a ligandbinding domain (LBD). Thirdly, promoter activity experiments showed that the region from PGL3-basic-ElovI5-5 (-146 bp to +459 bp) was defined as the core promoter by progressive deletion mutation of *ElovI5*. Moreover, PPAR $\alpha$ b overexpression led to a clear time-dependent enhancement of ToElov/5 promoter expression in HEK 293T cells. Fourth, the agonist of PPARab prominently increased PPARab and Elov/5 expression, while PPARab depletion by RNAi or an inhibitor was correlated with a significant reduction of ElovI5 transcription in T. ovatus caudal fin cells (TOCF). In conclusion, the present study provides the first evidence of the positive regulation of *ElovI5* transcription by PPARab and contributes to a better understanding of the transcriptional mechanism of PPARab in fish.

Keywords: Trachinotus ovatus, promoter activity, transcription factors, PPARa, ElovI5

## INTRODUCTION

Long-chain polyunsaturated fatty acids (LC-PUFA) biosynthesis initiates from  $C_{18}$  PUFA and requires a series of elongation and desaturation steps catalyzed by elongases of very long chain fatty acids (Elovls) and fatty acid desaturases (Fads) in vertebrates (Cook and McMaster, 2004; Castro et al., 2016). PPAR $\alpha$  is a ligand-activated nuclear transcription factor from the steroid receptor superfamily that regulates LC-PUFA biosynthesis (Kota et al., 2005; Sampath and Ntambi, 2005).

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In mammals, PPARa is activated by fatty acids or their derivatives and plays pleiotropic roles in lipid metabolism, such as stimulating the expression of genes related to peroxisomal and mitochondrial fatty acid oxidation and LC-PUFA biosynthesis (Desvergne et al., 2006). PPARa agonists (WY14643) affect fatty acid elongation pathways, thereby increasing Elov15 expression in adult Rattus norvegicus (Wang et al., 2005). Moreover, in PPARa-defective mice, PPARa was required for the WY14643-mediated induction of Elov15 and Elov16 (Wang et al., 2006). Cold-induced Elovl3 mRNA levels were under the control of PPARa in Mus musculus (Jakobsson et al., 2005). Nevertheless, the role of PPARa in the expression of Elov15 is less understood in fish. Furthermore, PPARa stimulates the expression of target genes directly through binding to PPAR response elements (PPREs) in the promoter regions of target genes. Dong et al. (2017) indicated that PPARa bound to the Fads2 promoter region and upregulated the transcription of Fads2 in fish. PPARa has been implicated as a transacting factor that promotes insulin-induced gene (Insig2a) expression, consequently suppressing sterol-regulatory element binding protein 1c (SREBP-1c) processing during fasting (Lee et al., 2017).

The rate-limiting condensation step is catalyzed by Elovls in the elongation of fatty acids in LC-PUFA biosynthesis (Nugteren, 1965; Jakobsson et al., 2006). *Elovl5* has been verified and functionally characterized as a critical enzyme in the elongation step of LC-PUFA biosynthesis (Castro et al., 2016; Li et al., 2017; Lin et al., 2018). *Elovl5* could effectively elongate C18, C20, and C22 PUFAs and has been isolated from various teleost species (Bell and Tocher, 2009; Monroig et al., 2012; Xie et al., 2016). In fish, *Elovl5* was isolated, and in PUFA biosynthesis, it was consistent with that in mammals and invertebrates (Monroig et al., 2012; Gregory and James, 2014; Kabeya et al., 2015; Li et al., 2016), suggesting a conserved function of *Elovl5* in metazoans.

Teleost fish, particularly marine fish, are unique and rich sources of omega-3 (n-3) LC-PUFAs in the human diet (Tocher, 2015). The golden pompano *Trachinotus ovatus* (Linnaeus 1758), Carangidae, and Perciformes are broadly cultivated in the Asia-Pacific region and considered important aquaculture species in China (Sun et al., 2014; Zhen et al., 2014). Furthermore, high levels of LC-PUFA content were detected in *T. ovatus* muscle (Zhang et al., 2010). Hence, to investigate whether *T. ovatus* PPARab (ToPPARab) would be a mediator of *ToElovl5*, the sequence characterization, tissue distribution and transcriptional regulation of *ToPPARab* were determined. The present study of ToPPARab presents a potential molecular pathway of LC-PUFA biosynthesis mechanisms.

#### MATERIALS AND METHODSS

#### **Ethics Statement**

All experiments in this study were approved by the Animal Care and Use Committee of South China Sea fisheries Research Institute, Chinese Academy of fishery Sciences (No. SCSFRI96-253) and performed according to the regulations and guidelines established by this committee.

#### **Gene Cloning and Bioinformatics**

The *Elovl5* and *PPARab* predicted sequence were obtained from genomic data for *T. ovatus* (Accession No. PRJEB22654 under ENA, Sequence Read Archive under BioProject PRJNA406847). To determine the accuracy of the encoding sequence of *Elovl5* and *PPARab*, gene-specific primers were designed (**Supplementary Table S1**) based on the putative sequence. Total RNA (1  $\mu$ g) was extracted from *T. ovatus* liver (Trizol reagent, Invitrogen, United States) and was reverse transcribed into cDNA by random hexamer primers (Cloned AMV First-Strand cDNA Synthesis Kit, Invitrogen, United States). The 3' of the transcript was cloned from liver cDNA using specific primers with the SMART<sup>TM</sup> RACE cDNA amplification kit (Clontech, Mountain View, CA, United States). PCR was conducted as previously described (Zhu et al., 2014).

Amino acid sequence of ToPPARab was used as queries to search for the homologous genes in NCBI database<sup>1</sup>. All available PPARa genes and mature peptides were downloaded from Ensembl<sup>2</sup> and Genome Browser<sup>3</sup>. The gene structure was predicted by the SANTA CRUZ Genome Browser (see footnote 3), and signal peptides were detected with SignalP software<sup>4</sup>. Molecular weight and theoretical isoelectric point were calculated by Compute pI/Mw software<sup>5</sup>. A three-dimensional (3D) model of the ToPPARab amino acid sequence was developed by the SWISS-MODEL Protein Modelling Server. To better understand the relationship of PPARas in metazoans, all PPARa amino acid sequences were aligned by ClustalW26. Artificially arranged the ambiguously aligned sequences, and then a maximum likelihood (ML) phylogenetic tree (LG + G model, bootstrap 1000) of PPARa putative proteins was constructed by MEGA 6 software (Tamura et al., 2013).

#### Heterologous Expression of the *ToElovI5* Elongase ORFs in Yeast

PCR fragment corresponding to the ORF of the Elov15 elongase was amplified from T. ovatus liver cDNA using primers that included *Hind*III and *Xho*I restriction sites (Supplementary Table S1). Subsequently, the DNA fragment was digested with the relevant restriction endonucleases (New England BioLabs, Herts, United Kingdom) and ligated into a coincident restricted pYES2 yeast expression vector (Invitrogen, Paisley, United Kingdom). The recombinant plasmid (pYES2-Elovl5) was then used to transform Saccharomyces cerevisiae competent cells (S.c. EasyComp Transformation Kit, Invitrogen). Transformation and selection of yeast with recombinant plasmids, and yeast culture were prepared according to previously described methods (Li et al., 2017). Fatty acids are: 18:3n-3 ( $\alpha$ -linolenic acid), 18:3n-6 (y-linolenic acid), 18:4n-3 (stearidonic acid), 20:4n-6 (arachidonic acid, ARA) and 20:5n-3 (eicosapentaenoic acid, EPA) were used as substrates for detecting the elongase activity

<sup>&</sup>lt;sup>1</sup>http://blast.ncbi.nlm.nih.gov/Blast.cgi

<sup>&</sup>lt;sup>2</sup>http://asia.ensembl.org/

<sup>&</sup>lt;sup>3</sup>http://genome.ucsc.edu/cgi-bin/hgBlat

<sup>&</sup>lt;sup>4</sup>http://www.cbs.dtu.dk/services/SignalP/

<sup>&</sup>lt;sup>5</sup>http://web.expasy.org/protparam/

<sup>&</sup>lt;sup>6</sup>http://www.ebi.ac.uk/Tools/msa/clustalw2/

of *ToElovl5*. Final concentrations of FA substrates varied according to their fatty acyl chain lengths, 0.5 mM (C18) and 0.75 mM (C20). Yeast cultures were incubated for 2 days at  $30^{\circ}$ C, and then were harvested, washed twice as described previously (Li et al., 2010). Under the same conditions, yeast transformed with pYES2 contain no insert was grown as a control.

# Plasmid Construction, Cell Culture, and Dual-Luciferase Reporter Assays

Total DNA was extracted from *T. ovatus* muscle using a Genomic DNA Isolation Kit (Invitrogen, United States). To investigate the role of PPARab in the transcriptional regulation of ToElov15, five different promoter regions of ToElov15 were amplified by specific primers (Supplementary Table S1) and subcloned into the KpnI and XhoI restriction sites of the pGL3-basic luciferase reporter plasmid (Promega, United States). Five recombinant plasmids, denoted pGL3-basic-Elovl5-1 (-382 to +89), pGL3basic-Elovl5-2 (-793 to +89), pGL3-basic-Elovl5-3 (-1262 to +89), pGL3-basic-Elovl5-4 (-146 to +265) and pGL3basic-Elovl5-5 (-146 to +459), were constructed (Figure 5). Moreover, the ORF of ToPPARab was amplified with primers including restriction sites for NheI and HindIII, respectively. The DNA fragment was digested with the corresponding restriction endonucleases (Takara, Japan) and ligated into a pCDNA3.1 vector (Invitrogen, United States).

The Renilla luciferase plasmid pRL-TK (Promega, United States) was used as an internal control. Plasmids for transfection were prepared using the TransGen Plasmid Mini Kit (Beijing, China). Human embryonic kidney (HEK 293T) and *T. ovatus* caudal fin (TOCF) cell culture and transfection experiments were performed according to Li et al. (2017) and Wei et al. (2018), respectively.

## *PPAR*αb Overexpression and Knockdown

RNA interference (siRNA) of PPAR $\alpha$ b (PPAR $\alpha$ b-si) and corresponding negative controls (si-NC) were purchased from Genecreate (Wuhan, China). Lipofectamine RNAiMAX transfection reagent (Invitrogen, United States) was used for transfection in TOCF cells. The PPAR $\alpha$ b siRNA sequence is listed in **Supplementary Table S1**. Additionally, the agonist and inhibitor of PPAR $\alpha$  were used to clarify the role of the transcription factor in the regulation of *ToElovl5* elongases. WY-14643 (0.1, 1, and 4  $\mu$ mol/L, Sigma, United States) was used as a PPAR $\alpha$ b agonist, whereas GW6471 (0.1, 1, and 4  $\mu$ mol/L, Sigma, United States) was used as vasued as a PPAR $\alpha$ b inhibitor. Total RNA was extracted from TOCF cells as described above. The experiment was performed according to Li et al. (2017).

#### **Quantitative Real-Time PCR**

The tissue distributions of *PPAR* $\alpha b$  mRNA levels were described by quantitative real-time polymerase chain reaction (qRT-PCR) using adult *T. ovatus* tissues (n = 6), including small intestine, liver, white muscle, brain, spleen, fin, gill, head-kidney, stomach, blood, and male (n = 3) and female gonad (n = 3) cDNA, as templates. Then, total RNA was isolated from 12 tissues as described above. The PrimeScript<sup>®</sup> RT reagent Kit with gDNA Eraser (Takara, Japan) was used to synthesize cDNA from total RNA (1 µg). Specific primers and the housekeeping gene *EF-1* $\alpha$  (elongation factor 1, alpha) are displayed in **Supplementary Table S1**. The qRT-PCR was performed as previously described (Zhang et al., 2018). Relative expression was evaluated by the  $2^{-\Delta\Delta C_T}$  method (Livak and Schmittgen, 2001).

#### **Statistical Analysis**

Statistical analysis was performed using SPSS 19.0 software (IBM, United States). The data from different tissues and groups were analyzed by the Duncan test using one-way ANOVA. Data are shown as the means  $\pm$  SD, and p < 0.05 indicates statistical significance.

