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Review

Physiological role of genes involved in taurine biosynthesis in fishes and in silico approach to determine transcription factors in their promoters' zone

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ABSTRACT. Taurine, an amino sulfonic acid that is sometimes referred to as an amino acid, is endogenously synthesized by the action of the key genes/enzymes: cysteine dioxygenase (*cdo*), cysteine sulfonate decarboxylase (*csad*), glutamate decarboxylase (*gad*), and 2-amino ethanethiol dioxygenase (*ado*). The taurine transporter (*taut*) also distributes this taurine formation across the plasma. These genes have been identified as important in different physiological processes such as reproduction, digestion, olfactory, visual, circulatory, and muscular systems. Thus, a literature review of these genes in fish has been described in the present work. Moreover, there is null information regarding the study of regulatory elements such as transcription factors (TFs) in taurine biosynthesis and transportation genes of fishes. In this interest and taking advantage of the availability of different sequence databases, bioinformatics can be applied as a first approach for an in silico identification of the putative TFs and transcription factor binding sites (TFBS) that might play an important role in regulating these genes. The results showed that some are commonly shared, whereas TFs and TFBs vary among fish species. Hence, binding sites for homeobox protein BarH-like 1 (BARX1), brain-specific homeobox protein homolog (BSX), helicase-like transcription factor (HLTF), homeobox protein Hox-A7 (HOXA7), homeobox protein Hox-B3 (HOXB3), homeobox protein Hox-B6 (HOXB6), homeobox protein Meis1 (MEIS1), homeobox protein Meis3 (MEIS3), nuclear factor of activated T cells 1 (NFATC1), and homeobox protein Nkx-6.2 (NKX6-2) were commonly found in the promoter regions of genes involved in taurine transportation and biosynthesis. Additionally, our results suggested that the frequency of HOXB3, a transcription factor involved in development, has repetitive TFBS sites in the promoter region of all species analyzed in the present study. Although bioinformatics gives us an approach to determine putative TFs and TFBS, further work is needed to verify how the found regulatory elements play a key role in taurine biosynthesis and transportation.

Keywords: ß-aminosulfonic acid; taurine biosynthesis; taurine transporter; transcription factor

INTRODUCTION

Taurine, also known as 2-aminoethanesulfonic acid, is a simple molecule first isolated from the bile acid of the ox (*Bos taurus*) in 1827 by Leopold Gmelin and Friedrich Tiedemann (Tiedemann & Gmelin, 1827). It can be found in free form in most animals and is often called an amino acid (Huxtable & Sebring 1986). However, due to its structure, it is not part of the α-amino acids that synthesize proteins since it lacks the fundamental and less acid carboxyl group, what gives it its zwitterionic nature similarity to neutral membrane

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phospholipids, phosphatidylcholine, and phosphatidylethanolamine (Huxtable 1992); hence its high-water solubility and low lipophilicity, explaining its impermeability of biological membranes (Lambert et al. 2015). Moreover, some small peptides are known to exist naturally; nonetheless, there is no evidence of transfer RNA (tRNA) that codes for taurine, and its sulfonate group replaces the carboxyl group necessary for the formation of a peptide bond, therefore, cannot be part of translated peptide chains (Bittner et al. 2005).

The taurine pool can be found in vertebrate species' brains, retina, liver, kidney, heart, and muscle (Jacobsen & Smith 1968, Huxtable 1992). Furthermore, in mammals, the physiological role of taurine has been extensively investigated (Huxtable & Sebring 1986, Pion et al. 1987, Huxtable 1992, Militante et al. 2000, Parsons et al. 2001, Goodman et al. 2009, Ueki et al. 2012, Han et al. 2015) while in fishes different studies have demonstrated its relevance in the physiology of marine and freshwater fishes (El-Sayed 2014, Salze & Davis 2015, Mezzomo et al. 2018, Zhang et al. 2019, Sampath et al. 2020). As in mammals, different physiological roles of taurine have been observed in fishes that are involved in respiration, circulation, digestion, osmoregulation, sensorial system, muscular system, central nervous system (CNS), and reproduction (Higuchi et al. 2012, Mezzomo et al. 2018, Brill et al. 2019, Ceccotti et al. 2019, Salze et al. 2019). Most species can acquire taurine through food absorption in the intestine or endogenous synthesis from its precursor's methionine/cysteine (Kuzmina et al. 2010).

Most studies in taurine have been focused on the use of supplemented taurine. Moreover, transcriptomics has been applied to identify the effects on visual and olfactory system (Hu et al. 2018, 2020). Hu et al. (2018) studied the effects of taurine as a feed attractant in plant protein-based diets for large yellow croaker. Thus, the sequencing of the olfactory epithelium was conducted to identify genes differentially expressed in the taurine group (TAU) *vs*. controls. They detected 77 olfactory receptor genes, including 37 up-regulated unigenes, validating the expression of eight genes (52N4 (olfactory receptor family 52 subfamily N member 4), 10C1 (olfactory receptor family 10 subfamily C member 1), 2D3 (olfactory receptor family 2 subfamily D member 3), 13C2 (olfactory receptor family 13 subfamily C member 2), 4C11 (olfactory receptor family 4 subfamily C member 11), 2A12 (olfactory receptor family 2 subfamily A member 12) and 1361) using quantitative reverse transcription-PCR (RT-qPCR). The function of the differentially expressed genes was defined by the gene ontology (GO) and the Kyoto encyclopedia of genes and genomes (KEGG) and found that they are mainly involved in signaling and cell communication (GO) and olfactory transduction (KEGG), allowing further insights into the detailed mechanism of the olfactory system of fishes.

Consequently, this study demonstrates that using transcriptomics might be a better approach to understanding taurine roles. Another example of the role of taurine in the sensory system has been the work realized by Brill et al. (2019) in seabass *Dicentrarchus labrax* also fed protein diets. Although no effect on retinal anatomy or functional properties of luminous sensitivity were found in this work, authors found that the spectral sensitivity peak of individuals fed a 5% taurine diet was rightward shifted (i.e. towards longer wavelengths) relative to that of fish fed a 0 or 1.5% taurine diet.

Although taurine supplementation has widely been studied in fish species (Salze & Davis 2015, Sampath et al. 2020, Li et al. 2022) including the identification of genes involved in taurine biosynthesis of different species such as zebrafish *Danio rerio* (Liu et al. 2017), goldfish *Carassius auratus* (Luo et al. 2019), and tropical gar *Atractosteus tropicus* (Martínez-Burguete et al. 2023), there is no information regarding regulatory elements in those genes involved in the endogenous synthesis of taurine. Gene regulatory elements include promoters, enhancers, silencers, and insulators, where the promoter includes a core promoter and a proximal promoter region (Chatterjee & Ahituy 2017). In eukaryotes, the core promoter represents the minimal elements required to initiate transcription (Taher et al. 2015). Thus, these elements required to initiate transcription in the promoter region contain the general transcription machinery and transcription factors (Riethoven 2010). Transcription factors are proteins that can bind to specific DNA sequences of promoter regions (Mitsis et al. 2020). TFs and their binding sites in these promoter regions can be predicted using bioinformatic tools. Large data sets can be analyzed using bioinformatics to find patterns among organisms, whether model or non-model species.

Hence, in the present work, we have summarized the main physiological roles played by taurine biosynthesis and transport genes in different fish species based on a literature review. Moreover, due to the lack of information regarding putative transcription factors (TFs) and transcription factors binding sites (TFBS) that could be involved in regulating taurine biosynthesis and transportation genes in fishes, a bioinformatic approach was applied to investigate them.

