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On the tubulin polymerization promoting proteins of zebrafish

Ferenc Orosz

Institute of Enzymology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Magyar Tudósok körútja 2, Budapest H-1117, Hungary

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ABSTRACT

Recently, Aoki et al. [15] have been published a paper (Biochem. Biophys. Res. Commun. 445 (2014) 357–362.) in which they identified possible downstream genes required for the extension of peripheral axons in primary sensory neurons of zebrafish. *Tppp* was claimed as one of them but, as I show, it is the *tppp3-like* gene, a paralog of *tppp*, which plays this role. There are three tppp paralogs in fishes: *tppp1* (named also *tppp*), *tppp3* and *tppp3-like*. *Tppp1* and *tppp3* are the orthologs of the corresponding human genes, however, the classification of the third one is ambiguous. It is known that the genomes of the early vertebrate lineage underwent two complete genome duplications, which result in the presence of several paralogs in vertebrates. A teleost fish specific third whole genome duplication also occurred. Thus the *tppp3-like* gene can be either an ortholog of human *TPPP2* or a fourth paralog (*tppp4*) absent in tetrapods but present in fishes; finally a *tppp3a* gene which can be originated from the third, fish specific, whole genome duplication. Comparing the sequences of vertebrate and recently available lamprey tppps I show that the *tppp3-like* gene is a *TPPP2* ortholog. Synteny data are in accordance with this suggestion.

1. Introduction

The family of TPPP-like proteins was described recently [1]. Its first member, tubulin polymerization promoting protein (TPPP or TPPP1) was first isolated from bovine brain [2] and later found to promote tubulin polymerization and stabilization of microtubules [3,4]. There are three TPPP paralogous genes in human, *TPPP1*, *TPPP2* and *TPPP3* (TPPP/p25, TPPP2/p18 and TPPP3/p20 at protein level) [5]. These paralogs can also be found in mammals, birds and reptiles. In fish, three paralogs exist as well; *tppp1* and *tppp3* are the orthologs of the corresponding human genes/proteins, however, the classification of the third one is ambiguous. Sometimes it is named as *tppp3-like* gene in databases. The reason of this name can be the fact that these proteins are more similar, indeed, to tetrapod TPPP3s than to TPPP2s or TPPP1s [6]. It is known that the genomes of the early vertebrate lineage underwent two complete genome duplications, which result in the presence of several paralogs in vertebrates in comparison with the single copy of their invertebrate orthologs [7–10]. A teleost fish specific third whole genome duplication also occurred [11–14]. Earlier, I have shown by synteny analysis that the probable history of the two-rounds duplication of the single invertebrate *tppp* gene was that the diversification of *tppp1* and the precursor of *tppp2*/*tppp3* occurred in the first round of whole-genome duplication which was followed by two further splits, *tppp1*/lost and *tppp3*/*tppp2*, in the second round [6]. However, it remained an open question the position of the fish-specific group of *tppps*. It can be considered either as *TPPP2* ortholog or as the fourth paralog (*tppp4*) that was lost in tetrapods but remained in fish; finally as *tppp3a* gene which is originated from the third, teleost fish specific, whole genome duplication [6].

Recently, Aoki et al. [15] have been published a paper in Biochemical and Biophysical Research Communications, in which they identified possible downstream genes required for the extension of peripheral axons in primary sensory neurons of zebrafish. *Tppp* was claimed as one of the several candidate genes. However, there is confusion in the paper since the three tppp paralogs are mixed up. In the text *tppp* is mentioned and the properties of vertebrate TPPP1 are discussed. It is claimed that its expression was investigated in various tissues. However, the supplementary table showing the genes investigated lists not *tppp* but "*tubulin polymerization-promoting protein family member 3*" i.e. *tppp3*. To reach a complete confusion, the NCBI Accession number XM_682834 is given in a table, which is the mRNA of the *tubulin polymerization-promoting protein family member 3-like* gene according to the NCBI Database.

Thus it seems to be necessary to clarify this question.

Abbreviations: TPPP, tubulin polymerization promoting protein.

E-mail address: orosz.ferenc@ttk.mta.hu.

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Table 1
TPPP genes/proteins of *Danio rerio*.