### RESULTS

# Sequence Characterization of ToElovl5 and ToPPAR $\alpha$ b

The genomic sequence of *ToElov15* elongase is 6,617 bp, including seven exons and six introns, while the full-length cDNA sequence is 3,764 bp, containing 185 bp of 5' untranslated region (5'-UTR), a 885 bp ORF encoding a polypeptide of 294 amino acids and a 2,694 bp 3'-UTR including a polyA signal sequence (GenBank accession number: KY860144; **Supplementary Figure S1**). Furthermore, similar to other teleost Elov15 proteins, *ToElov15* deduced proteins possess three highly conserved domains (CD1-3), including the histidine box motif (HXXHH) (CD2), conserved in the elongase family (**Figure 1A**) (Xie et al., 2016). KXRXX motif was regarded as putative endoplasmic reticulum (ER) retention signal in Elov15 carboxyl terminal (C-terminal). Five putative transmembrane-spanning regions, including hydrophobic amino acid (aa) stretches were predicted by comparison with other vertebrate Elovl proteins.

The genomic sequence of  $ToPPAR\alpha b$  is a 13,262 bp sequence, including six exons and five introns, containing a 1,407 bp ORF encoding a polypeptide of 469 amino acids (GenBank accession number: MH321826; **Supplementary Figure S2**) with a predicted molecular weight of 52.644 kDa and theoretical isoelectric point of 5.48. Furthermore, similar to other teleost PPAR $\alpha b$  proteins, ToPPAR $\alpha b$  deduced proteins possess four domains containing an N-terminal hypervariable region (A/B), conserved DNAbinding domain (DBD) (C), flexible hinge domain (D) and ligand-binding domain (LBD) (E/F) (**Figure 1B**). The twelve  $\alpha$ -helices (H) and four parts of the  $\beta$ -sheet (S) were predicted by comparison with other vertebrate PPAR $\alpha$  proteins, and two zinc finger domains (Amino acid residues located in the C<sup>103</sup>-C<sup>123</sup> and C<sup>140</sup>-C<sup>157</sup>) were in the DBD.

# Functional Characterization of the ToElovI5 Elongase

The role of the *ToElovl5 elongase* in LC-PUFA biosynthesis was investigated by growing transgenic yeast expressing the *ToElovl5* 