Taurine biosynthesis and its transporters

In fishes, the biosynthesis of taurine occurs through three different pathways (Fig. 1), and the predominant pathway will depend on the species, type of tissue, stage of development, feeding habits, and the environment in which they live (Haga et al. 2015, Salze & Davis 2015, Sampath et al. 2020). One different pathway is pathway I (cysteine sulfinate-dependent pathway), where cysteine is oxidized by cysteine dioxygenase (CDO) and converted into cysteine sulfinic acid, which is then decarboxylated by cysteine sulfonate decarboxylase (CSAD) to form hypotaurine which is converted in taurine by hypotaurine dehydrogenase (HP-DH), CDO regulates the cysteine concentration, and CSAD enzyme is the rate-limiting step in taurine biosynthesis; pathway II (cysteine acid pathway), is also regulated by CDO. However, the product is metabolized to cysteic acid and converted to taurine by decarboxylation through glutamate decarboxylase (GAD). In pathway III (cysteamine pathway), taurine is obtained by converting cysteine into coenzyme A and then converted to cysteamine, which is oxidized by 2-aminoethanethiol dioxygenase (ADO) to form hypotaurine and form taurine by HP-DH. However, in the case of hypotaurine to taurine conversion by the action of HP-DH in pathways I and III, it is known that this reaction can also occur spontaneously, in addition to the fact that HP-DH has not been characterized (Roysommuti & Wyss 2015). The distribution of taurine endogenously synthesized or acquired from food is mainly regulated by the taurine transporter (*taut*; Wang et al. 2017, Xiong et al. 2020)

Cysteine dioxygenase (*cdo*)

Cysteine dioxygenase (*cdo*) is a gene that codes for the CDO protein (EC 1.13.11.20) and is one of the main enzymes in the formation of taurine and sulfate (2:1 ratio). It is found at high levels in the liver, while low levels predominate in the kidney, brain, and lungs (Stipanuk 2004). This iron metalloenzyme catalyzes the addition of molecular oxygen to the thiol group of cysteine, producing cysteine sulfinic acid, thus playing an important role in the catabolism of cysteine (Stipanuk et al. 2006). In mammals, it has extensively been studied (Driggers et al. 2015, Stipanuk et al. 2015, Dawson et al. 2020), and among these works, it has been shown that the deletion or silencing of *cdo* can produce abnormalities in organisms. For example, in rodents, Ueki et al. (2011) observed the differences in the physiological function of CDO and what happened after the loss of its activity. To achieve this, they crossed mice carrying a CDO null allele ($CDO^{+/-}$) to generate $CDO^{-/-}$, $CDO^{+/-}$ and $CDO^{+/+}$ mice and observed that $CDO^{-/-}$ mice had higher postnatal mortality, deficit growth and pathology of the connective tissue in the elastic fibers of the foot, as well as low levels of taurine and high levels of cysteine, which is due to the lack of flow of the CDO dependent catabolic pathways. However, in fishes, the depletion through knockout models of CDO has not been explored. The reported works in fishes regarding CDO are focused on the identification, isolation, and regulation of the gene in some species like rainbow trout *Oncorhynchus mykiss* (Wang et al. 2015), zebrafish *D. rerio* (Liu et al. 2017) and goldfish *C. auratus* (Luo et al. 2019).

Cysteine sulfonate decarboxylase (*csad*)

The cysteine sulfonate decarboxylase (*csad*) gene is a gene that codes for the CSAD protein (EC 4.1.1.29) and is considered the limiting enzyme in the production of taurine, which is produced mainly in the liver (De la Rosa & Stipanuk 1985). CSAD catalyzes a decarboxylation reaction to cysteine sulfinic acid to form hypotaurine, which is then converted to taurine (Yokoyama et al. 2001). It is known that the lack of enzyme activity in cats can cause blindness, which is why taurine is considered an essential nutrient in their diet (Hayes et al. 1975). Its expression has been measured in organs such as the brain, gills, heart, kidney, spleen, liver, intestine, muscle, adipose tissue, ovary, and testis (Haga et al. 2015, Betancor et al. 2019, Poppi et al. 2019). In fish, species of the family Labridae, Scombridae, Soleidae, and Rajidae have been reported to lack the activity of CSAD (Salze & Davis 2015). Some studies on the silencing or elimination of the gene suggest that mortality and cardiac abnormalities may be the effects that organisms suffer when this occurs (Chang et al. 2013) and that, in turn, they can be recovered through taurine supplementation in the diet (Park et al. 2014). Among the works carried out in fish, which allow us to observe what happens when one of the genes involved in the biosynthesis of taurine is silenced or eliminated, is that carried out by Chang et al. (2013) in zebrafish. In this work, the researchers mutated a part of the *csad* gene, presumed to be the limiting enzyme in endogenous taurine production. In this work, they found that by mutating the gene and therefore not producing the CSAD protein, there was a reduction in taurine levels in embryos, early mortality increased, and cardiac abnormalities were found (pericardial edema, cardiac tube malformation). Therefore, to test whether taurine supplementation could influence embryos with the phenotype of cardiac abnormalities, they supplemented taurine in the environ-

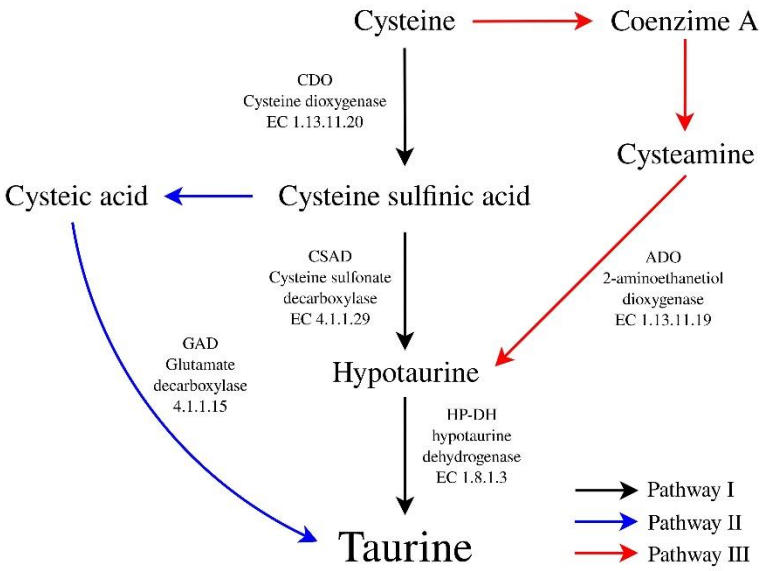

Figure 1. Pathways of taurine biosynthesis (adapted from Salze & Davis 2015). Pathway I, cysteine sulfinate-dependent pathway; Pathway II, cysteine acid; Pathway III, cysteamine.

ment in which the embryos were and managed to rescue these embryos. Nevertheless, most works on fish species have been conducted to identify their punctual identification and expression (Huang et al. 2014, Haga et al. 2015, Betancor et al. 2019, Poppi et al. 2020, Ma et al. 2021).