Name	Short name	Gene	GeneID	mRNA	Protein	Chromosome
Tubulin polymerization-promoting protein	*tppp*	*LOC100333482*	100333482	XM_002667721 EH550983[a] EH572114[b]	XP_002667767	Dre16 Unknown
Tubulin polymerization-promoting protein family member 3-like	*tppp3-like*	*LOC559490*	559490	XM_682834	XP_687926	Dre5
Tubulin polymerization-promoting protein family member 3	*tppp3*	*tppp3*	393825	NM_201335	NP_958492	Dre7

[a] 5′ Read.
[b] 3′ Read.

2. Materials and methods

2.1. Database homology search

TPPP homologs were identified with an NCBI blast search using the sequences of human TPPP proteins (NP_008961; NP_776245; NP_057048) as queries. BLASTP or TBLASTN analysis [16] was performed on complete genome sequences and EST collections available at the NCBI website (http://www.ncbi.nlm.nih.gov/BLAST/). Similar search was carried out on various fish databases: http://www.fugu-sg.org/; http://www.sanger.ac.uk/Projects/D_rerio/; http://www.ensembl.org/Tetraodon_nigroviridis/; http://dolphin.

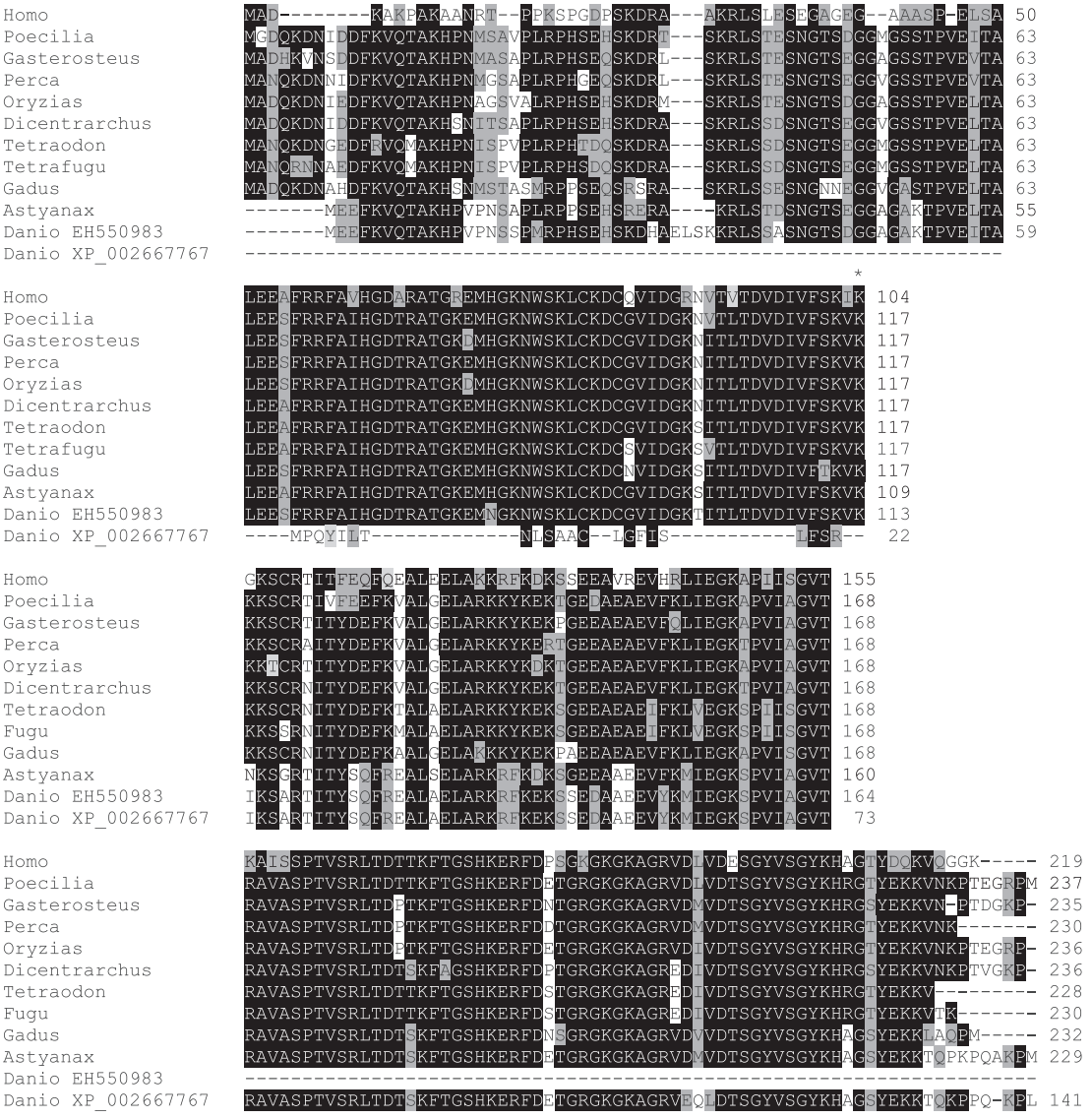

Fig. 1. Multiple sequence alignment of several fish TPPP1s by ClustalOmega. The alignment was refined manually. Residues identical and similar in the majority of the species are indicated by black and grey backgrounds, respectively. The first two lines represent the first coding exon; the third and the fourth lines correspond to the second and third exons, respectively. Asterisk notes that these amino acids are coded by the last two nucleotides of the first and the first nucleotide of the second exon. Proteins and ESTs (*) are: *Homo sapiens* NP_008961; *Poecilia reticulate* XP_008430776; *Gasterosteus aculeatus* DN734108*; *Perca flavescens* GO572248*; *Oryzias latipes* XP_004078142; *Dicentrarchus labrax* FM023946*; *Tetraodon nigroviridis* CAG11971; *Takifugu rubripes* XP_003966223; *Gadus morhua* GW848004*; *Astyanax mexicanus* XP_007234837; *Danio rerio* EH550983*, *Danio rerio* XP_002667767.

lab.nig.ac.jp/medaka/. The homepage of the Ensembl project [17]), http://www.ensembl.org/, was also checked for orthologs. Nucleotide sequences identified in TBLASTN searches were translated in the reading frames denoted in the TBLASTN hit, taking frame shifts or introns of genomic sequences into account.

2.2. Alignments of sequences

Multiple alignments of sequences were done by the *Clustal Omega* program [18].

2.3. Synteny analysis

Large scale investigation of synteny among TPPP loci Genomicus (http://www.dyogen.ens.fr/genomicus-76.01/cgi-bin/search.pl) [19] was used.