	EFLDATINSYSEILLGPR			KYMQNKQPYSCRG1LVVY					
	ERLDKTINSYLDVWLGPR			KYMRNKQPFSCRG ILVVY					
	IEVLDKAVNGYIDHLLGPK IETFNHQLNTYIESWMGPR			KYMQNRPPVSCRGILVVY KYMKHRQPYSCRGLLVLY				WWYYFSKLIEFMDTFFF: WWYYFSKLIEFMDTFFF:	
	ESFNQKLNSQLESWIGPR			KYMKHRQPCSCRGLLVLY					
	ETFNHKLNAYIDSWMGPR			KYMKHRQPYSCRAVMVFY					
	DSLNHKLNTYFESWLGPR			KYMRHRQPYSCRGLMLLY					
i M	EAFGQKLNAYLESWLGPR	DRRVRG <mark>MLLLDSYLP</mark>	TLGLTLAYLLIVWVGP	KYMKGRQAYSCRGAMMLY	NLGITILSFGMF:	<mark>SE</mark> LVSAVWPGGYSFYCQO	GTHGPPDVDQKIIDVL	WYYFSK <mark>LIEFMDTFFF</mark>	I L R KNNHQVTF <mark>LH I Y</mark>
	EPFNHRLNIYIESWMGPR			KFMRDRKPLSCRPLLVAY				WWYYFSKLIEFMDTFFF	ILRKNNHQITF <mark>LH IY</mark>
	ETFSHRVNSYIDSWMGPR			KYMKNRQAYSCRALLVPY				WYYFSKLIEFMDTFFF.	ILRKNNHQITFLHVY
	IEALDTALTKMLDDKIGPRGIR IEHFDASLSTYFKALLGPR			KYMRNKQPFSCRGILVVY				WIYYLSKLIEFLDTVFF:	I VKKKNIQVI VLHVI
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a H c H	HATMLNIWWFVMN <mark>WVPCGHSY</mark> HASMLNIWWFVMN <mark>WVPCGHSY</mark>	FGATLNSFIHVLMYSYY		YITQGQLIQFVLTIFQTS		WLYFQIF IMISLIILFII WLYFQNCYMISLIILFGN			
7 H	HATMLNIWWFVMWVPCGHSY					WLYFQISYMVTLIILFSN			
B	ASMLNIWWFVMNWVPCGHSY		and the second se			WLYFQISYMVTLIFLFSM			and the second se
i H	HASMLNIWWFVMN <mark>WIPCGHSY</mark>	FGASLNSFIHVVMYSYY	<mark>GL</mark> SAIPAIRPY <mark>LWWKK</mark>	YITQLQLIQFFLTVTQTT	LAV I WPCGFP <mark>IG</mark> V	WLYFQISYMFTLIILFMN	<mark>√F</mark> ¥IQTYKKS-GSQRKI	HPQNSSLLSTNGHANGTI	PSTDFT-APK <mark>KLRVD</mark>
a H	HASMLNIWWFVMN <mark>WIPCGHSY</mark>			YITQMQLIQFILTICQTA					PLVERG-TSK <mark>KLRTD</mark>
iH	HISMLNIWWFVMNWIPSGHSF			HITQLQLIQFGLTVFHAL				DHQNGSPALKNGHAH	KKRRVD
e H	HASMPNIWWFVMN <mark>WVPCGHSY</mark> HATMLNIWWFVMN <mark>WVPCGHSY</mark>			YITQGQLIQFFMTMTQTL YITQGQLVQFVLTMFQTS				DVPNCSVNCUTNCV	MSSEKT_KUDKADAD
a H	HASMPTIWWFVLNWVPCGHSY			YITQAQLTQFVMTMVQSG					
s H	HASMLNIWWFVMNWVPCGHSS			DFPDCSLHKLLHSDLQQE					E.IOI.DIRQIU
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ppa ppa ppa ppa ppa ppa ppa	<ul> <li>arab 1 MVDMESHYHPPSPI</li> <li>arab 1 MVDMESHYHPPSPI</li> <li>arab 1 MVDMETQYHPPSPI</li> <li>arab 1 MVDMENRYRPPSPI</li> <li>ara 1 MVDTESPLCPLSPI</li> </ul>	.EDSVLGSPLCTDDDFMG .EDSVLGSPLCADDDFIG .EDSVLGSPLCADDDFMG .DDSVLDSALFVR .EAGDLESPLSEEFLQ	GMEEFQDISQSIDNDA GMEELQDISQSIDNDA GMEQLQDISQSISDDA GMEELRDISQSMDEDA EMGNIQEISQSIGEDS	ALSSFDVPEYQ-SSS-NGS ALSSFDVPDYQ-SSS-NGS ALSSFQVPEYP-SSS-NGS ALSSFGVPKYQ-SSS-NGS ALSSFGVPKYQ-SGLGSGS SSGSFGFTEYQYLGSCPGS SSGSFGFADVOYLGSCPGS	SEGSTVLDALTPA SEGSTVLDALTPA SDGSTVLDALTPA SESSTELDALTPA SDGSVITDTLSPA	ASSPSSVVYGVAAGQEEF ASSPSSIVYGLATGQEDF ASSPSSVVYGVVASQEEL ASSPSSGVYGCPVGQDEF ASSPSSVTYPVVPGSVDE	SSSTSSLSLE <mark>CRVC</mark> AI SSSSSSLNLECRVCAI SSSSTSLNLECRVCSI TS—TSLNLECRVCSI SPS–GALNIE <mark>CRIC</mark> GI	DRASGYHYGVHACEGCKO DRASGYHYGVHACEGCKO DRASGYHYGVHACEGCKO DRASGYHYGVHACEGCKO DKASGYHYGVHA <mark>CEGC</mark> KO	GFFRRTIRLKL 135 GFFRRTIRLKL 135 GFFRRTIRLKL 135 GFFRRTIRLKL 129 GFFRRTIRLKL 134
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ppa ppa ppa ppa ppa ppa ppa	arab 1 MVDMESHYHPPSPI arab 1 MVDMESHYHPPSPI arab 1 MVDMETQYHPSPSI arab 1 MVDMETQYHPSPSPi ara 1 MVDTESPICPLSPI arab 1 MVDTESPICPLSPI arab 136 EYDKGVRRCKIQK	EDSVLGSPLCTDDDFMG EDSVLGSPLCADDDFIG EDSVLGSPLCADDDFIG DDSVLDSALFVR EAGDLESPLSEEFLQ GDPIMYSPLSGELIG : : *.* :: ::::::::::::::::::::::::::::	GMEEFQDISQSIDNDA GMEELQDISQSIDNDA GMEQLQDISQSISDDA GMEQLIDISQSMDEDA EMGNIQEISQSIGEDS EMGNIQEISQSIGEDS EMGNIQEISQSLSDDT * :::****:::: GMSHNAIRFGRMPQSE	LLSSFDVPDYQ-SSS-NG LLSSFDVPEYP-SSS-NG LLSSFCPKYQ-SSS-NG LLSSFCPADYQ-SGLGSG SGSFGFADYQULGSCPG SGSFGFADYQULGSCPG SGSFGFADYQULGSCPG KLSLKAEMVTGDREVEDF CKLKLKAEMVTGDREVEDF	SEGSTVLDALTPA SEGSTVLDALTPA SDGSTVLDALTPA SESSTELDALTPA SEGSVITDTLSPA SEGSVITDTLSPA 'DNSSILDVLTPA :.* *.*:** 'QIADQKTLABG1	ISSPSSIVYGVAAGQEEF ISSPSSIVYGLATOQDF ISSPSSVYGCPVGQDF ISSPSSVYGCPVGQDEF ISSPSSVTYPVVPGSVDE ISSPSSVSCPVIPASTDE ISSPSSEVFSASTGQDEN ******	SSSTSSLSLECRVCAL SSSSSSLNLECRVCAL SSSSSSLNLECRVCSI TS—TSLNLECRVCSI SPS—GALNIECRICGI SFG—SALNIECRICGI SSG—SLTLECRVCAL :. :******	DRASGYHYGVHACEGCKO DRASGYHYGVHACEGCKO DRASGYHYGVHACEGCKO DRASGYHYGVHACEGCKO DRASGYHYGVHACEGCKO DRASGFHYGVHACEGCKO Extra the	3FFRRTIRLKL         135           3FFRRTIRLKL         135           3FFRRTIRLKL         135           3FFRRTIRLKL         134           3FFRRTIRLKL         134           3FFRRTIRLKL         134           3FFRRTIRLKL         131           3SAGV         264
ppa ppa ppa ppa ppa ppa ppa ppa ppa	arab     1     MVDMESHYHPPSPI       arab     1     MVDMESHYHPPSPI       arab     1     MVDMETGYHPSPSPI       arab     1     MVDMETGYHPSPSPI       arab     1     MVDMETGYHPSPSPI       arab     1     MVDMETGYHPSPSPI       arab     1     MVDMESPLCPLSPI       arab     1     MVDMPSLYSPSSPI       ****     ****       arab     136     EYDKCVRRCKIQR       arab     136     EYDKERRKXIQN	EDSVLGSPLCTDDDFIG EDSVLGSPLCADDDFIG EDSVLGSPLCADDDFIG DDSVLDSALFVR EAGDLESPLSEFFLQ GDPIMYSPLSGELIG : : *.* :: :: :::::::::::::::::::::::::	GMEEFQD1SQSIDNDA GMEELQD1SQSIDNDA GMEQLQD1SQSIDNDA GMEQLQD1SQSIDDDA EMGNIQEISQSIGEDS EMGNIQEISQSIGEDS DMQVLEDISQSISDDT * ::*****:::: GMSHNAIRFGRMPQSE GMSHNAIRFGRMPQSE	LLSSFDVPDYQ-SSS-NG LLSSFDVPEYP-SSS-NG LLSSFGPKYQ-SSS-NG LLSSFGFTEYQYLGSCGS SGSFGFDYQYLGSCCG SGSFGFDYQYLGSCCG FINSFHMLDYQNCDTAV ** A/B domain EKLKLKAEMVTGDREVEDF KLKLKAEMVTGDREVEDF	SEGSTVLDALTPA SEGSTVLDALTPA SDGSTVLDALTPA SESSTELDALTPA SEGSVITDTLSPA ZEGSVITDTLSPA ZDNSSILDVLTPA :.* *.*:** PQIADQKTLABCT PQIADQKTLARQT	ISSPSSVYGVAGGEEF ISSPSSVYGVAGGEG ISSPSSVYGVAGGEG ISSPSSVYGCVGODEF ISSPSSCYGCVGODEF ISSPSSEVFIASTO ISSPSSEVFASTGODEN ****** TEATLKFNMHKAKART	SSSTSSLSLECRVCAL SSSSSSLNLECRVCS SSSSTSLNLECRVCSI SSSTSLNLECRVCSI SPS-GALNIECRICGI SSG-SLTLECRICGI SSG-SLTLECRVCAI :. :*.:****:*.*	DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGC DRASGFHYGYHACEGCK *:***:*******************************	SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SSAGV         264           SSAGV         264
ppa ppa ppa ppa ppa ppa ppa ppa ppa ppa	rab 1 MVDMESHYHPPSPI rab 1 MVDMETGYHPPSPI rab 1 MVDMETGYHPPSPI rab 1 MVDMETGYHPPSPI rab 1 MVDTESPICPLSPI raa 1 MVDTESPICPLSPI raa 1 MVDTESPICPLSPI rab 136 EYDKCERKCKIQA rab 136 EYDKCERRCKIQA rab 136 EYDKCERRCKIQA	LEDSULGSPLCTDDDFMG LEDSULGSPLCADDDFMG LEDSULGSPLCADDDFMG LDSULDSALFVR LAGDLESPLSEEFLQ LGDPIMYSPLSGELIG : : : *.* : :: ::::::::::::::::::::::::	GMEEFQD1SQS1DNDA GMEELQD1SQS1DNDA GMEQLQD1SQS1SDDA GMEQLQD1SQS1SDDA EMGN1QETSQS1GEDS EMGN1QETSQS1GEDS EMGN1QETSQS1GEDS MQVLED1SQSLSDDT * ::*****:::: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE	LLSSFDVPDYQ-SSS-NG LLSSFDVPEYP-SSS-NG LLSSFCPKYQ-SSS-NG LLSSFCPADYQ-SGLGSG SGSFGFADYQULGSCPG SGSFGFADYQULGSCPG SGSFGFADYQULGSCPG HMLDYQNCDTAV ** A/B domain EKLKLKAEMVTGDREVEDF EKLKLKAEMVTGDREVEDF EKLKLKAEMVTDREVEDF EKLKLKAEMVTDREVEDF	SEGSTVLDALTPA SEGSTVLDALTPA SEGSTVLDALTPA SESSTELDALTPA SEGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA QIADQKTLAB91 QIADQKTLAB91 QIADQKTLAR91 QIADQKTLAR91	ISSPSSVVJCVAGGEEF ISSPSSIVJCVAGGEG ISSPSSVVJCVASGEL ISSPSSGVVCVGVGSUGE ISSPSSEVFSASTGQEN ****** YEATLKFNNKAKART YEATLKFNNKAKART YEATLKNNNKAKART	SSSTSSLSLEGRVCAI SSSSSSLNLEGRVCSI SSSSTSLNLEGRVCSI SPS-GALNIEGRICGI SPG-SALNIEGRICGI SSG-SLTLEGRVCAI :. :: :****** ILTGKTS-TPPFVIHI ILTGKTS-TPPFVIHI ILLTGKTS-TPPFVIHI ILLTGKTS-TPPFVIHI	PRASCHYGVHACEGCK DRASCHYGVHACEGCK DRASCHYGVHACEGCK DRASCHYGVHACEGCK MASCHYGVHACEGCK MASCHYGVHACEGCK DRASCHYGVHACEGCK ************************************	SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFRRTIRLKL         134           SAGV         264           SATA         264           SVGA         264
ppa ppa ppa ppa ppa ppa ppa ppa ppa ppa	rab     1     MVDMESHYHPPSPI       rab     1     MVDMESHYHPPSPI       rab     1     MVDMETGYHPSPSPI       rab     1     MVDMETGYHPSPSPI       raa     1     MVDFSPLCPLSPI       raa     1     MVDMSSYLPSPSPI       raa     1     MVDMSSYLPSPSPI       ****     ****       *     ****       *     ****       *     ****       *     ****       *     ****       *     ****       *     ****       *     ****       *     ****       *     ****       *     ****       *     ****       *     ****	EDSVLGSPLCTDDDFIG EDSVLGSPLCADDDFIG EDSVLGSPLCADDDFIG DDSVLDSALFVR EAGDLESPLSEFFLQ GDPIMYSPLSGELIG : : *.* :: :KNRNKCQYCRFQKCLSV KNRNKCQYCRFQKCLSV :KNRNKCQYCRFQKCLSV :KNRNKCQYCRFQKCLSV	GMEEFQD1SQSIDNDA GMEELQD1SQSIDNDA GMEQLQD1SQSIDDDA GMEQLQD1SQSIDDDA EMGNIQEISQSIGEDS EMGNIQEISQSIGEDS DMQVLEDISQSIGEDS DMQVLEDISQSISDDT * :: *****: :: GMSHNAIRFGRMPQSE GMSHNAIRFGRMPQSE GMSHNAIRFGRMPQSE GMSHNAIRFGRMPQSE	LLSSFDVPDYQ-SSS-NG LLSSFDVPEYP-SSS-NG LLSSFGPTEYQYLGSCGS SSGSFGFDYQYLGSCCG SSGSFGFDYQYLGSCCG FINSFHMLDYQNCDTAV ** A/B domain SELKLKAEMVTGDREVEDF KLKLKAEMVTGDREVEDF KLKLKAEMVTGDREVEDF KLKLKAEMVTGDREVENF KLKLKAEMTGREVENF KLKLKAEMTLOREVENF	SEGSTVLDALTPA SEGSTVLDALTPA SESSTELDALTPA SESSTELDALTPA SESSTELDALTPA SEGSVTIDTLSPA ZEGSVTIDTLSPA ZIADKTLABGI QIADQKTLABGI QIADQKTLARQI QLADQKTLARQI QLADQKTLARQI QLADQKTLARQI	ISSPSSVYGVAGGEEF ISSPSSVYGVAGGEG ISSPSSVYGVAGGEG ISSPSSVYGVYGVASGEL ISSPSSCYGCPVGDEF ISSPSSEVFASTGQDEN ISSPSSEVFSASTGQDEN ISSPS	SSSTSSLSLEGRVCAI SSSSSSLNLECRVCAI SSSSTSLNLECRVCSI SSSTSLNLECRVCSI SSG-SALNIECRICGI SSG-SLTLECRICGI SSG-SLTLECRUCAI : :*: :***:** ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI	DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGCK *:***:*******************************	SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         131           ************************************
ppa ppa ppa ppa ppa ppa ppa ppa ppa ppa	rab 1 WDMESHYHPPSPI irab 1 WDMESHYHPPSPI irab 1 WDMETQYHPPSPI irab 1 WDMETQYHPPSPI ira 1 WDDESNLPSPI ira 1 WDTESPLCPLSPI iraa 1 WDTESPLCPLSPI iraa 1 WDTESPLCPLSPI irab 136 EYDKCVRRCKIQA irab 136 EYDKCVRRCKIQA irab 136 EYDKCERRCKIQA irab 136 EYDKCERRCKIQA irab 136 EYDKCERRCKIQA irab 136 EYDKCERRCKIQA irab 130 EYDKCERRCKIQA irab 130 EYDKCERRCKIQA	LEDSVLGSPLCTDDDFMG LEDSVLGSPLCADDDFMG LEDSVLGSPLCADDDFMG LDSVLDSALFVR LEADLESPLSEEFLQ LEADDLESPLSEEFLQ GDPIMYSPLSGELIG (KNRNKCQYCRFQKCLSV KNRNKCQYCRFQKCLSV KNRNKCQYCRFQKCLSV KNRNKCQYCRFQKCLSV KNRNKCQYCRFHKCLSV	GMEEFQD1SQS1DNDA GMEELQD1SQS1DNDA GMEQLQD1SQS1SDDA GMEQLQD1SQS1SDDA EMGKUQE1SQS1GEDS EMGKUQE1SQS1GEDS EMGKUQE1SQS1GEDS MAQVLED1SQSLSDDT * :: *****: :::: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE	LLSSFDVPDYQ-SSS-NG LLSSFDVPEYP-SSS-NG LLSSFGVPKYQ-SSS-NG LLSSFGPHTENQ-SGLGSG SGSGFGFEYQVLGSCPG SGSGFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG KLKLKAEWYTGDREVED KLKLKAEWYTGDREVED KLKLKAEWYTDREVED KLKLKAEWTTDREVED KLKLKAEHTTDREVED KLKLKAEHTTDREVED KLKLKAELTCREPTDE	SEGSTVLDALTPA SEGSTVLDALTPA SEGSTVLDALTPA SESSTELDALTPA SESSTELDALTPA SEGSVITDTLSPA TDNSSILDVLTPA QIADQKTLARQI QIADQKTLARQI QIADQKTLARQI QLADQKTLARQI QLADQKTLARQI QLADQKTLARQI SETADLKSAKRI	ISSPSSVVJCVAGGEEF ISSPSSIVJCVAGGEG ISSPSSVVGVASGEL ISSPSSGVJCCVGODE ISSPSSVSVVVGVAGSUE ISSPSSVSVVCVAGSUE ISSPSSVSVVGSVG ISSPSSVSCVIPAGDE ISSPSSEVFSASTGGDEN ISSPSSEVFSASTGGDEN IVEAVLKNFNMKAKART IVEAVLKNFNMKAKART IVEAVLKNFNMKAKART IVEAVLKNFNMKAKART	SSSTSSLSLERGRUCAN SSSSSSLNLEGRUCSI SSSSSSLNLEGRUCSI TS-TSLNLEGRUCSI SPS-GALNIEGRICGI SSG-SALNIEGRICGI SSG-SALNIEGRICGI :. :******* IDTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILLTCKTS-TPPFVIHI ILLTCKTS-TPPFVIHI ILLSCKASNNPFVIHI	DRASGYHYGVHACEGCK DRASGYHACEGCK DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHACEGCK DRASGYHACH DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHYGVHACEGCK DRASGYHACH	SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         136           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFGRT         264           SCAGV         264           SVGA         264           SVGA         264           SCAGV         264           SCAGC         264           SCAGC         264           SCAG         264