Glutamate decarboxylase (*gad*)

Glutamate decarboxylase (*gad*), also known as cysteic acid decarboxylase (*cad*), is a gene that codes for the GAD/CAD protein (EC 4.1.1.15) and is synthesized and expressed mainly in the brain (Wu et al. 1979). This enzyme participates in an alternative route to the main one for the formation of taurine, where cysteine is oxidized to cysteine sulfinic acid by the action of CDO, and later, instead of being decarboxylated, cysteine sulfinic acid is metabolized to cysteic acid which GAD/CAD decarboxylates to become taurine (Salze & Davis 2015).

It is known that there are three different isoforms of the gene in vertebrates (Grone & Maruska 2016). In fishes, some studies have been directed at the deep sea armed grenadier *Coryphaenoides* (*Nematonurus*) *armatus* (Trudeau et al. 2000), goldfish (Lariviere et al. 2002), zebrafish (Mueller & Guo 2009), and detected by RNAseq in gulf pipefish *Syngnathus scovelli* (Beal et al. 2018). Hence, in zebrafish, Cocco et al. (2017) studied *gad* localization in different brain regions and found three different paralogs, of which two resemble the *gad1* paralog of mammals and the third one the *gad2*. However, it has yet to be studied in fish in recent years. Therefore, with the advances in sequencing technology and bioinformatics, it would be interesting to study the regulation of the gene and its mechanism in fish.

2-aminoethanethiol dioxygenase (*ado*)

The 2-aminoethanethiol dioxygenase (*ado*) gene, also known as cysteamine dioxygenase (*cao*), encodes the ADO protein (EC 1.13.11.19) and participates in the alternate route of taurine biosynthesis by oxidizing cysteamine to form hypotaurine, which subsequently action of hypotaurine dehydrogenase to produce taurine (Stipanuk et al. 2015). Although it is the least studied gene of those involved in taurine biosynthesis, its expression in fishes may have been studied in different tissues and organs such as the hepatopancreas, brain, gills, intestine, muscles, eye, heart, spleen, kidney, and gallbladder of Atlantic bluefin tuna *Thunnus thynnus* (Watson et al. 2014, Betancor et al. 2019). Hence, Gonzales-Plasus et al. (2019) characterized the nucleotide and amino acid sequence in common carp *Cyprinus carpio* and quantified its expression in different tissues.

Taurine transporter

Taurine is distributed across the plasma membrane by taurine transporters (Mezzomo et al. 2018). These taurine transporters are the proton/amino acid symporter (PAT1) encoded by the solute carrier family 36 member 1 (*slc36a1*) and taurine transporter (TAUT) encoded by solute carrier family 6 membrane 6 (*slc6a6*)

being this last one the most studied (Lambert et al. 2015, Chen et al. 2019, Seidel et al. 2019). Hence, it is known that the adaptive response of *taut* to changes in the availability of taurine, when there are reduced levels of dietary taurine, elevated the expression of the gene (Han et al. 2006). In fishes, this regulation of *taut* availability can be observed in the distribution of different tissues of fishes like turbot *Scophthalmus maximus* (Wang et al. 2017, Wei et al. 2019), Atlantic bluefin tuna (Betancor et al. 2019), grass carp *Ctenopharyngodon idella* (Yan et al. 2019) and goldfish (Xiong et al. 2020). Kozlowski et al. (2008) characterized *taut* in zebrafish and observed its expression during embryogenesis.

Additionally, to understand the role of *taut*, they investigated the effect that a knockdown of the gene could have on these embryos. The results they found were a) the expression of *taut* is present from the very early stages of embryonic development in all tissues where taurine is known to be essential (retina, heart, brain, kidney, and blood vessels) and b) *taut* knockdown caused its low expression and results in a phenotype that involves cell apoptosis in the brain and spinal cord. These results determine the importance of *taut* during embryogenesis.

Therefore, further work regarding the use of different tools in molecular biology, such as site-directed mutagenesis or bioinformatics, to identify transcription factors that regulate taurine biosynthesis genes and the transportation of taurine should be accomplished for a better understanding of the physiological roles played by taurine.

METHODOLOGY

Retrieval of promoters, nucleotide, and amino acid sequences of organisms can be obtained from different public databases such as Ensembl, NCBI, and Uniprot (Yates et al. 2020, Madeira et al. 2022 Martin et al. 2023). For the present study, the Ensembl database (https://www.ensembl.org/index.html) was accessed to retrieve sequences for promoter analysis.

Promoter analysis of TFBS involved in taurine biosynthesis and transportation

Promoter regions spanning +2000 to -1 bp for *cdo*, *csad*, *gad*, *ado*, and *taut* of different species were retrieved from Ensembl (https://www.ensembl.org/) and converted to FASTA files. Species and their gene identifiers used for the analysis can be found in Table 1. The retrieved sequences were used to identify the TFs and TFBS using the software CiiiDER, version 0.9 (Gearing et al. 2019) using the Jaspar 2020 core vertebrate sequences. Because TFBS varies and rarely matches the model perfectly, a default deficit score of 0.05 was used, where a deficit score of 0 represents a perfect match. Once the software was run, results were obtained in .csv format, converted to .xls format, and used to calculate TFBS frequency to construct heatmaps using GraphPad Prism version 9.3.0 (San Diego, CA, USA).

Identification of TFs share among the promoter region of genes in the study was obtained using the http://bioinformatics.psb.ugent.be/webtools/Venn/ webtool of the Van de Peer Lab.

RESULTS

Complete raw results from the program CiiiDER can be found in Supplementary Material 1. The CiiiDER program predicted the presence of several TFs and TFBS on the promoter regions of all species in the study (Table 2). Identification of putative TFs exclusive of the promoter zone of the genes in each species is shown (Table 3).

Cysteine dioxygenase (*cdo*)

The promoter sequences of different fish species were used to identify the putative TFs and TFBS in *cdo*. Our finding shows that Arid3a, Arid3b, BARX1, BSX, Foxf, FOXL1, GATA3, GATA5, GSX1, GSX2, HLTF, HOXA7, HOXB3, HOXB6, LHX1, MEIS1, MEIS3, NFATC1, NFATC3, NFATC4, NKX6-2, RHOXF1, SOX15, Sox17, ZNF354C were present in all species while Alx3, Dlx1, Dlx2, Dlx3, DRGX, HOXB2 and HOXB8 were present in all except zebrafish. A representation of the comparison among the promoter zone of some of the species in the study can be observed (Fig. 2). The frequency of the TFBS of the TFs present in all species was also identified (Fig. 3). Moreover, the frequency of the TFBS for BSX, HLTF, and HOXB3 is constant among species. In addition, it can also be observed that LHX1 frequency in zebrafish is higher than in the rest of the species.

Cysteine sulfonate decarboxylase (*csad*)

Four hundred eighty-six putative TFs were found in the promoter region of *csad* of different fish species (Suppl. Mat. 1). We also found that Arid3b, BARX1, BSX, EVX1, EVX2, GSX1, HLTF, HOXA7, HOXB2, HOXB3, HOXB6, MEIS1, MEIS3, NFATC1, NFATC3, NKX6-2, PDX1, and RHOXF1 are present in all the species in study. The frequency of the TFBS

Table 1. Species and accession number of the genes in Ensembl used for the in silico approach to determine transcription factors (TFs) and transcription factor binding sites (TFBS) using CiiiDER software version 0.9 (Gearing et al. 2019).