3. Results and discussion

3.1. TPPPs of the zebrafish (*Danio rerio*)

The zebrafish (*Danio rerio*) possesses the three TPPP-paralogs characteristic for teleost fishes (Table 1). TTTP3 and TPPP3-like proteins are very similar to the corresponding fish orthologs (not shown). The chromosomal localization of the coding genes is on Dre7 and Dre5, respectively. The position of *tppp* gene has been unknown until very recently and its tentative sequence based on whole genome shotgun scaffolds; now it is localized on Dre16. It can be seen that the second and third exon of the hypothetical XP_002667767 protein fits well to the sequences of the corresponding exons of the fish orthologs (Fig. 1) but the long first exon, which is very characteristic for TPPP1 paralogs, is much shorter and absolutely different. However, there are two ESTs (5′ and 3′ reads) whose translated sequences are homologous to the first two exons of TPPP1s. It worth to mention that the first exon contains the characteristic KRLS sequence, a phosphorylation site [20], which is present in all vertebrate TPPP1s without exception [1,5]. Moreover, the sequence of the second exon is completely identical with that of the second exon of XP_002667767, even at nucleotide level. (The third exon is missing which is not astonishing in the case of EST sequences.) Thus the TPPP1 protein of the zebrafish has very probably a similar sequence as TPPP1s of other teleost fishes and the sequence suggested here and not the hypothetical XP_002667767 corresponds to zebrafish TPPP1. This suggestion is supported by the result of TBLASTN search of the whole genome shotgun sequences of *D. rerio* against any of the fish TPPP1s which identified the Zv8_scaffold2999. Its manual translation shows that it encodes the whole TPPP1 including the three protein coding exons with the correct sequence (Fig. 2; Supplementary Fig. 1). This sequence is very similar (86% identity, 94% similarity) to that of the phylogenetically nearest relative, *Astyanax mexicanus* TPPP1 (Fig. 1).

The authors gave the sequence of the antisense oligonucleotide used to block protein translation. BLAST search and Clustal Omega alignment show unequivocally that the given sequence corresponds to a part of the mRNA of the *tppp3-like* gene exhibiting a 100% identity (data not shown). It enlightens that Aoki and co-workers' paper identifies this gene as possible downstream gene required for the extension of peripheral axons in primary sensory neurons.