ppa ppa ppa ppa ppa ppa ppa ppa ppa ppa	radb         1         MVDMESHYHPPSPI           radb         1         WVDMESHYHPPSPI           radb         1         WVDMETQYHPSPSPI           radb         1         WVDESPLCPLSPI           rad         1         WVDESPLCPLSPI           rad         1         WVDESPLCPLSPI           rad         1         WVDESPLCPLSPI           rad         1         WVDESPLCPLSPI           radb         136         EVDKCERRCKIQ           radb         135         VDKCRSCKIQ	EDSVLGSPLCTDDDFIG EDSVLGSPLCADDDFIG EDSVLGSPLCADDDFIG DDSVLDSALFVR EAGDLESPLSEEFLQ GDPIMYSPLSGELIG : : *.* :: EXNRNK GQYCRFQKCLSV EXNRNK GQYCRFQKCLSV EXNRNK GQYCRFQKCLSV EXNRNK GQYCRFQKCLSV EXNRNK GQYCRFQKCLSV EXNRNK GQYCRFFKCLSV EXNRNK GQYCRFFKCLSV EXNRNK GQYCRFFKCLSV	GMEEFQD1SQSIDNDA GMEELQD1SQSIDNDA GMEQLQD1SQSIDDDA GMEQLQD1SQSIDDDA EMGNIQEISQSIGEDS DMQVLED1SQSIGEDS DMQVLED1SQSISDDT * : :*****:::: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE	LLSSFDVPDYQ-SSS-NG LLSSFDVPEYP-SSS-NG LLSSFCPVFYQ-SSS-NG SGSSFGFEVQLSCCGG SGSSFGFADVQVLGSCPG SGSSFGFADVQVLGSCPG FNSFHMLDYQNCDTAV ** A/B domain EKLKLAEMVTGDREVEDF EKLKLAEMVTGDREVEDF EKLKLAEMVTGDREVEDF EKLKLAEMVTGDREVEDF EKLKLAEMTUTDFEVEDF EKLKLAEMUTDFUEDE EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKLAEMITDERDVED- EKLKAEMITDERDVED- EKLKAEMITDERDVED- EKLKKAEMITDERDVE	SEGSTVLDALTPA SEGSTVLDALTPA SESSTELDALTPA SESSTELDALTPA SESSTELDALTPA SESSTELDALTPA SEGSVITDTLSPA ZOSSILDVLTPA UDNSSILDVLTPA SEGSVITALSPA QLADQKTLARQI QLADQKTLARQI QLADQKTLARQI SETADLKSLARKI QQCPDMRSLANQM	ISSPSSVYGVAGGEEF ISSPSSVYGVAGGEG ISSPSSVYGVGVASGEL ISSPSSGVYGCPVG0DE ISSPSSCVFGPVG0DE ISSPSSEVFSASTGQDEN ****** IYEATKKPNNKKAKARS IYEATKKPNNKKKKAKAS IYEATKKPNNKKKKAKAS	SSSTSSLSLEGRVCAI SSSSSSLNLECRVCAI SSSSTSLNLECRVCSI TS—TSLNLECRVCSI SPS-GALNIECRICGI SSG—SLTLECRVCAI :. :*.:******* II.TCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH ILTCKTS-TPFVIH	DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGCK SKASGYHYGYHACEGCK METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEKLYTYAKM	SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SSAGV         264           SAGV         264           SVGA         264           SCGG         254           SVGA         264           SVASGDIST         265
ppa ppa ppa ppa ppa ppa ppa ppa ppa ppa	radb         1         MVDMESHYHPPSPI           radb         1         WVDMESHYHPPSPI           radb         1         WVDMETQYHPSPSPI           radb         1         WVDESPLCPLSPI           rad         1         WVDESPLCPLSPI           rad         1         WVDESPLCPLSPI           rad         1         WVDESPLCPLSPI           rad         1         WVDESPLCPLSPI           radb         136         EVDKCERRCKIQ           radb         135         VDKCRSCKIQ	EDSVLGSPLCTDDDFMG EDSVLGSPLCADDDFMG EDSVLGSPLCADDDFMG DDSVLDSAL	GMEEFQD1SQSIDNDA GMEELQD1SQSIDNDA GMEQLQD1SQSIDDDA GMEQLQD1SQSIDDDA EMGNIQEISQSIGEDS DMQVLED1SQSIGEDS DMQVLED1SQSISDDT * : :*****:::: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE	LLSSFDVPDYQ-SSS-NG LLSSFDVPEYP-SSS-NG LLSSFGVPKYQ-SSS-NG LLSSFGVPKYQ-SSS-NG SGSFGFEVQVLGSCPG SGSGFGFEVQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSC SGSFGFADYC	SEGSTVLDALTPA SEGSTVLDALTPA SEGSTVLDALTPA SESSTELDALTPA SEGSVITDTLSPA SEGSVITDTLSPA VDNSSILDVLTPA QIADQKTLARDI QIADQKTLARDI QIADQKTLARDI QIADQKTLARDI QIADQKTLARDI DQADQKTLARDI SETADLKSLKRI QQPDMRSLARQU * :: * :: ::	ISSPSSVV/GVAGGEEF ISSPSSIV/GVAGGEG ISSPSSVV/GVVASGEL ISSPSSGV/GCV/GDUE ISSPSSVSCPV IPASTDE ISSPSSVSCPV IPASTDE ISSPSVSCPV IPASTDE ISSP	SSSTSSLSLERGRUCAL SSSSSSLNLEGRUCAL SSSSSSLNLEGRUCSL TS-TSLNLEGRUCSL SPS-GALNIEGRUCGL SPG-SALNIEGRUCGL SSG-SLTLEGRUCAL : :******* IDTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILSCKASNNPPFVIHI ILSCKASNNPPFVIHI ILSCKASNNPPFVIHI ILSCKASNNPPFVIHI ***:******	DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK DRASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGCK MASGYHYGYHACEGCK SKASGYHYGYHACEGCK METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEQTLYAKMY METLQLAEKLYTYAKM	SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFGRT         264           SAGV         264           SVGA         264           SCGG         254           SVGA         264           SVASGDIST         265
ppa ppa ppa ppa ppa ppa ppa ppa ppa ppa	<ul> <li>Involueshythepespi irab 1 WUMESNYthepespi irab 1 WUMETQYthepespi irab 1 WUMETQYthepespi irab 1 WUMETSLYEPespi ira 1 WUMESNYSPSSPi iraa 1 WUMPSLYSPSSPi iraa 1 WUMPSLYSPSSPi iraa 1 WUMPSLYSPSSPi irab 136 EYDKCVRRCKIQ irab 136 EYDKCVRRCKIQ irab 136 EYDKCERRCKIQ irab 132 EYDKCERCKIQ iras 132 E</li></ul>	EDSVLGSPLCTDDDFMG EDSVLGSPLCADDDFMG EDSVLGSPLCADDDFMG EDSVLGSPLCADDDFMG DDSVLDSALFVR EACDLESPLSEEFLQ EADDLESPLSEEFLQ EADDLESPLSEEFLQ EADDLESPLS	GMEEFQD1SQS1DNDA GMEELQD1SQS1DNDA GMEQLQD1SQS1SDDA GMEQLQD1SQS1SDDA EMGNIQE1SQS1GEDS EMGNIQE1SQS1GEDS EMGNIQE1SQS1GEDS MAQVLED1SQSLSDDT * :: *****: :::: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE	LLSSFDVPDYQ-SSS-NG LLSSFDVPEYP-SSS-NG LLSSFGVPKYQ-SSS-NG LLSSFGPHYQ-SGLGSG SGSGFGF2VQVLGSCPGS SGSFGF4DYQVLGSCPGS SGSFGF4DYQVLGSCPG SKLKLAAEMVTGDREVEDF SKLKLAAEMVTGDREVEDF SKLKLAAEMVTGDREVEDF SKLKLAAEMVTGDREVEDF SKLKLAAELLTCEHDLEDS SKAKLAAE LLTCEHDLEDS SKAKLAAE LLTCEHDLEDS SKARLAAE LLTCEHDLESS SKARLAAE LLTCEHDLESS	SEGSTVLDALTPA SEGSTVLDALTPA SEGSTVLDALTPA SEGSVLTDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA VIADQKTLARGI VIADQKTLARGI VIADQKTLARGI VIADQKTLARGI VIADQKTLAKHI VIADQKTLAKHI SETADLKSLKRI SQQPDMRSLARQU *::*:*:*:*:*	ISSPSSVVGVAGGEEF ISSPSSIVGVGVAGGEG ISSPSSVVGVASGEL ISSPSSGVGCVGODS ISSPSSVVPVGVASUE ISSPSSVSVVPVGSVD ISSPSSVSVVPASUD ISSPSSVSVVPASUD ISSPSSVSVVFASU ISSPSSVSVPASUD ISSPSSVSVPASUD ISSPSVFASU ISSPSVFAS	SSSTSSLSLERCRUCAI SSSSSSLNLECRUCSI SSSSSTSLNLECRUCSI TS-TSLNLECRUCSI SPS-GALNIECRUCGI SSG-SALNIECRUCGI SSG-SALNIECRUCGI : :::::::::::::::::::::::::::::::::::	PRASCHHVCHALEGCK DRASCHHVCHALEGCK DRASCHHVCHALEGCK DRASCHHVCHALEGCK SRASCHVCHALEGCK KASCHVCHALEGCK KASCHVCHALEGCK KASCHVCHALEGCK KASCHVCHALEGCK MASCHVCHALEGCK MASCHVCHALEGCK MASCHVCHALEGCK METLOLACTLVAKUV METLOLACTLVAKUV METLOLACTLVAKUV METLOLACTLVAKUV METLOLACTVAKUV	SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         136           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFGRT         264           SCATA         264           SCGG         262           SNVASGDIST         265            265
ppa ppa ppa ppa ppa ppa ppa ppa ppa ppa	Involueshythepspl       urab     MVDMESNYthepspl       urab     MVDMETQYthepspl       urab     MVDMETQYthepspl       urab     MVDMETQYthepspl       urab     MVDTESPLCPLSPl       urab     MVDTESPLCPLSPl       urab     136       EVDKCVRRCK10k       urab     136       EVDKCERRCK10k       urab     136       EVDKCERRCK10k       urab     136       EVDKCERRCK10k       urab     136       EVDKCERRCK10k       urab     130       Urad     135       VDKCERSCK10k       urab     135       urab     136       EVDKCERKCK10k       urab     136       Urad     135       VDKCERSCK10k       urad     135       urad     135       VDKCERSCK10k       urad     135       urad     135       VDKCERSCK10k       urad     136       urad     136       EVDKCERSCK10k       urad     136       urad     136       EVDKCERKCK10k       urad     136       Urad     137       Urad     138       Urad	LEDSVLGSPLCADDDFIG LEDSVLGSPLCADDDFIG LEDSVLGSPLCADDDFIG LEDSVLGSPLCADDDFIG LDSVLDSALFVR LACDLESPLSEFLQ LEADDLESPLSEFLQ GDPIMYSPLSEFLQ GDPIMYSPLSEFLG GUPYGPGKCLSV KNRNK GUYGRFGKCLSV KNRNK GUYGRFGKCLSV KNRNK GUYGRFGKCLSV KNRNK GUYGRFGKCLSV KNRNK GUYGRFHKCLSV KNRNK GUYGRFHKCLSV KNRNK GUYGRFHKCLSV C domain CQCTSVETVTELTEFAK	GMEEFQD1SQS1DNDA GMEELQD1SQS1DNDA GMEQLQD1SQS1DDDA GMEQLQD1SQS1SDDA GMEQLQD1SQS1SDDA EWGNTQE1SQS1GEDS EMGN1QE1SQS1GEDS EMGN1QE1SQS1GEDS GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPRSE SVPGFSSLDLNQVTL SVPGFSSLDLNQVTL	LLSSFDVPDYQ-SSS-NG LLSSFDVPDYQ-SSS-NG LLSSFGVPKYQ-SSS-NG LLSSFGVPKYQ-SSS-NG SGSFGFTEVQVLGSCPG SGSGFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYGALFANLASSM LGCQVFALFANLASSM LGCQVFALFANLASSM	SEGSTVLDALTPA SEGSTVLDALTPA SEGSTVLDALTPA SEGSVITDTLSPA SEGSVITDTLSPA VDNSSILDVLTPA VDNSSILDVLTPA VDNSSILDVLTPA VQIADQKTLARQI VQIADQKTLARQI VQIADQKTLARQI VQIADQKTLAKQI SETADLKSLKARQI *::*.:: MCGLUAVGSFF KDGLUAVGSFF	ISSPSSVVYGVAGGEEF ISSPSSVVGVAGGEG ISSPSSVVGVASGEL ISSPSSVVGVVGVASGEL ISSPSSVSVVGVASGEL ISSPSSVSVVGVASGEL ISSPSSVSVVGVAST ISSPSSVSVVGVAST VEAVLKVVMVAAAART IVEAVLKVVMVAAAAART IVEAVLKVVMVAAAAART IVEAVLKVVMVAAAAART IVEAVLKVVMVAAAAART IVEAVLKVVMVAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA	SSSTSSLSLERGRUCAL SSSSSSLNLEGRUCAL SSSSSSLNLEGRUCAL SSSSSSLNLEGRUCAL SSSSTSLNLEGRUCAL SPS-GALNIEGRUCAL SPS-GALNIEGRUCAL SSG-SLTLEGRUCAL I.: :***********************************	PRASCHHVCHALEGCK PRASCHHVCHALEGCK PRASCHHVCHALEGCK PRASCHHVCHALEGCK PRASCHHVCHALEGCK PRASCHHVCHALEGCK PRASCHVCHALEGCK PRASCHVCHALEGCK PRASCHVCHALEGCK PRASCHVCHALEGCK PRASCHVCHALEGCK PRASCHVCHALEGCK PRASCHVCHALEGCK PREIZLAEQTLVAKING METLQLAEQTLVAK	SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFGV         264           SAGV         264           SCGG         254           SCGG         254           NG         262           NVASGDIST         265            399           PRCLVN/AH         399