Species	Common name	*cdo*	*csad*	*gad*	*ado*	*taut*
Poecilia formosa	Amazon molly	ENSPFOG00000002497	ENSPFOG00000001389	ENSPFOG00000011193	ENSPFOG00000020791	ENSPFOG00000008415
Salmo salar	Atlantic salmon	ENSSSAG00000045718	ENSSSAG00000077542	ENSSSAG00000081646	ENSSSAG00000071248	ENSSSAG00000068263
Salmo trutta	Brown trout	ENSSTUG00000030331	ENSSTUG00000049081	ENSSTUG00000030337	ENSSTUG00000021119	ENSSTUG00000013971
Ictalurus punctatus	Channel catfish	ENSIPUG00000025116	ENSIPUG00000022545	ENSIPUG00000020814	ENSIPUG00000023869	ENSIPUG00000009147
Cyprinus carpio	Common carp	ENSCCRG00000019916	ENSCCRG00000050160	ENSCCRG00000009363	ENSCCRG00000009651	ENSCCRG00000028865
Electrophorus electricus	Electric eel	ENSEEEG00000007791	ENSEEEG00000020397	ENSEEEG00000004961	ENSEEEG00000006255	ENSEEEG00000023351
Dicentrarchus labrax	European seabass	ENSDLAG00005030923	ENSDLAG00005001675	ENSDLAG00005000274	ENSDLAG00005020461	ENSDLAG00005010961
Takifugu rubripes	Fugu	ENSTRUG00000020607	ENSTRUG00000001632	ENSTRUG00000017805	ENSTRUG00000012216	ENSTRUG00000009909
Sparus aurata	Gilthead seabream	ENSSAUG00010005231	ENSSAUG00010018857	ENSSAUG00010026343	ENSSAUG00010014882	ENSSAUG00010000496
Carassius auratus	Goldfish	ENSCARG00000068233	ENSCARG00000017734	ENSCARG00000023792	ENSCARG00000047487	ENSCARG00000058589
Poecilia reticulata	Guppy	ENSPREG00000013161	ENSPREG00000020183	ENSPREG00000004050	ENSPREG00000012002	ENSPREG00000017002
Oryzias latipes	Japanese medaka	ENSORLG00000003390	ENSORLG00000008058	ENSORLG00000017268	ENSORLG00000027492	ENSORLG00000010119
Cyclopterus lumpus	Lumpfish	ENSCLMG00005007809	ENSCLMG00005009685	ENSCLMG00005021952	ENSCLMG00005021103	ENSCLMG00005002451
Oreochromis niloticus	Nile tilapia	ENSONIG00000014479	ENSONIG00000012260	ENSONIG00000008762	ENSONIG00000021007	ENSONIG00000000371
Esox lucius	Northern pike	ENSELUG00000018836	ENSELUG00000018621	ENSELUG00000021349	ENSELUG00000005239	ENSELUG00000018892
Oncorhynchus mykiss	Rainbow trout	ENSOMYG00000029549	ENSOMYG00000024325	ENSOMYG00000008187	ENSOMYG00000041907	ENSOMYG00000033005
Pygocentrus nattereri	Red-bellied piranha	ENSPNAG00000002994	ENSPNAG00000021775	ENSPNAG00000019728	ENSPNAG00000014619	ENSPNAG00000024574
Lepisosteus oculatus	Spotted gar	ENSLOCG00000008927	ENSLOCG00000006576	ENSLOCG00000007840	ENSLOCG00000018234	ENSLOCG00000013551
Seriola lalandi dorsalis	Yellowtail amberjack	ENSSLDG00000009729	ENSSLDG00000003612	ENSSLDG00000002119	ENSSLDG00000024277	ENSSLDG00000006439
Danio rerio	Zebrafish	ENSDARG00000099389	ENSDARG00000026348	ENSDARG00000093411	ENSDARG00000053571	ENSDARG00000098438

Table 2. Total transcription factor (TF) and transcription factor binding sites (TFBS) found in the fish under study.

Species	Common name	*cdo*		*csad*		*gad*		*ado*		*taut*	
		TF	TFBS	TF	TFBS	TF	TFBS	TF	TFBS	TF	TFBS
Poecilia formosa	Amazon molly	222	743	188	1135	233	919	137	404	179	472
Salmo salar	Atlantic salmon	184	965	198	533	173	526	201	746	189	441
Salmo trutta	Brown trout	201	649	191	502	189	606	216	643	190	541
Ictalurus punctatus	Channel catfish	164	385	214	795	211	685	228	723	219	1052
Cyprinus carpio	Common carp	262	968	224	783	198	618	213	937	213	545
Electrophorus electricus	Electric eel	227	963	179	778	132	309	203	624	212	729
Dicentrarchus labrax	European seabass	198	658	147	385	201	797	187	526	210	678
Takifugu rubripes	Fugu	222	652	183	544	223	494	259	956	222	506
Sparus aurata	Gilthead seabream	233	651	220	840	225	725	244	919	195	605
Carassius auratus	Goldfish	242	717	177	525	192	442	206	586	210	1064
Poecilia reticulata	Guppy	221	720	186	704	170	809	135	408	180	516
Oryzias latipes	Japanese medaka	211	1526	197	567	160	554	184	474	203	718
Cyclopterus lumpus	Lumpfish	189	458	204	754	223	854	251	1366	222	921
Oreochromis niloticus	Nile tilapia	226	953	220	472	198	736	285	688	202	675
Esox lucius	Northern pike	155	374	199	571	205	987	184	781	193	485
Oncorhynchus mykiss	Rainbow trout	186	557	241	951	197	631	217	651	199	508
Pygocentrus nattereri	Red-bellied piranha	189	494	230	680	211	904	206	505	225	652
Lepisosteus oculatus	Spotted gar	185	828	88	125	196	978	246	1048	189	543
Seriola lalandi dorsalis	Yellowtail amberjack	245	709	223	774	203	755	238	740	216	585
Danio rerio	Zebrafish	150	490	184	648	199	1064	196	866	219	815

of the TFs present in all species was also identified (Fig. 4). It can be observed that the frequencies of HLTF and HOXB3 in most of the species are higher than in the rest of the TFs. However, the frequency of the TFBS for spotted gar is really low.

Glutamate decarboxylase (*gad*)

The promoter region of *gad* was revised among 20 fish species, and 488 putative TFBS were found (Suppl. Mat. 1). The search retrieved that ALX3, Arid3a, BARHL2, BARX1, BSX, Dlx1, Dlx2, DRGX, EVX1, EVX2, GATA3, GATA5, HESX1, HLTF, HOXA6, HOXA7, HOXB3, HOXB6, HOXB8, LHX1, MEIS1, MEIS3, MIXL1, NFATC1, NFATC3, NFIX, NKX6-2, PRRX1, RAX, RAX2, RHOXF1, SHOX, Shox2, SOX15, Sox17, SRY, TLX2, UNCX, and ZNF354C were present in all studied species. Moreover, the TFBS frequency of these TFs is described in Figure 5, where it can be observed that HOXB3 in the studied promoter regions in the different fish species appears more frequently. In addition, Nile tilapia *Oreochromis niloticus* also presents high frequencies for EVX1, EVX2, and NKX6-2.