Many data are known about the properties and function of human TPPP1, much less about TPPP3 and almost nothing about TPPP2. Thus one should be very cautious if predicts the properties and function of *tppp3-like* gene/protein on the basis of mammalian TPPP1 as the authors did. E.g., it was shown that TPPP1 and TPPP3 but not TPPP2 promoted tubulin polymerization and bundling of microtubules [5]. However, it should be emphasized that Aoki and co-workers' paper is the first one which provides data about a *tppp3-like* gene.

One of their findings may have an interesting consequence which can contribute to the clarification of the nature of the third fish tppp paralog (*tppp3-like*). They studied zebrafish embryos not adult animals and found that *tppp3-like* gene is expressed in various neurons. It is known that both TPPP1 and TPPP3 can be found in adult brains of various mammals. The exact localization of TPPP3 in brain is not known but TPPP1 can be found physiologically in oligodendroglia not in neurons [21–23]. Whilst TPPP1 seems to be brain-specific, TPPP3 has been found in other tissues as well [24–26]. The developmental expression of TPPP1 in rat brain shows that it is practically absent in embryos and after birth its amount increases continuously by aging [21]. On the contrary, mammalian TPPP2 is absent in adult brain but is expressed in fetal one [27]; i.e. the novel finding by Aoki et al. [15] may suggest that the third fish

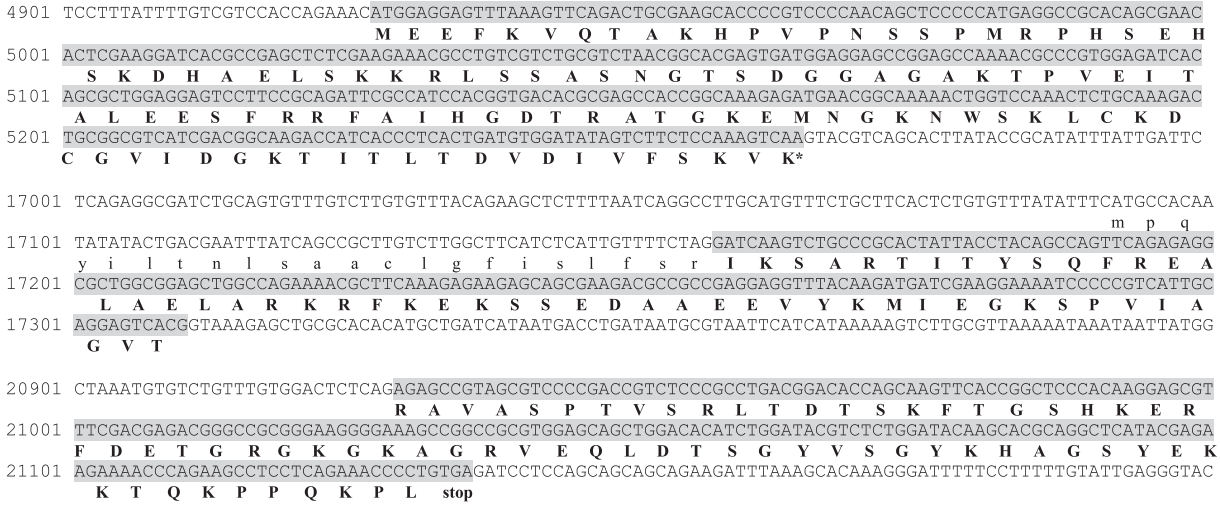

Fig. 2. Suggested sequence of *Danio rerio* TPPP1. Numbers indicate the order of nucleotides in Zv8_scaffold2999 of whole genome shotgun sequences of *Danio rerio*. Gray background indicates the three exons. The corresponding amino acids are shown with bold capital letters. Small letters stands for tentative amino acids of XP_002667767 which are suggested to be erroneous.