ppa ppa ppa ppa ppa ppa ppa ppa ppa ppa	rdb         1         MVDMESHYHPPSPI           rrab         1         MVDMETGYHPPSPI           rrab         1         MVDMETGYHPSPSI           rrab         1         MVDMETGYHPSPSI           rrab         1         MVDTESPLCPLSPI           rrab         1         MVDTESPLCPLSPI           rrab         136         EYDKCFRCKIQ           rrab         136         EYDKCERRCKIQ           rrab         135         EYDKCERRCKIQ           rrab         135         EYDKCERRCKIQ           rraa         135         EYDKCERRCKIQ	LEDSVLGSPLCTDDDFMG LEDSVLGSPLCADDDFIG LEDSVLGSPLCADDDFMG LEDSVLGSPLCADDDFMG LDSVLDSALFVR LEADDLSSPLSEEFLQ GDPIMYSPLSEEFLQ GDPIMYSPLSEEFLQ KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFKKLSV KNRNK QYCRFKKLSV COCTSVETVTELTEFAK	GMEEFQD1SQS1DNDA GMEELQD1SQS1DNDA GMEQLQD1SQS1SDDA GMEQLQD1SQS1SDDA EMGN1QE1SQS1GEDS EMGN1QE1SQS1GEDS EMGN1QE1SQS1GEDS MQVLED1SQSLSDDT * :: *****: :::: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPSSE GMSHNA1RFGRMPSSE SMSHNA1	LISSFDVPDYQ-SSS-NG LISSFDVPEYP-SSS-NG LISSFGVPKYQ-SSS-NG LISSFGPHTENQ-SGLGSG SGSFGFEYQYULGSCPG SGSFGFADYQYLGSCPG SGSFGFADYQYLGSCPG *** A/B domain EKLKLKAEWTGDREVEDF KLKLKAEWTGDREVEDF SKLKLKAEWTGDREVEDF SKLKLKAEWTGDREVEDF SKLKLKAELTCEHDLENS SKAKLKAE LITCEHDLENS SKAKLKAE LITCEHDLENS SKAKLKAE LITCEHDLENS SKAKLKAE LITCEHDLENS SKAKLKAE LITCEHDLENS SKAKLKAE LITCEHDLENS SKAKLKAE LITCEHDLENS LICGVY EAL FAMLASSIN LICGVY EAL FAMLASSIN LICGVY EAL FAMLASSIN	SEGSTVLDALTPA SEGSTVLDALTPA SEGSTVLDALTPA SESSTELDALTPA SESSTELDALTPA SESSTIDVLTPA SUBSVITTSLSPA SUBSVITTSLSPA SUBSVITTSLSPA SUBSVITS	ISSPSSVVGVAGGEEF ISSPSSTVGVAGGEG ISSPSSVVGVASGEL ISSPSSVVGVGVASGEL ISSPSSVTPVVFGSVDE ISSPSSVEVFASTO ISSPSSVEVFASTO ISSPSSVEVFASTO ISSPSSVEVFASTO ISSPSSVEVFASTO ISSPSSVEVFASTO ISSPSSVEVFASTO ISSPSVE ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVE ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVEVFASTO ISSPSVE ISSPSVEVFASTO IS	SSSTSSLSLEFERVCAI SSSSSSLNLECRVCSI SSSSSTSLNLECRVCSI TS-TSLNLECRVCSI SPS-GALNIECRICGI SSG-SALNIECRICGI SSG-SALNIECRICGI SSG-SLTLECRVCAI LITCKTS-TPPFVIH ILTCKTS-TPPFVIH ILTCKTS-TPPFVIH ILSCKJSNPPFVIH ILSCKJSNPPFVIH ILSCKSSNPPFVIH ELSCKJSNPPFVIH ELSCKJSNPPFVIH ELSCKJSNPFVIH EFFCFGAMKFNSLELL EPKFQFGMKFNALELL	PRASCHHVCHALEGCK DRASCHHVCHALEGCK DRASCHHVCHALEGCK DRASCHHVCHALEGCK SRASCHVCHALEGCK SRASCHVCHALEGCK SRASCHVCHALEGCK SRASCHVCHALEGCK SRASCHVCHALEGCK SRASCHVCHALEGCK SRASCHVCHALEGCK SRASCHVCHALEGCK SRASCHVCHALEGCK SRASCHVCHALEX METLOLAETLVAKUV	FFFRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         134           SFGRT         264           SCATA         264           SCGC         264           SCGG         265           SNVASGDIST         265           SNVASGDIST         265           SCG         399           SPELVWARH         399           SPELVWARH         399
ppa ppa ppa ppa ppa ppa ppa ppa ppa ppa	rab         1         MVDMESNYHPPSPI           rab         1         MVDMESNYHPPSPI           rab         1         MVDMETQYHPPSPI           rab         1         MVDMETQYHPSPSI           rab         1         MVDTESPLCPLSPI           rab         1         MVDTESPLCPLSPI           rab         136         EYDKCERRCKIQ           rab         137         VYDKCDRSCKIQ           rab         132         EYDKCERRCKIQ           rab         132         EYDKCERRCKIQ           rab         265         LKDREVERKIQ           rab         265         LKDREVERTH           rab         265 <td>LEDSULGSPLCTDDDFMG LEDSULGSPLCADDDFAG LEDSULGSPLCADDDFAG LEDSULGSPLCADDDFMG LESULGSPLS-UEFLQ GDPIMYSPLS-GELLG GDPIMYSPLS-GELLG CADDLESPLS-EFLQ GDPIMYSPLS-GELLG CKNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFKCLAV COCTSVETVTELTEFAK CQCTSVETVTELTEFAK CQCTSVETVTELTEFAK</td> <td>GMEEFQD1SQS1DNDA GMEELQD1SQS1DNDA GMEELQD1SQS1DDDA GMEELD1SQS1SDDA EMGN1QETSQS1GEDS EMGN1QETSQS1GEDS EMGN1QETSQS1GEDS MQVLED1SQSLSDDT * :: *****: :: :: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPSSE GMSHNA1</td> <td>LISSFDVPDYQ-SSS-NG LISSFDVPDYQ-SSS-NG LISSFCPNTENQ-SGLGSG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG FNSFHMLDYQNCDTAV ** A/B domain EKLKLKAEMVTGDREVEDF EKLKLKAEMVTGDREVEDF EKLKLKAEMVTGDREVEDF EKLKLKAEMVTGDREVEDF EKLKLKAEILTCERDVED- SKAKLKAEILTCERDVED- SKAKLKAEILTCERDVED- SKAKLKAEILTCERDVED- SKAKLKAEILTCERDVED- SKAKLKAEILTGERDVED- SKAKIKAEILTGERDVED- SK</td> <td>SEGSTVLDALTPA SEGSTVLDALTPA SEGSTVLDALTPA SEGSVITDTLSPA SDGSVITDTLSPA SDGSVITDTLSPA SDGSVITDTLSPA SDGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTLSPA SEGSVITDTSPA SE</td> <td>ISSPSSVVJCVAGGEEF ISSPSSTVJCVAGGEG ISSPSSVVGVASGEL ISSPSSVJCCVGDSGEL ISSPSSVCVCVASGEL ISSPSSVCVCVASGEL ISSPSSVCVTPAVFSV ISSPSSVCVTPATF ISSPSSVCVTPATFA ISSPSSVCVTPATFA IVEATLKVTPATF</td> <td>SSSTSSLSLEGRVCAI SSSSSSLNLECRVCSI SSSSSSLNLECRVCSI SPS-GALNIECRUCSI SPS-GALNIECRUCGI SSG-SLTLECRVCAI :. :*:****** ILTCKTS-TPPFVIH ILTCKTS-TPPFVIH ILTCKTS-TPPFVIH ILTCKTS-TPPFVIH ILTCKTS-TPPFVIH ILTCKTS-TPPFVIH ILTCKTS-TPPFVIH ILTCKTS-TPPFVIH SSKASNNPPVIH EFLORTS-TPPFVIH SST SI EPKF0FAMKFNALELL EPKF0FAMKFNALELL</td> <td>PRASCHYHCVHACEGCK DRASCHYHCVHACEGCK DRASCHYHCVHACEGCK NASCHYHCVHACEGCK KASCHYHCVHACEGCK KASCHYHCVHACEGCK KASCHYCVHACEGCK METCOLAEGTLVAKHVC METLONG METLONG</td> <td>SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         134           SFFRRTIRLKL         131           SAGV         264           SATA         264           SCGC         254           SCGC         254           MG         262           XVASGDIST         265            399           RPGLVVAHI         399           RPGLVVAHI         399           RPGLVVAHI         399</td>	LEDSULGSPLCTDDDFMG LEDSULGSPLCADDDFAG LEDSULGSPLCADDDFAG LEDSULGSPLCADDDFMG LESULGSPLS-UEFLQ GDPIMYSPLS-GELLG GDPIMYSPLS-GELLG CADDLESPLS-EFLQ GDPIMYSPLS-GELLG CKNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFQKCLSV KNRNK QYCRFKCLAV COCTSVETVTELTEFAK CQCTSVETVTELTEFAK CQCTSVETVTELTEFAK	GMEEFQD1SQS1DNDA GMEELQD1SQS1DNDA GMEELQD1SQS1DDDA GMEELD1SQS1SDDA EMGN1QETSQS1GEDS EMGN1QETSQS1GEDS EMGN1QETSQS1GEDS MQVLED1SQSLSDDT * :: *****: :: :: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPSSE GMSHNA1	LISSFDVPDYQ-SSS-NG LISSFDVPDYQ-SSS-NG LISSFCPNTENQ-SGLGSG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG SGSFGFADYQVLGSCPG FNSFHMLDYQNCDTAV ** A/B domain 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GYCRFQKCLSV COCTSVFTTELFFAR COCTSVFTTELFFAR COCTSVFTTELFFAR COCTSVFTTELFFAR COCTSVFTVELFFAR COC</td><td>GMEEFQD1SQSIDNDA GMEELQD1SQSIDNDA GMEELQD1SQSIDDDA GMEELQD1SQSIDDDA GMEELRD1SQSMEDDA EMGN1QETSQSIGEDS EMGN1QETSQSIGEDS * :: *****: :::: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPSE SVPGFSSLDLNDQVTI SVPGFSSLDLNDQVTI SVPGFSSLDLNDQVTI SVPGFSSLDLNDQVTI SVPGFSSLDLNDQVTI SVPGFSNLDLNDQVTI A1PGFANLDCVTI A1PGFANLDCVTI A1PGFANLDCVTI A1PGFANLDCVTI A1</td><td>LSSFDVPDYQ-SSS-NG LLSSFDVPDYQ-SSS-NG LLSSFCPNEVQ-SSS-NG LSSFCPAUPQ-SSS-NG LSSFCPAUPQ-SSS-NG SGSFGFAUVGVLSCPGS SGSFGFAUVGVLGSCPG SGSFGFAUVGVLGSCPG KLKLKAEWTGDREVEDF KLKLKAEWTGDREVEDF KLKLKAEWTGDREVEDF KLKLKAEWTTGREVEDF KLKLKAEWTTGREVEDF KLKLKAEUTCEHDLBD SKAKLKAE ILTCEHDLBD SKAKLKAE ILTCEHDLBD KKLKAE ILTCEHDLBD KKGVVEALFANLASSM LKYGVFALFANLASSM</td><td>EGSTVLDALTPA EGSTVLDALTPA EGSTVLDALTPA EGSTVLDALTPA EGSVTDTLSPA CONSTLDULTPA EGSVTDTLSPA POLADQKTLARGI QIADQKTLARGI QIADQKTLARGI QIADQKTLARGI QIADQKTLARGI COLADQKTLASI ETADLKSLKKI SCALVAYSSF KOCLVAYSF KOCLVAYSSF KOCLVAYSSF KOCLVAYSSF KOCLVAYSSF KOCLVAYSF KOCLVAYSF KOCLVAYSSF KOCLVAYSSF KOCLVAYSSF KOCLVAYSF</td><td>ISSPSSVV/GVAGGEEF ISSPSSIV/GVAGGEG ISSPSSVVGVASGEL ISSPSSGV/GVGVASGEL ISSPSSVVGVVASUEL ISSPSSVSVVPGVASUE ISSPSSVSVVPGSVDE ISSPSSVSVVPAGSVDE ISSPSSVSVVFAGA ISSPSSVSVVGSVAGA IVEAVLKNVMKAKART IVEAVLKNVMKAKART IVEAVLKNVMKKAKART IVEAVLKNVMKKAKART IVEAVLKNVMKKAKART IVEAVLKNVMKKAKART IVEAVLKNVMKKAKART IVEAVLKNVMKKAKART IVEAVLKNVMKKAKART III EFLKSLRAFSDM III EFLKSLRAFSDM III EFLKSLRAFSDM III EFLKSLRAFSDM III EFLKSLRAFSDM III EFLKSLRAFSDM III EFLKSLRAFSDM</td><td>SSSTSSLSLEFERVCAI SSSSSSLNLECRVCSI SSSSTSLNLECRVCSI TS-TSLNLECRUCSI SPS-GALNIECRLCGI SPG-SALNIECRLCGI SSG-SALNIECRLCGI : :: :******* IDTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILTCKTS-TPPFVIHI ILSCKSSNPPFVIHI ILSCKSSNPPFVIHI ILSCKSSNPPFVIHI 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PGLVVAHI         397           PGLSNPOPI         397           PGLSONPOPI         400  </td></td<>	EDSVLGSPLCTDDDFMG EDSVLGSPLCADDDFIG EDSVLGSPLCADDDFMG EDSVLGSPLCADDDFMG DDSVLDSALFVR EAGDLESPLSEFLQ GDPIMYSPLSGELG : : *.* : : KNRNK GYCRFQKCLSV KNRNK GYCRFQKCLSV COCTSVFTTELFFAR COCTSVFTTELFFAR COCTSVFTTELFFAR COCTSVFTTELFFAR COCTSVFTVELFFAR COC	GMEEFQD1SQSIDNDA GMEELQD1SQSIDNDA GMEELQD1SQSIDDDA GMEELQD1SQSIDDDA GMEELRD1SQSMEDDA EMGN1QETSQSIGEDS EMGN1QETSQSIGEDS * :: *****: :::: GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPQSE GMSHNA1RFGRMPSE SVPGFSSLDLNDQVTI SVPGFSSLDLNDQVTI SVPGFSSLDLNDQVTI SVPGFSSLDLNDQVTI SVPGFSSLDLNDQVTI SVPGFSNLDLNDQVTI A1PGFANLDCVTI A1PGFANLDCVTI A1PGFANLDCVTI A1PGFANLDCVTI A1	LSSFDVPDYQ-SSS-NG LLSSFDVPDYQ-SSS-NG LLSSFCPNEVQ-SSS-NG LSSFCPAUPQ-SSS-NG LSSFCPAUPQ-SSS-NG SGSFGFAUVGVLSCPGS SGSFGFAUVGVLGSCPG SGSFGFAUVGVLGSCPG KLKLKAEWTGDREVEDF 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SFGRV         264           SCGC         254           SCGG         262           SNVASGDIST         265            399           PGLVVVAHI         399           PGLVVVAHI         399           PGLVVAHI         397           PGLSNPOPI         397           PGLSONPOPI         400
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DRASGYHYGVHACEGCK MASGYHYGV</td> <td>SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         135           SFFRRTIRLKL         134           SFGRCV         264           SCGC         254           SCGC         264           SCGC         262           SNVASGDIST         265           SCG         399           PGLVVAHI         399           PGLVVAHI         399           PGLVVAHI         399           PGLVVAHI         397           PGLSNVPH         397           PGLSNVPH         300</td>	EDSVLGSPLCTDDDFMG EDSVLGSPLCADDDFIG EDSVLGSPLCADDDFMG EDSVLGSPLCADDDFMG DDSVLDSALFVR EAGDLESPLSEEFLQ EADDLESPLSEEFLQ EADDLESPLSEEFLQ GOPTMYSPLSGELLG KNNRKGQYGFQKCLSV KNNRKGQYGFQKCLSV KNNRKGQYGFQKCLSV KNNRKGQYGFQKCLSV KNNRKGQYGFQKCLSV KNNRKGQYGFQKCLSV KNNRKGQYGFQKCLSV KNNRKGQYGFQKCLSV KNNRKGQYGFFKCLSV KNNRKGYGFFFKCLSV KNNRKGYGFFFKCLSV KNNRKGYGFFFKCLSV KNNRKGYGFFFKCLSV KNNRKGYGFFFKCLSV KNNRKGYGFFFKCLSV KNNRKGYGFFFKCLSV KNNRKGYGFFFKCLSV 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**FIGURE 1** Amino acid sequences of ElovI5 (A) and PPAR $\alpha$ b (B) homologs in vertebrate. (A) Indicated are the highly conserved domains (CD1-3), five putative membrane-spanning domains (MS1-5) and the ER retrieval signal. (B) The four domains indicated by arrows are the N-terminal hypervariable region (A/B), DNA-binding domain (C), flexible hinge domain (D), and ligand-binding domain (E/F). Yellow and blue outlines indicate the eight zinc-binding sites in the DBD and the nine ligand-binding sites in the LBD, respectively. Moreover, the 12  $\alpha$ -helices (H) and four parts of the  $\beta$ -sheet (S) are indicated by a red oval and box, respectively. The accession numbers of the ElovI5 and PPAR $\alpha$ b sequences used and species abbreviation are listed in **Supplementary Table S3**.