2-aminoethanethiol dioxygenase (*ado*)

In silico search for TFBS among 20 fish species, we retrieved 508 putative TFs (Suppl. Mat. 1). Our search found the following TFs to be present in all species: ALX3, Arid3a, ARNT::HIF1A, BARHL2, BARX1, BSX, Dlx1, Dlx2, Dlx3, DLX6, DRGX, ESX1, EVX1, EVX2, GATA3, GSX1, HESX1, HLTF, HOXA7, HOXB3, HOXB6, LHX1, MEIS1, MEIS3, MIXL1, NFATC1, NFIX, NKX6-2, OTX1, PRRX1, RAX, RAX2, SHOX, Shox2, SOX15, Sox17, TBX3, TLX2, UNCX, ZNF384. The frequency of the TFs can be observed in Figure 6. The frequency of HOXB3 in the promoter region of all species in the study was considerably higher than in the rest of the TFs. However, in species like seabass *Dicentrarchus labrax*, Japanese medaka *Oryzias latipes*, and red-bellied piranha *Pygocentrus nattereri*, the frequency of HLTF was higher than in HOXB3. Meanwhile, the frequency of ZNF384 TFBS for electric eel was higher than in the rest of the TFs.

Taurine transporter

The identification of TFBS among promoters' sequences of the gene *taut* for fish species gave back a total of 506 putative TFs (Suppl. Mat. 1). A total of at least 45 TFs are present in all fish species. These TFs are: ALX3, Arid3a, BARX1, BSX, Dlx1, Dlx2, Dlx3, DLX6, DRGX, ESX1, GATA3, GATA5, GSX1, GSX2, HESX1, HLTF, HOXA7, HOXB2, HOXB3, HOXB6, ISX, LBX2, LHX1, MEIS1, MEIS3, MIXL1,

Table 3. Putative transcription factors identified to appear only in each species of fish for the promoter sequence of cysteine dioxygenase (*cdo*), cysteine sulfonate decarboxylase (*csad*), glutamate decarboxylase (*gad*), 2-amino ethanethiol dioxygenase (*ado*), and taurine transporter (*taut*).

Species	Common name	*cdo*	*csad*	*gad*	*ado*	*taut*
Poecilia formosa	Amazon molly	ZBTB7C		SMAD3, SMAD5, TGIF2LY, Zic2, JUND(var.2)	POU4F3	ATF4, IRF2, JUN, SOX14, STAT1::STAT2, TAL1::TCF3
Salmo salar	Atlantic salmon	DUX4	HNF4A, HNF4G, HOXA13, MEF2A, OSR1, Znf423			CEBPA, MAX::MYC
Salmo trutta	Brown trout	ELK1, ELK3, ERF, ERG, ETS1, ETV3, FEV, FLI1, ZBTB33	ATF6, CREB3, CREB3L1, KLF15, XBP1, ZBTB18	RORA(var.2), RORC		CREB1, Hmx1, HSF1, HSF4, Klf1
Ictalurus punctatus	Channel catfish		FOXH1, HNF1A, HNF1B, MEF2C, Sox3, ZBTB6, ZNF148	Prdm15, ZNF148	TFAP2B(var.2), TFAP2E, YY1	CEBPG, Ebf2, JDP2, JUNB, Mecom, PHOX2B, TBX2, TBX4, TBX5
Cyprinus carpio	Common carp	ATOH7, BHLHE23, OLIG1, PBX3, Zic2	POU4F1, Pou5f1::Sox2	TBX1, TBX15, TBX18, TBX20	HOXA13, HOXD10, ZBTB18	ESR2, ESRRA, ESRRB, Nr5a2, POU3F3, RORA(var.2)
Electrophorus electricus	Electric eel	SREBF1	Crx, NFIC(var.2), NFIX(var.2), PBX1	NHLH1, NR1I2	DPRX, NR6A1, Plagl1, SOX21, ZNF740	NRF1, OSR1, TEAD1, TEAD4, ZFP57
Dicentrarchus labrax	European seabass	ESRRA, ESRRB, Esrrg, Nr5a2	DBP, FOXE1	Ebf2, EBF3, EGR1, HOXA13, HOXD13, PBX3, PKNOX1, SP1, SP2, SP4, SP9	Gfi1b, PROX1, SREBF1(var.2)	ZNF274
Takifugu rubripes	Fugu	MAFF, NR4A1, NRL, POU4F1, POU4F3, Rhox11, SOX12, ZFP57	USF1, USF2	CTCFL, ELF1, ELF5, ETV1, ETV5,,FOXC2, FOXD2, GABPA, HEY2, IKZF1, POU2F1, POU3F2, POU3F3, SCRT1, SCRT2, SPIB, SREBF1(var.2), TFEC	ETS2, FOXN3, HES2, NR2C2, PBX3, TFAP2A, TFAP2C(var.2), THRB	Creb3l2, ELK1, ELK4, ETS2, ETV3, HES2, HEY2, KLF11, SPDEF, TFEB, TFEC, ZBTB7A
Sparus aurata	Gilthead seabream	CTCFL, IRF2, NR1I2, SOHLH2	ETS2, RXRA::VDR, SPDEF, TFAP2B, TFAP2C, TFAP2C(var.2), TFAP2E, TFCP2	CEBPG, GCM1, GCM2, Wt1	CREM, MYBL1, ZBTB7C	RFX1
Carassius auratus	Goldfish	ATF7, CEBPG, Creb5, FOS::JUN(var.2), FOSB::JUN, FOSL1::JUN(var.2), JDP2(var.2), JUNB(var.2), STAT1, Stat4, Stat5a::Stat5b	ETV5, ETV6, ONECUT3	Crx, CUX2, ESR1, ESR2, PHOX2A, PHOX2B, PROP1, RELA, TFDP1	CEBPG(var.2), PROP1, SMAD3, SMAD5	MEF2A, RELB
Poecilia reticulata	Guppy		E2F6, E2F7, E2F8, GRHL2	SOX9	POU3F2	PBX3, PKNOX1, TCF7L1
Oryzias latipes	Japanese medaka	GFI1, Gfi1b, Hmx2, Hmx3, NR3C1, NR3C2, SP8	KLF4, Sox1	CEBPD, CEBPG(var.2), Sox3, TEF		SP1, TFAP2A(var.2), Wt1