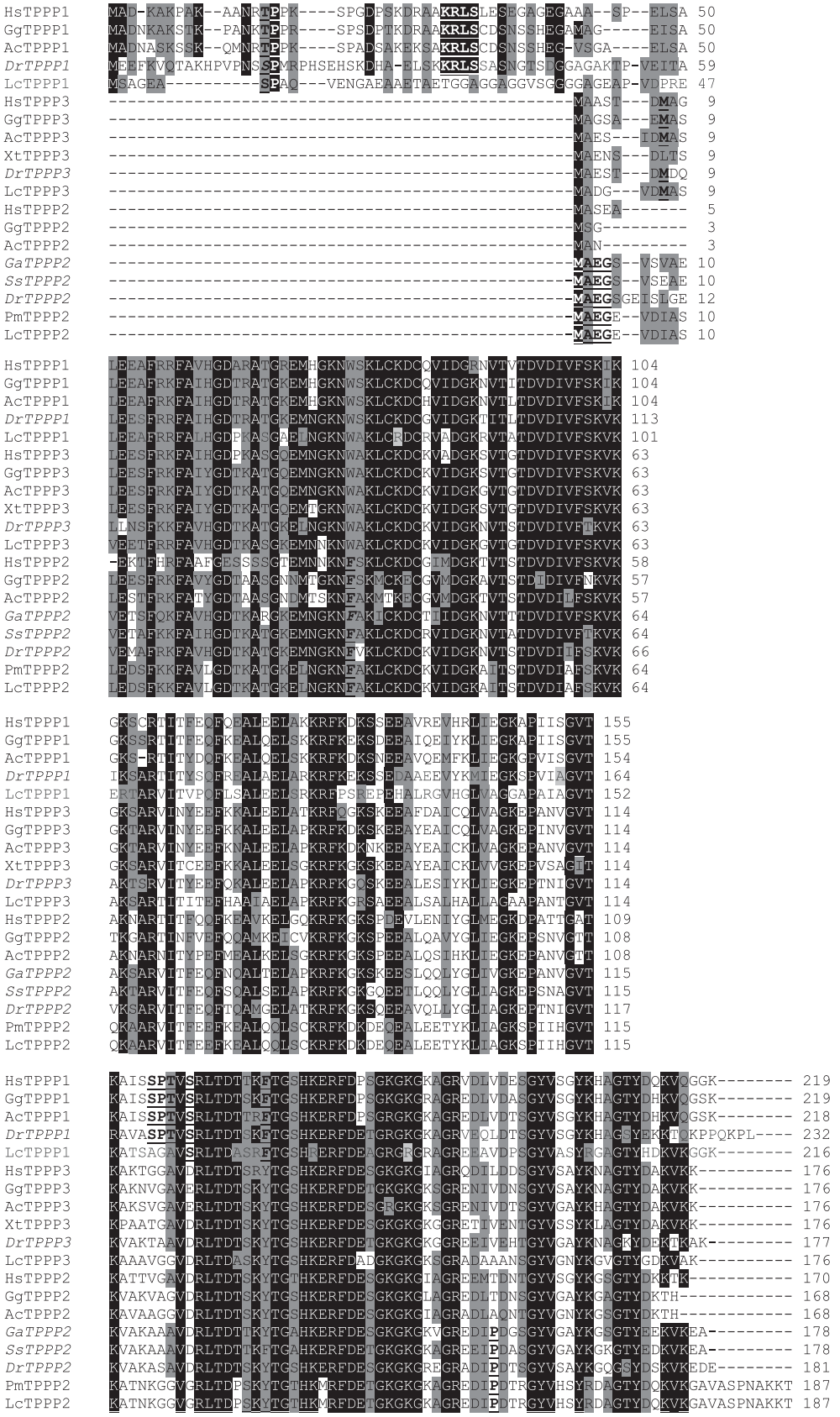

Fig. 3. Multiple sequence alignment of several TPPPs by ClustalOmega. The alignment was refined manually. Residues identical and similar in the majority of the species are indicated by black and grey backgrounds, respectively. Some amino acids characteristic for TPPP1s, TPPP2s or TPPP3s are labeled by bold and underlined letters. Proteins and nucleotids (*) are: HsTPPP1, HsTPPP2, HsTPPP3: *Homo sapiens* NP_008961, NP_776245, NP_057048; GgTPPP1, GgTPPP2, GgTPPP3: *Gallus gallus* XP_001231864, XP_424853, CR385779*; Ac TPPP1, AcTPPP2, AcTPPP3: *Anolis carolinensis* XP_003222359, XP_003224558, XP_003225414; XtTPPP3: *Xenopus tropicalis* NP_001096466; DrTPPP1, DrTPPP2, DrTPPP3: *Danio rerio* EH550983*-XP_002667767, XP_687926, NP_958492; GaTPPP4: *Gasterosteus aculeatus* DN725593*; SsTPPP4: *Salmo salar* GE789580*; PmTPPP2: *Petromyzon marinus* AEFG01009639*; LcTPPP1, LcTPPP2, LcTPPP3: *Lethenteron camtschaticum* APJL01058685-APJL01058681*, APJL01053114-APJL01053112*, APJL01048780*. Fish species are indicated by italic letters.

TPPP paralog is a TPPP2 ortholog or, at least, is in accordance with this hypothesis.