cDNA in the presence of potential PUFA substrates. The results of heterologous expression showed that *ToElovl5* possessed high conversion activity toward C20 PUFA, especially 20:5n-3 (86.6 %)

and 20:4n-6 (84.8 %), followed by C18 substrates containing 18:3n-6 (67.4 %), 18:4n-3 (58.3 %), and 18:3n-3 (49.7 %) (**Figure 2** and **Table 1**).



**FIGURE 2** | Functional characterization of the putative *Elovl5* in transgenic yeast. Fatty acid methyl esters (FAMEs) were extracted from yeast transformed with the pYES2-Elovl5 and grown in the presence of PUFA substrates 18:3n-3 (A), 18:3n-6 (C), 18:4n-3 (E), 20:4n-6 (G), and 20:5n-3 (I). Based in retention times, additional peaks (marked with a triangular sign) were identified as 20:3n-3 (B), 20:3n-6 (D), 20:4n-3 (F), 22:4n-6 (H), and 22:5n-3 (J). Peaks 1–4 represent the main endogenous FAs of *T. ovatus*, namely C16:0, C16:1 isomers, C18:0 and C18:1n-9, respectively. Raw data are presented in **Supplementary Data Sheets 1–12**.

**TABLE 1** | Conversion rates of pYES2-ElovI5 transformed yeast grown in presence of 18:3n-3, 18:3n-6, 18:4n-3, 20:4n-6, and 20:5n-3 substrates.

FA substrate	Product	Conversion (%)	Activity
18:3n-3	20:3n-3	49.7%	C18→C20
18:3n-6	20:3n-6	67.4%	C18→C20
18:4n-3	20:4n-3	58.3%	C18→C20
20:4n-6	22:4n-6	84.8%	C20→C22
20:5n-3	22:5n-3	86.6%	C20→C22

Conversions are expressed as a percentage of total FA substrate converted to elongated products.

#### **ToPPARαb Structural Analyses**

In general, the 3D structure of ToPPAR $\alpha$ b was highly similar to that of the *Danio rerio* and *Homo sapiens* homologs



(Figure 3) (Liang et al., 2016; Ning et al., 2016). Moreover, the genomic structural features of  $PPAR\alpha b$  were further examined in metazoans. The phylogenetic relationship of PPARa in T. ovatus and other representative species was constructed (Figure 4A). The distribution and lengths of the exons and introns of each *PPAR*α gene are also shown in **Supplementary Table S2**. All PPAR $\alpha a$  and PPAR $\alpha b$  sequences had seven exons and six introns in fish, except for *Gasterosteus aculeatus* PPAR $\alpha a$ , which possessed eight exons and seven introns, while D. rerio PPARaa possessed six exons. Furthermore, the sizes of homologous intron sequences are different, while the exonic sequences showed nearly no diversity. Moreover, ToPPARab was grouped together with Oreochromis niloticus, which was also in the order Perciformes. The homology with ToPPARa, from close to distant, was other Osteichthyes, Amphibia, Aves, Mammalia, and Invertebrates. This result corresponded with the findings of conventional taxonomy.

#### Tissue Expression of ToPPARαb

The tissue expression pattern of *ToPPARab* was analyzed by qRT-PCR. The *PPARab* gene was extensively expressed in twelve tissues (**Figure 4B**). The transcription of *ToPPARab* was tissue specific, and this gene was highly expressed in small intestine and head-kidney, followed by white muscle, stomach, gonads and brain (P < 0.05), with lower expression in the spleen, fin and blood (P < 0.05).



**FIGURE 4** The structure and tissue expression of the *ToPPAR* $\alpha$ b gene. (A) Genome structure analysis of *PPAR* $\alpha$  genes according to the phylogenetic relationship. Lengths of exons and introns of each *PPAR* $\alpha$  gene are displayed proportionally. Different color boxes and lines represent exons and introns, respectively. The identical color boxes represent homologous sequences. (B) Gene transcription of *ToPPAR* $\alpha$ b in various tissues. The twelve tissues are small intestine (In), head-kidney (Ki), white muscle (Wm), stomach (St), female gonad (Fg), male gonad (Mg), brain (Br), liver (Li), gill (Gi), spleen (Sp), fin (Fi), and blood (BI). The data from different tissues were analyzed by the Duncan test using one-way ANOVA. Data are shown as the means  $\pm$  SD. Different letters indicate significant differences (p < 0.05).



**FIGURE 5** Promoter activity analysis of the *ToElovI5* gene. **(A)** The structure and transcriptional activity of *ToElovI5* promoters. Five recombinant plasmids, denoted ElovI5-1 (-382 to +89), ElovI5-2 (-793 to +89), ElovI5-3 (-1262 to +89), ElovI5-4 (-146 to +265) and ElovI5-5 (-146 to +459) were constructed and transfected with transcription factor PPAR $\alpha$ b into HEK 293T cells. **(B)** Dual-luciferase activity driven by the *ToElovI5*-5 core promoter upon the transfection of pcDNA3.1-PPAR- $\alpha$  and pcDNA3.1 in HEK 293T cells. All values are presented as the means  $\pm$  SD (n = 3). Asterisks indicate that the values are significantly different from the individual controls (\*p < 0.05 and \*\*p < 0.01). Bars on the same group with different letters are statistically significant from one another (p < 0.05).

## PPARαb Positively Promotes ToElovI5 Expression

A total of 1,721 bp of the 5' flanking sequence of the *Elovl5* gene was cloned and defined as the candidate promoter. To determine the promoter activity of *ToElovl5* with the transcription factor PPAR $\alpha$ b in HEK 293T cells, a series of progressive deletion constructs were made (**Figure 5A**). Compared with the activity of the promoter candidate (Elovl5-4), a deletion of fragment from -146 bp to +459 bp (Elovl5-5) increased promoter activity with PPAR $\alpha$ b. The expression levels of Elovl5-5 were 6.8-fold greater than those of Elovl5-4 with PPAR $\alpha$ b (**Figure 5A**), suggesting that the core promoter region was located at +265 bp to +459 bp, which contained the PPAR $\alpha$ b binding sites. To further confirm the interaction of ToPPAR $\alpha$ b with *ToElovl5*, the influence of ToPPAR $\alpha$ b overexpression increased the promoter activity of ToElovl5-5 at all tested time points in heterologous HEK 293T cells, and the maximum difference occurred at 24 h posttransfection, which was detected as 6.2-fold higher in PPARαb-overexpressing cells than that in the controls (**Figure 5B**). These results indicated that constitutively expressed PPARαb positively regulated *ToElovl5* expression in HEK 293T cells.

### ToPPARαb Knockdown Decreased ToElovI5 Transcription in TOCF Cells

In addition to the above results in HEK 293T cells, the function of PPAR $\alpha$ b on *Elovl5* was further confirmed in TOCF cells (**Figures 6A,B**). In the RNAi experiment, the mRNA expression of *ToPPAR\alphab* was drastically reduced in a time-dependent manner, except at 0 h, suggesting the effective knockdown of *ToPPAR\alphab* expression. When *ToPPAR\alphab* mRNA was depleted, *ToElovl5* transcription was significantly repressed compared with the control at the corresponding time points. This result



demonstrated a positive regulatory role for  $ToPPAR\alpha b$  on ToElovl5 mRNA expression in the native *T. ovatus* host.