Continuation

Species	Common name	*cdo*	*csad*	*gad*	*ado*	*taut*
Cyclopterus lumpus	Lumpfish	SMAD2::SMAD3::SMAD4	PKNOX1, POU3F1, POU4F3, Pparg::Rxra	Dmrt1, MYC, TFAP2B(var.2), TFAP2E, TFCP2	Lhx3, Nr2f6(var.2), ONECUT1, ONECUT2, PAX5, Rarg, RFX1, ZBTB6	HOXD10, KLF4, NR2C2, NR2F1(var.2),,Pparg::Rxra, SP8, THRB
Oreochromis niloticus	Nile tilapia	GATA1::TAL1, POU3F1, Pou5f1::Sox2, POU5F1B, TEAD1, TEAD4	EHF, ELF1, ETV1, FOXC2, GABPA, GCM2, GFI1, KLF9, MEF2B, MEF2D, NKX2-2, SP8, STAT1, Stat4, Stat5a::Stat5b, Stat5b	GFI1, KLF4	BACH2(var.2), Crx, Mecom, TBX1, TBX15, TBX18, TBX20, TBX21, TCFL5, USF2, ZNF143	RELA, ZNF341
Esox lucius	Northern pike	CTCF, DMRTC2, Klf1	PAX3	DUXA, FOXN3		ONECUT2, ONECUT3, PBX1, TCF21(var.2)
Oncorhynchus mykiss	Rainbow trout	FOS::JUN, FOS::JUNB, FOS::JUND, FOSL1, FOSL1::JUN, IRF7, JUNB, JUND, TFAP2B(var.2)	BACH2, RFX1, RFX3, ZBTB7C	JUN		ATOH1(var.2)
Pygocentrus nattereri	Red-bellied piranha	HOXB9, HOXC12, HOXC9, HOXD12, KLF15, KLF16	STAT1::STAT2	FOSL1::JUND(var.2), TEAD1, TEAD4, TFAP2A	BACH2, BHLHE22, ELF1, ETV1, GABPA, IKZF1, OLIG3, SIX1	DBP
Lepisosteus oculatus	Spotted gar	RUNX2, ZBTB32	CTCF, CTCFL, Plagl1	OVOL2, TFAP2B(var.3)	CEBPA, CEBPB, CEBPD, CEBPE, CEBPG, FOXB1, MAX::MYC, ORA(var.2), RORC, SCRT1, SCRT2, ZNF449	FOSB::JUN, FOSB::JUNB(var.2), FOSL1::JUN(var.2), FOSL1::JUND(var.2), FOSL2::JUN(var.2), FOSL2::JUND(var.2), JUND(var.2)
Seriola lalandi dorsalis	Yellowtail amberjack	IRF6, KLF11, KLF6, SCRT1, TCF21(var.2), ZNF449		ONECUT2, ONECUT3, PLAGL2	HOXD13, MAFF, MAFG, NKX2-2, PLAGL2, Stat5a	
Danio rerio	Zebrafish	CREM, HES2, MYF6, TEF, TFEC	PROP1, YY2	BHLHE23, GATA1, OLIG1, OLIG2, SMAD2::SMAD3::SMAD4, TCF21(var.2)	POU2F2, POU2F3, Prdm15	

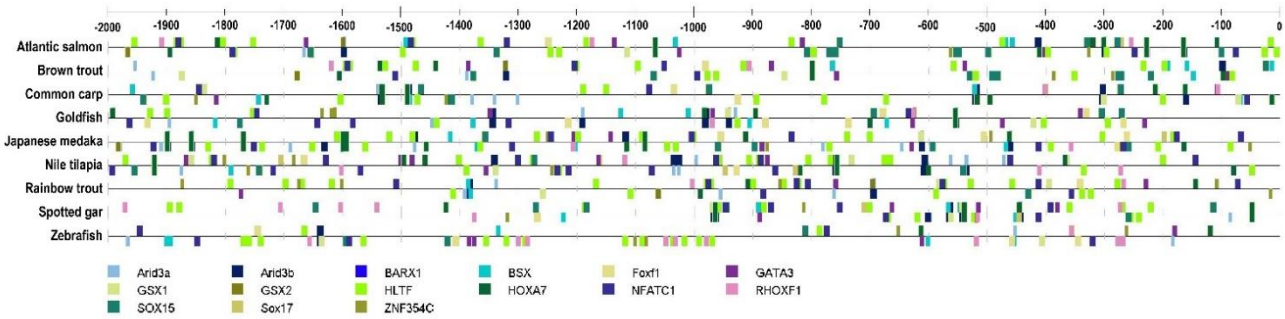

Figure 2. Top 15 putative transcription factors found in the promoter regions of *cdo* among some of the fish studied in the present review.

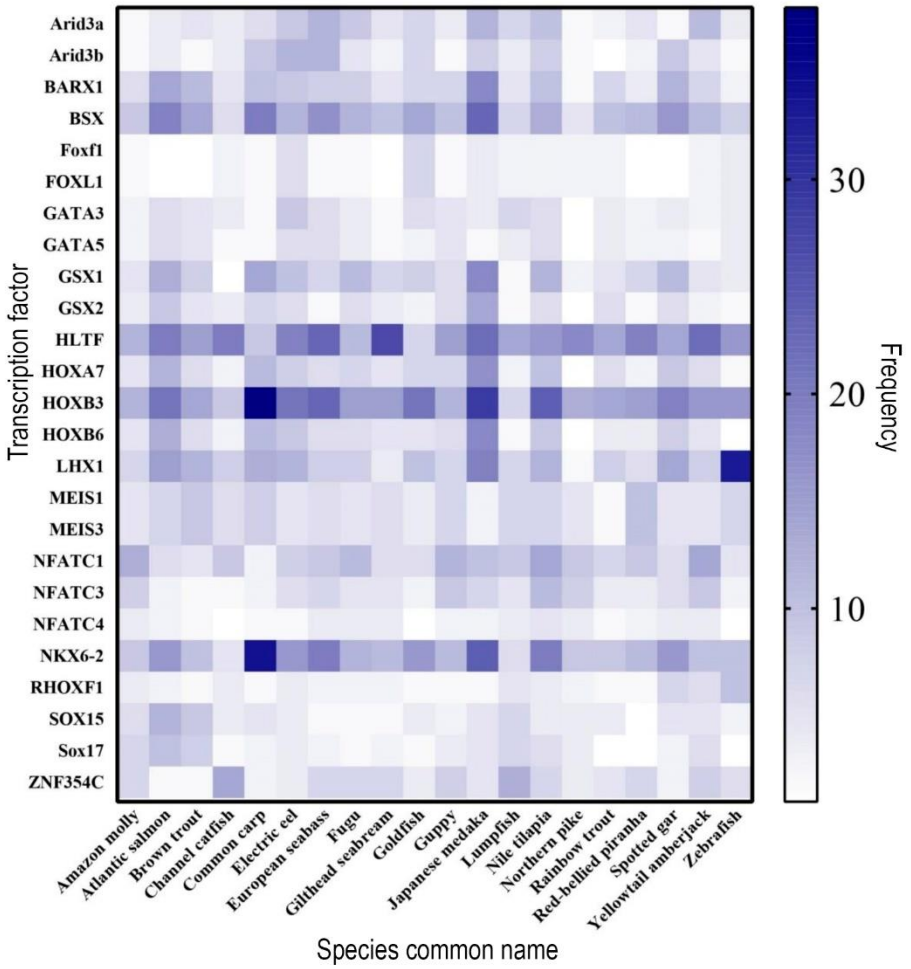

Figure 3. Frequency of transcription factors binding sites (TFBS) of transcription factors (TFs) found in the promoter region of *cdo* from fish species examined in the present study. Each column represents one species in study. The color of each cell is determined by the frequency of the TFBS in the promoter zone. Darker blue represents higher frequency within the promoter region of a TFBS of each TF and lighter blue represents low to absence of the TFBS.

NFATC1, NFATC3, NFATC4, NFIX, NKX6-2, NR2C1, PDX1, PRRX1, RAX, RAX2, SHOX, Shox2, Sox17, SRY, TLX2, UNCX, ZNF354C, ZNF384. The frequency of these TFs is graphed (Fig. 7). It can be observed that TFBS for HOXB3 is the most frequent for almost all species. However, ZNF384 in fugu presents higher frequencies in its promoter region.