3.2. Nature of the third tppp gene (tppp2, tppp3-like or tppp4)

As I mentioned, the *tppp3-like* gene/protein can be considered either as *tppp2* ortholog or as the fourth paralog (*tppp4*) absent in tetrapods or as *tppp3a* originated from the fish specific whole genome duplication. On the basis of statistical analysis of phylogenetic trees, neither these cases could be excluded since this TPPP group could be placed on the phylogenetic tree into several different positions of almost equal probabilities [6]. Since all the phylogenetic analysis showed unequivocally that *tppp3-like* genes were not sister to *tppp1* genes thus comparing the phylogenetic and synteny data (cf. Introduction), the two possibilities remained that they were fish orthologs of tetrapod TPPP2s or fish specific paralogs (*tppp3a*) resulted from the fish specific whole genome duplication.

The recently published sequencing data of the sea lamprey (*Petromyzon marinus*) genome [28] may help finding the answer. The analysis of the data indicated that two whole-genome duplications likely occurred before the divergence of ancestral lamprey and gnathostome lineages [28]. Since the teleost fish specific third round duplication did not take place in lampreys thus *tppp3-like*, if it is present in these species, cannot be *tppp3a* but *tppp2*. A member of the tppp family was found on the scaffold_451.1-439126, namely the PMZ_0004762 gene. The presence of some amino acid sequences characteristic only for TPPP3-like proteins suggests that this lamprey gene/protein belongs to this “fish-specific” group. E.g., the N-terminal “MAEG” sequence is the same in the vast majority of the TPPP3-like proteins [6] but does not occur in any other TPPP (cf. Fig. 3). The phenylalanine in the “FAKL” sequence of the first exon is characteristic for the fish TPPP3-like and the tetrapod TPPP2 proteins, without exception, while in TPPP1s and TPPP3s there is always tryptophan in this position. TBLASTN search of the whole genome shotgun sequences of another lamprey species, *Lethenteron camtschaticum*, a phylogenetically very near relative of *P. marinus*, revealed that its genome contains three *tppp* genes, corresponding to the three genes occurring in fishes as well: *tppp1, tppp3, tppp3-like* (Fig. 3). (The translated sequences of *tppp3-like* genes in the two lamprey species are identical in 100%.) Thus it can be concluded that the *tppp3-like* gene existed before the divergence of ancestral cyclostome (including lampreys) and gnathostome lineages which means that *tppp3-like* genes are the orthologs of tetrapod *tppp2* genes. (Detailed phylogenetic analysis will be shown elsewhere.)

Smith et al. [28] provides also data in their paper mentioned above (in its Supplementary Table 10) that the neighbors of this sea lamprey *tppp3-like* gene are similar to human *CEP72* (Centrosomal protein of 72 kDa) and *ZDHHC11* (Probable palmitoyltransferase ZDHHC11), the genes next to human *TPPP1*. The orthologs of these two genes (*cep72* and *zdhhc11)* are neighbor to most of the fish *tppp1*s (Fig. 3). The neighbors of human *TPPP3* are the paralogs of these two genes; a *zdhhc11* paralog, *zdhhc1*, is nearby to fish *tppp3*s. In general, the genomic positions of *tppp1* and *tppp3*, but not that of *tppp2*, are stabilized in vertebrates: there are shared synteny among mammals, birds and teleost fishes in their case [6]. It means the preserved co-localization of a group of genes on chromosomes of different species. The situation is the same among various fishes as well: the position of *tppp1* and *tppp3* are conserved (Fig. 4). However, in the case of *tppp3-like (tppp2)* gene it does not hold. Comparing the chromosomal organization of *tppp1*, *tppp3* and *tppp3-like (tppp2)*, there are 22, 7 and 1 gene(s), respectively, which share their positions in a 30 gene window of the neighborhood of the *tppp* genes in the majority of the fish species (Fig. 4). This instability is in accordance with the finding that the fish-specific tppp3-like gene/proteins are tppp2 orthologs.

Fig. 4. Co-localization of *tppp* genes with other genes on chromosomes of various bony fishes. Genomicus version 76.01 was used to obtain the data for the figure. Genes conserved in the majority of the species are indicated with black background. Genes conserved in two and at least in three but not more than in the half of the species have white and gray background, respectively. Non-conserved genes are represented with empty boxes. Question marks label unknown genes.

Conflict of interest

The author declares no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.bbrc.2014.12.099.

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