# The Expression of ElovI5 Was Monitored by the Specific Inhibition and Activation of PPAR $\alpha$ b

After stimulation for 24 h, the mRNA expression of ToPPAR $\alpha$ b was drastically increased by a PPAR $\alpha$ b activator (WY-14643) and memorably decreased by an inhibition (GW6471) in a concentration-dependent manner (**Figures 6C,D**). Moreover, both *ToPPAR\alphab* and *ToElovl5* showed the same expression trend. The mRNA levels of *Elovl5* (P < 0.05) dramatically increased with the addition of the PPAR $\alpha$ b activator (**Figure 6C**), nevertheless the expression of *Elovl5* was suppressed after addition of the PPAR $\alpha$ b inhibitor (**Figure 6D**) in a concentration-dependent manner. These results demonstrated that ToPPAR $\alpha$ b played a positive regulatory role in *ToElovl5* transcription in *T. ovatus*.

#### DISCUSSION

Trachinotus ovatus is widely cultured because of its great commercial value in China. Recently, a study investigating

the LC-PUFA content in *T. ovatus* muscle showed that high retention of LC-PUFA occurred in muscle (Zhang et al., 2010). Elongases play core roles in the biosynthesis of LC-PUFA in fish (Castro et al., 2016). Consequently, a better understanding of the potential regulating mechanisms for the transcription of *ElovI5* elongase would conduce to improve the endogenous LC-PUFA synthetic ability of the *T. ovatus*.

Similar to other teleost Elov15 proteins, the isolated T. ovatus Elov15 possessed all the features of the elongase family including a histidine box (HXXHH), canonical C-terminal ER retrieval signal (KXRXX), and transmembrane domains, supporting its role in LC-PUFA biosynthesis (Jakobsson et al., 2006; Monroig et al., 2012; Xie et al., 2016). The ToElov15 could efficiently elongate C18 (18:3n-3, 18:3n-6, and 18:4n-3) and C20 (20:4n-6 and 20:5n-3) substrates to C20 and C22 PUFA, respectively, consistent with previously reported specificities in mammal (Leonard et al., 2000) and teleost (Hastings et al., 2005; Zheng et al., 2009; Gregory et al., 2010; Mohd-Yusof et al., 2010; Morais et al., 2011; Castro et al., 2016), clearly demonstrating that vertebrate ElovIs universally had extensive substrate specificity. Furthermore, the Siganus canaliculatus Elovl5 had a predilection for n-3 over n-6 PUFA substrates, which was similar to that in most species studied previously, containing both freshwater and marine fish (Mohd-Yusof et al., 2010; Morais et al., 2011).

Additionally, previous studies found that LC-PUFA and their metabolites can regulate transcription of lipid metabolism related genes through modulation of transcription factors including, among others, PPARs (Sampath and Ntambi, 2005). Thus far, three major types of PPARs have been identified, namely, PPAR $\alpha/\beta/\gamma$ . PPAR $\alpha$  is the major PPAR subtype found in hepatocytes and is involved in the regulation of lipid and carbohydrate metabolism genes. Three PPARs function by dimerization with the retinoid X receptor (RXR) and binding to a prescribed DNA sequence, termed the PPAR response element (PPRE) (Desvergne and Wahli, 1999). Similar to PPARa in other species, the ToPPARab amino acid sequence revealed four representative domains. The DBD domain, the most conserved domain in PPARs, comprises two zinc finger-like motifs folded in a circular structure that identifies the DNA target sequence AGGNCA, and the binding of the PPAR/RXR heterodimer to the PPRE regulates the target gene (Ijpenberg et al., 1997). Analysis of the ToElovl5 promoter region revealed the presence of typical binding sites of PPARa and Elovl5, and putative binding sites of between ToPPARab and the ToElovl5 promoter region need further verification. Nevertheless, the regulatory mechanism of ToElovl5 is complex. PPARab is one of the important factors for the increased expression of ToElovl5 in T. ovatus.

Based on the tissue expression profile of  $ToPPAR\alpha b$ , high mRNA levels were detected in metabolically active adipose tissues containing fatty acids, such as intestine, kidney, muscle, stomach, gonads and brain. A similar expression pattern was determined in several other marine fish species, such as *Liza haematocheila*, *O. niloticus*, and *Lateolabrax japonicus*, which also showed limited LC-PUFA biosynthesis capacity (Dong et al., 2015; Ning et al., 2016; Yang et al., 2017). Since these tissues are major metabolic sites for LC-PUFA (Agbaga et al., 2010), it was reasonable that the *ToPPAR\alphab* gene showed relatively high expression.

Numerous studies have shown that PPARa was necessary for the clofibrate stimulation of peroxisomal and microsomal enzymes, such as acyl-CoA oxidase (AOX) (Berthou et al., 1995), the rate-limiting enzyme for fatty acid  $\beta$ -oxidation (Brandt et al., 1998), SREBP-1c (Yoshikawa et al., 2003) and fatty acid transport proteins and translocases in the liver (Frohnert et al., 1999). Moreover, PPARs are ligand-activated transcription factors that regulate gene expression in the PUFAs biosynthesis pathway (Sampath and Ntambi, 2005). In the present study, the positive regulatory role of ToPPARab in ToElovl5 transcription in T. ovatus was characterized. The results of the luciferase reporter assay, as well as RNAi analysis, clearly demonstrated that ToElovl5 expression was regulated by PPARab in T. ovatus (Figures 5, 6A,B). These results provided the first evidence of the involvement of PPARab in the expression of the rate-limiting enzyme Elov15. ToElov15 transcription indicated increasing profiles in either native TOCF cells or heterologous HEK 293T cells. These results were reasonable due to the stress caused by the disturbed biological environment during in vitro TOCF cell culture or Elov15 promoter expression in the heterologous host (Liu et al., 2018).

To further determine the transcription mechanism of ToPPAR $\alpha$ b in *T. ovatus*, the mRNA levels of *ToPPAR\alphab* and *ToElovl5* were detected. The transcription of *ToPPAR\alphab* and *ToElovl5* was prominently increased or decreased in a concentration-dependent manner of activator or inhibition, respectively (**Figures 6C,D**). This observation was consistent with the results of studies implemented in mammals (Wang et al., 2005, 2006), suggesting that *ToPPAR\alphab* could up-regulate *ToElovl5* in fish. The results of the *in vitro* experiment in the present study confirmed the above findings by over-expression and suppression of *ToPPAR\alphab*. These results verified the direct stimulatory role of PPAR $\alpha$ b on *Elovl5* and suggested that such regulatory mechanisms operated differently compared to mammals.

In general, structural complexity was caused by intron gain or loss, which is a core evolutionary mechanism in most gene families (Yu et al., 2018). An exon-intron structure analysis of the *ToPPARab* gene indicated that all *PPARab* genes had six exons, while *PPARaa* had seven exons in fish, except *G. aculeatus PPARaa*, which possessed eight exons, and *D. rerio PPARaa*, which possessed six exons. These findings might represent introns gained or lost during evolution and may also suggest that the metazoan *PPARa* genes consisted of highly conserved numbers of exons and introns. The results of the phylogenetic analysis were consistent with the findings of conventional taxonomy, suggesting that *ToPPARa* exhibited a closer genetic relationship with Perciformes, such as *O. niloticus PPARa*.

In summary, we demonstrated clear associations between PPAR $\alpha$ b and the *ToElovl5* promoter, as well as the positive regulatory functions of PPAR $\alpha$ b in *ToElovl5* transcription in *T. ovatus*. Moreover, the proposed synthesis pathway of LC-PUFA in *T. ovatus* (**Supplementary Figure S3**). The present study provided the first evidence of a positive regulator of *ToElovl5* transcription. It would be interesting to further clarify the interactions between PPAR $\alpha$ b and the proposed cooperative companions to better comprehend the mechanisms underlying the PPAR $\alpha$ b-mediated regulation of *ToElovl5* transcription. Furthermore, the specific mechanism of PPAR $\alpha$ b in regulating *ToElovl5* by directly binding or being assisted by other proteins still needs further investigation.

#### **AUTHOR CONTRIBUTIONS**

K-CZ, S-GJ, and D-CZ designed the research and wrote the paper. LS, C-PZ, and K-CZ performed the research. H-YG and NZ analyzed the data. B-SL and LG contributed reagents, materials, and analysis tools.

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#### SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys. 2018.01340/full#supplementary-material

FIGURE S1 | The nucleotide sequence of *ElovI5* gene and the deduced amino acid sequence of *Trachinotus ovatus*. Initiation and termination codons are

#### REFERENCES

- Agbaga, M. P., Mandal, M. N., and Anderson, R. E. (2010). Retinal very longchain PUFAs: new insights from studies on ELOVL4 protein. *J. Lipid Res.* 51, 1624–1642. doi: 10.1194/jlr.R005025
- Bell, M. V., and Tocher, D. R. (2009). "Biosynthesis of polyunsaturated fatty acids in aquatic ecosystems: General pathways and new directions," in *Lipids in Aquatic Ecosystems*, eds M. T. Arts, M. T. Brett, and M. J. Kainz (New York, NY: Springer-Verlag), 211–236.
- Berthou, L., Saladin, R., Yaqoob, P., Branellec, D., and Calder, P. (1995). Relation of rat liver apolipoprotein A-I, apolipoprotein A-II and acyl-coenzyme A oxidase gene expression by fibrates and dietary fatty acids. *Eur. J. Biochem.* 232, 179–187. doi: 10.1111/j.1432-1033.1995.tb20797.x
- Brandt, J. M., Djouadi, F., and Kelly, D. P. (1998). Fatty acids activate transcription of the muscle carnitine palmitoyltransferase I gene in cardiac myocytes via the peroxisome proliferator-activated receptor-α. J. Biol. Chem. 273, 23786–23792. doi: 10.1074/jbc.273.37.23786
- Castro, L. F., Tocher, D. R., and Monroig, Ó (2016). Long-chain polyunsaturated fatty acid biosynthesis in chordates: insights into the evolution of Fads and Elovl gene repertoire. *Prog. Lipid Res.* 62, 25–40. doi: 10.1016/j.plipres.2016.01.001
- Cook, H. W., and McMaster, C. R. (2004). *Fatty Acid Desaturation and Chain Elongation in Eukaryotes*, 4th Edn, eds D. E. Vance and J. E. Vance (Amsterdam: Elsevier).
- Desvergne, B., Michalik, L., and Wahli, W. (2006). Transcriptional regulation of metabolism. *Physiol. Rev.* 86, 465–514. doi: 10.1152/physrev.00025.2005
- Desvergne, B., and Wahli, W. (1999). Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr. Rev.* 20, 649–688. doi: 10.1210/er.20.5. 649
- Dong, X. J., Tan, P., Cai, Z. N., Xu, H. L., Li, J. Q., Ren, W., et al. (2017). Regulation of FADS2 transcription by SREBP-1 and PPAR-α influences LC-PUFA biosynthesis in fish. *Sci. Rep.* 7:40024. doi: 10.1038/srep40024
- Dong, X. J., Xua, H. G., and Mai, K. S. (2015). Cloning and characterization of SREBP-1 and PPAR-α in Japanese seabass *Lateolabrax japonicus*, and their gene expressions in response to different dietary fatty acid profiles. *Comp. Biochem. Physiol. B* 180, 48–56. doi: 10.1016/j.cbpb.2014.10.001
- Frohnert, B. I., Hui, T. Y., and Bernlohr, D. A. (1999). Identification of a functional peroxisome proliferator-responsive element in the murine fatty acid transport protein gene. J. Biol. Chem. 27, 3970–3977. doi: 10.1074/jbc.274.7.3970
- Gregory, M. K., and James, M. J. (2014). Rainbow trout (Oncorhynchus mykiss) Elov15 and Elov12 differ in selectivity for elongation of omega-3 docosapentaenoic acid. Biochim. Biophys. Acta 1841, 1656–1660. doi: 10.1016/j. bbalip.2014.10.001
- Gregory, M. K., See, V. H., Gibson, R. A., and Schuller, K. A. (2010). Cloning and functional characterization of a fatty acyl elongase from southern bluefin tuna (*Thunnus maccoyii*). Comp. Biochem. Physiol. B Biochem. Mol. Biol. 155, 178–185. doi: 10.1016/j.cbpb.2009.11.002
- Hastings, N., Agaba, M. K., Tocher, D. R., Zheng, X., Dickson, C. A., Dick, J. R., et al. (2005). Molecular cloning and functional characterization of fatty acyl desaturase and elongase cDNAs involved in the production of eicosapentaenoic and docosahexaenoic acids from  $\alpha$ -linolenic acid in Atlantic salmon (Salmo salar). *Mar. Biotechnol.* 6, 463–474. doi: 10.1007/s10126-004-3002-8

marked by box. The structure and functional domains is underlined. Yellow marked endoplasmic reticulum retention signal.