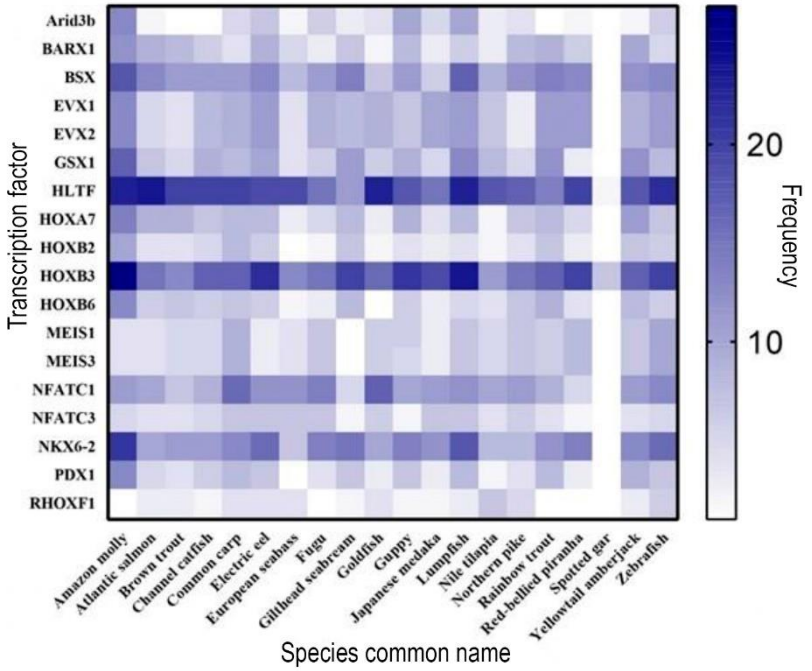

Figure 4. Frequency of transcription factors binding sites (TFBS) of transcription factors (TFs) found in the promoter region of *csad* from fish species examined in the present study. Each column represents one species in study. The color of each cell is determined by the frequency of the TFBS in the promoter zone. Darker blue represents higher frequency within the promoter region of a TFBS of each TF and lighter blue represents low to absence of the TFBS.

Identification of transcription factors among taurine biosynthesis and transport

In addition to identifying TFBS among species, the identification of putative transcription factors was compared among the genes involved in taurine biosynthesis. We found that binding sites for homeobox protein BarH-like 1 (BARX1), brain-specific homeobox protein homolog (BSX), helicase-like transcription factor (HLTF), homeobox protein Hox-A7 (HOXA7), homeobox protein Hox-B3 (HOXB3), homeobox protein Hox-B6 (HOXB6), homeobox protein Meis1 (MEIS1), homeobox protein Meis3 (MEIS3), nuclear factor of activated T cells 1 (NFATC1), and homeobox protein Nkx-6.2 (NKX6-2) were commonly found in the promoter regions of genes involved in taurine transportation and biosynthesis.

DISCUSSION

In the present study, a literature review was conducted to identify the major physiological roles played by genes involved in taurine transportation and biosynthesis in fishes. Taurine biosynthesis depends on each species' production capacity (Sampath et al. 2020). Thus, it has been reported that physiological damage can occur when this capacity is limited, or taurine is not being acquired from food sources (Li et al. 2022). This limited capacity has been identified in some species of the family Labridae, Scombridae, Soleidae, and Rajidae because of CSAD's lack of activity (Salze & Davis 2015). Meanwhile, the disruption of *csad* and *taut* has identified cardiac anomalies in zebrafish (Kozlowski et al. 2008, Chang et al. 2013, Park et al. 2014) as has been observed in other vertebrates such as mice, when elimination of *cdo* has been accomplished (Ueki et al. 2011).

Additionally, the identification of TFs and TFBS in the promoter regions of different fish species was also investigated to have a first look into the identification of putative TFs that might be regulating genes involved in the biosynthesis and transport of taurine due to the lack of information regarding this issue. Regulatory elements, such as TFs, play a key role in the regulation of genes, inducing or repressing their expression (Tellechea-Luzardo et al. 2023), while the combination of the TFBS with the promoter determines the condition of the gene expression (Lu & Rogan 2018). Therefore, our results showed that a wide distribution of TFs and TFBS are present in the promoter zone of the different fish studied. It was observed that a set of

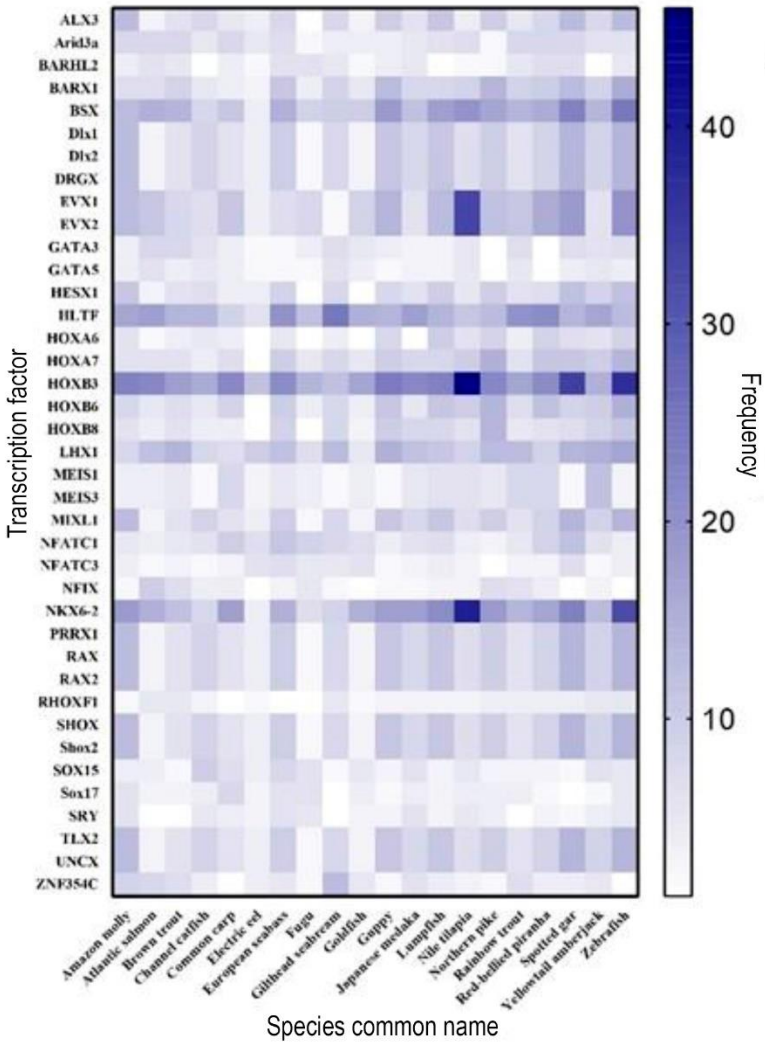

Figure 5. Frequency of transcription factors binding sites (TFBS) of transcription factors (TFs) found in the promoter region of *gad* from fish species examined in the present study. Each column represents one species in study. The color of each cell is determined by the frequency of the TFBS in the promoter zone. Darker blue represents higher frequency within the promoter region of a TFBS of each TF and lighter blue represents low to absence of the TFBS.