**FIGURE S2** | The nucleotide sequence of *PPAR* $\alpha$ b gene and the deduced amino acid sequence of *Trachinotus ovatus*. Initiation and termination codons are marked by red. Yellow boxes indicate the two zinc finger domains (amino acid residues located in the C<sup>103</sup>-C<sup>123</sup> and C<sup>140</sup>-C<sup>157</sup>) were in DBD.

**FIGURE S3** The proposed synthesis pathway of PUFA in *T. ovatus*. Red arrows represent the pathway confirmed in *T. ovatus*.

 
 TABLE S1 | Primers used for sequence cloning, deletion mutant construction, mRNA construction and qRT-PCR.

**TABLE S2** | Lengths of exons and introns of each  $PPAR\alpha$  gene.

- **TABLE S3** | PPAR $\alpha$  and ElovI5 proteins used in multiple alignment.
- Ijpenberg, A., Jeannin, E., Wahli, W., and Desvergne, B. (1997). Polarity and specific sequence requirements of peroxisome proliferator-activated receptor (PPAR)/retinoid X, receptor heterodimer binding to DNA-A functional analysis of the malic enzyme gene PPAR response element. J. Biol. Chem. 272, 20108–20117. doi: 10.1074/jbc.272.32.20108
- Jakobsson, A., Jorgensen, J. A., and Jacobsson, A. (2005). Differential regulation of fatty acid elongation enzymes in brown adipocytes implies a unique role for Elovl3 during increased fatty acid oxidation. *Am. J. Physiol. Endocrinol. Metab.* 289, 517–526. doi: 10.1152/ajpendo.00045.2005
- Jakobsson, A., Westerberg, R., and Jacobsson, A. (2006). Fatty acid elongases in mammals: their regulation and roles in metabolism. *Prog. Lipid Res.* 45, 237–249. doi: 10.1016/j.plipres.2006.01.004
- Kabeya, N., Yamamoto, Y., Cummins, S. F., Elizur, A., Yazawa, R., Takeuchi, Y., et al. (2015). Polyunsaturated fatty acid metabolism in a marine teleost, Nibe croaker *Nibea mitsukurii:* functional characterization of Fads2 desaturase and Elov15 and Elov14 elongases. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* 188, 37–45. doi: 10.1016/j.cbpb.2015.06.005

Kota, B. P., Huang, T. H., and Roufogalis, B. D. (2005). An overview on biological mechanisms of PPARs. *Pharmacol. Res.* 51, 85–94. doi: 10.1016/j.phrs.2004. 07.012

- Lee, J. H., Kang, H. S., and Park, H. Y. (2017). PPAR alpha-dependent Insig2a overexpression inhibits SREBP-1c processing during fasting. *Sci. Rep.* 7:9958. doi: 10.1038/s41598-017-10523-7
- Leonard, A. E., Bobik, E. G., Dorado, J., Kroeger, P. E., Chuang, L. T., Thurmond, J. M., et al. (2000). Cloning of a human cDNA encoding a novel enzyme involved in the elongation of long-chain polyunsaturated fatty acids. *Biochem. J* 350, 765–770. doi: 10.1042/bj3500765
- Li, S. L., Monroig, O., and Wang, T. J. (2017). Functional characterization and differential nutritional regulation of putative Elov15 and Elov14 elongases in large yellow croaker (Larimichthys crocea). Sci. Rep. 7:2303. doi: 10.1038/ s41598-017-02646-8
- Li, W. X., Feng, Z. F., Song, X. J., Zhu, W., and Hu, Y. J. (2016). Cloning, expression and functional characterization of the polyunsaturated fatty acid elongase (ELOVL5) gene from sea cucumber (*Apostichopus japonicus*). *Gene* 593, 217–224. doi: 10.1016/j.gene.2016.08.023
- Li, Y. Y., Monroig, Ó, Zhang, L., Wang, S. Q., and Zheng, X. (2010). Vertebrate fatty acyl desaturase with D4 activity. *Proc. Natl. Acad. Sci. U.S.A.* 107, 16840–16845. doi: 10.1073/pnas.1008429107
- Liang, X., Gao, J., and Li, D. P. (2016). Cloning and expressions of peroxisome proliferator activated receptor alpha1 and alpha2 (PPARa1 and PPARa2) in loach (*Misgurnus anguillicaudatus*) and in response to different dietary fatty acids. *Biochem. Biophys. Res. Commun.* 481, 38–45. doi: 10.1016/j.bbrc.2016. 11.022
- Lin, Z. D., Huang, Y. S., Zou, W. G., Rong, H., Hao, M. L., and Wen, X. B. (2018). Cloning, tissue distribution, functional characterization and nutritional regulation of a fatty acyl Elov15 elongase in chu's croaker Nibea coibor. *Gene* 659, 11–21. doi: 10.1016/j.gene.2018.03.046
- Liu, H. R., Xu, D. L., and Cui, M. (2018). The transcriptional factor YB-1 positively regulates Hsc70 transcription in *Crassostrea hongkongensis*. *Biochem. Biophys. Res. Commun.* 495, 2404–2409. doi: 10.1016/j.bbrc.2017. 12.110

- Livak, K. J., and Schmittgen, T. D. (2001). Analysis of relative gene expression data using real-time quantitative PCR and the  $2^{-\Delta\Delta C}$ <sub>T</sub> method. *Methods* 25, 402–408. doi: 10.1006/meth.2001.1262
- Mohd-Yusof, N. Y., Monroig, Ó., Mohd-Adnan, A., Wan, K. L., and Tocher, D. R. (2010). Investigation of highly unsaturated fatty acid metabolism in the Asian sea bass, Lates calcarifer. *Fish. Physiol. Biochem.* 3, 827–843. doi: 10.1007/ s10695-010-9409-4
- Monroig, Ó., Wang, S. Q., and Zhang, L. (2012). Elongation of longchain fatty acids in rabbitfish Siganus canaliculatus: cloning, functional characterization and tissue distribution of ElovI5- and ElovI4-like elongases. Aquaculture 350-353, 63–70. doi: 10.1016/j.aquaculture.2012.04.017
- Morais, S., Mourente, G., Ortega, A., Tocher, J. A., and Tocher, D. R. (2011). Expression of fatty acyl desaturase and elongase genes, and evolution of DHA: EPA ratio during development of unfed larvae of *Atlantic bluefin* tuna (*Thunnus thynnus* L.). *Aquaculture* 313, 129–139. doi: 10.1016/j.aquaculture.2011.01.031
- Ning, L. J., He, A. Y., and Li, J. M. (2016). Mechanisms and metabolic regulation of PPARα activation in Nile tilapia (*Oreochromis niloticus*). *Biochim. Biophys. Acta* 1861, 1036–1048. doi: 10.1016/j.bbalip.2016.06.005
- Nugteren, D. (1965). The enzymic chain elongation of fatty acids by rat-liver microsomes. *Biochim. Biophys. Acta.* 106, 280–290. doi: 10.1016/0005-2760(65) 90036-6
- Sampath, H., and Ntambi, J. M. (2005). Polyunsaturated fatty acid regulation of genes of lipid metabolism. Annu. Rev. Nutr. 25, 317–340. doi: 10.1146/annurev. nutr.25.051804.101917
- Sun, L. Y., Guo, H. Y., Zhu, C. Y., Jiang, S. G., and Zhang, D. C. (2014). Genetic polymorphism of breeding populations of golden pompano (*Trachinotus* ovatus). South China Fish. Sci. 10, 67–71.
- Tamura, K., Stecher, G., and Peterson, D. (2013). MEGA6: molecular evolutionary genetics analysis version 6.0. *Mol. Biol. Evol.* 3, 2725–2729. doi: 10.1093/molbev/ mst197
- Tocher, D. R. (2015). Omega-3 long-chain polyunsaturated fatty acids and aquaculture in perspective. *Aquaculture* 449, 94–107. doi: 10.1016/j. aquaculture.2015.01.010
- Wang, Y., Botolin, D., Christian, B., Busik, J., Xu, J. H., and Jump, D. B. (2005). Tissue-specific, nutritional, and developmental regulation of rat fatty acid elongases. *J. Lipid Res.* 46, 706–715. doi: 10.1194/jlr.M400335-JLR200
- Wang, Y., Botolin, D., Xu, J. H., Christian, B., Mitchell, E., Jayaprakasam, B., et al. (2006). Regulation of hepatic fatty acid elongase and desaturase expression in diabetes and obesity. *J. Lipid Res.* 47, 2028–2041. doi: 10.1194/jlr.M600177-JLR200
- Wei, S. N., Yu, W. P., and Qin, Q. W. (2018). Establishment of a new fish cell line from the caudal fin of golden pompano *Trachinotus ovatus* and its susceptibility to iridovirus. *J. Fish. Biol.* 92, 1675–1686. doi: 10.1111/jfb.13566
- Xie, D. Z., Chen, F., and Lin, S. Y. (2016). Long-chain polyunsaturated fatty acid biosynthesis in the euryhaline herbivorous teleost *Scatophagus argus*: functional characterization, tissue expression and nutritional regulation of two fatty acyl

elongases. Comp. Biochem. Physiol. B Biochem. Mol. Biol. 198, 37–45. doi: 10. 1016/j.cbpb.2016.03.009

- Yang, W. P., Wang, A. M., and Liu, F. (2017). Peroxisome proliferator-activated receptor alpha (pparα) in redlip mullet, Liza haematocheila: molecular cloning, mrna tissue expression, and response to dietary lipid levels. *Turk. J. Fish. Aquat. Sci.* 17, 689–699. doi: 10.4194/1303-2712-v17\_4\_05
- Yoshikawa, T., Ide, T., and Shimano, H. (2003). Cross-talk between peroxisome proliferator-activated receptor (PPAR) alpha and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. I. PPARs suppress sterol regulatory element binding protein-1c promoter through inhibition of LXR signaling. *Mol. Endocrinol.* 17, 1240–1254. doi: 10.1210/me.2002-0190
- Yu, P., Shen, X., and Yang, W. (2018). ZEB1 stimulates breast cancer growth by upregulating hTERT expression. *Biochem. Biophys. Res. Commun.* 495, 2505–2511. doi: 10.1016/j.bbrc.2017.12.139
- Zhang, L. L., Xu, D. L., and Cui, M. (2018). The guanine nucleotide-binding protein  $\alpha$  subunit protein ChGnaq positively regulates Hsc70 transcription in Crassostrea hongkongensis. *Biochem. Biophys. Res. Commun.* 499, 215–220. doi: 10.1016/j.bbrc.2018.03.130
- Zhang, S., Xu, J., and Hou, Y. (2010). Comparison of fatty acid composition among muscles and visceral organs of *Trachinotus ovatus. Food Sci.* 31, 192–195.
- Zhen, P. L., Ma, Z. H., Guo, H. Y., Jiang, S. G., and Zhang, D. C. (2014). Ontogenetic development of caudal skeletons in *Trachinotus ovatus* larvae. *South China Fish. Sci.* 10, 45–50.
- Zheng, X., Ding, Z., Xu, Y., Monroig, O., Morais, S., and Tocher, D. R. (2009). Physiological roles of fatty acyl desaturase and elongase in marine fish: characterisation of cDNAs of fatty acyl  $\Delta 6$  desaturase and Elov15 elongase of cobia (*Rachycentron canadum*). *Aquaculture* 290, 122–131. doi: 10.1016/j. aquaculture.2009.02.010
- Zhu, K. C., Chen, L. P., Zhao, J. K., Wang, W. M., and Wang, H. L. (2014). Molecular characterization and expression patterns of myogenin in compensatory growth of *Megalobrama amblycephala. Comp. Biochem. Physiol. B Biochem. Mol. Biol.* 170, 10–17. doi: 10.1016/j.cbpb.2014.01.001

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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