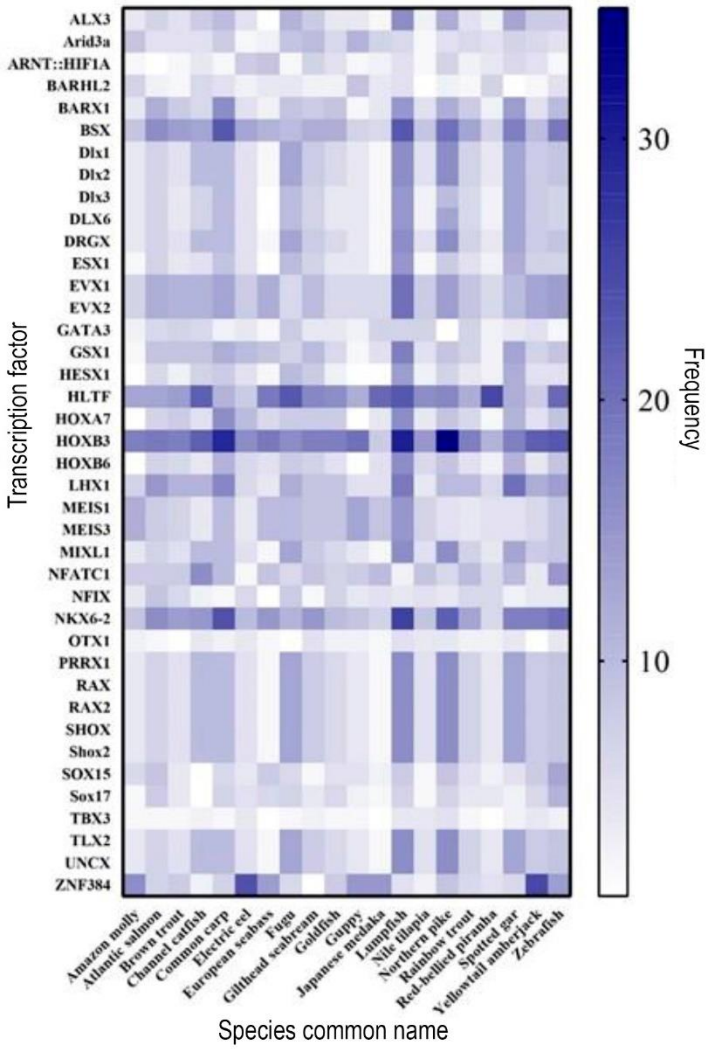

Figure 6. Frequency of transcription factors binding sites (TFBS) of transcription factors (TFs) found in the promoter region of *ado* from fish species examined in the present study. Each column represents one species in study. The color of each cell is determined by the frequency of the TFBS in the promoter zone. Darker blue represents higher frequency within the promoter region of a TFBS of each TF and lighter blue represents low to absence of the TFBS.

TFs is shared among species depending on the gene in the study. Nonetheless, it was also observed that in the case of zebrafish, some TFs are not shared with the other species for the promoter region of *cdo*. It was also noted that the promoter region of spotted gar for the gene *csad* was not completed as the rest of the species in the database Ensembl, limiting the recognition of TFs for this species.

There were the following shared set of TFs present in the promoter zone of the genes *cdo*, *csad*, *gad*¸ *ado*, and *taut* of all the fish analyzed: homeobox protein BarH-like 1 (BARX1), brain-specific homeobox protein homolog (BSX), helicase-like transcription factor (HLTF), homeobox protein Hox-A7 (HOXA7), homeob ox protein Hox-B3 (HOXB3), homeobox protein Hox-B6 (HOXB6), homeobox protein Meis1 (MEIS1), homeobox protein Meis3 (MEIS3), nuclear factor of activated T cells 1 (NFATC1), and homeobox

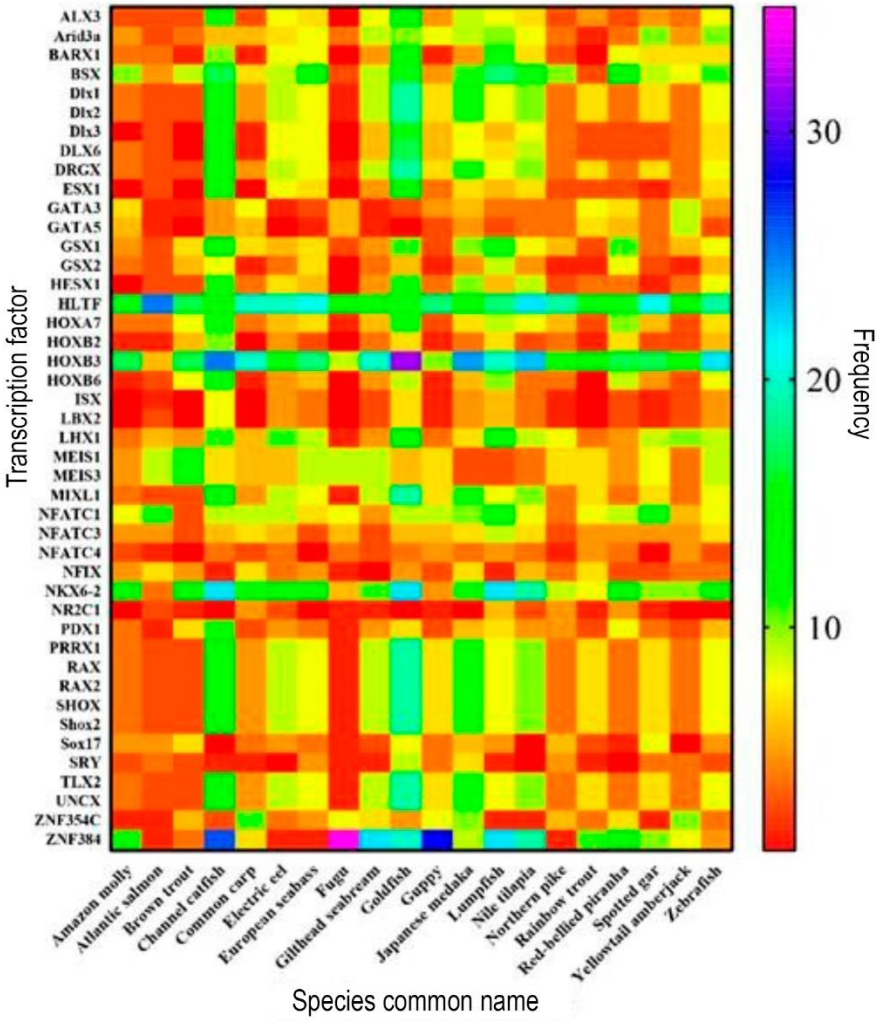

Figure 7. Frequency of transcription factors binding sites (TFBS) of transcription factors (TFs) found in the promoter region of *taut* from fish species examined in the present study. Each column represents one species in study. The color of each cell is determined by the frequency of the TFBS in the promoter zone. Purple represents higher frequency within the promoter region of a TFBS of each TF and red represents low to absence of the TFBS.

protein Nkx-6.2 (NKX6-2). These TFs have been described to play an important role in normal development, immunity, and the regulation of transcription by RNA polymerase II (Guner & Karlstrom 2007, Lyon et al. 2013, Uribe & Bronner 2015, Lu et al. 2019, Rittgers et al. 2021, Torres et al. 2023, Wan et al. 2023)

As mentioned in the introduction, other factors can affect the biosynthesis of taurine in fishes, such as species, type of tissue, stage of development, eating habits, and the environment in which they live (Haga et al. 2015, Salze & Davis 2015, Sampath et al. 2020), thus also affecting the regulation of the TFs that bind to the DNA sequence of different promoters zone. In this sense, the recent advantages in the sequencing of genomes and transcriptomes, as well as the availability of resources for the free use of different databases (i.e. NCBI, Ensembl), seems to be the following path to finding more about the mechanism and regulation of taurine biosynthesis. Furthermore, using bioinformatic and molecular tools to measure and analyze the expression levels of RNA should also be applied.

CONCLUSIONS

Taurine biosynthesis and taurine transportation genes regulate endogenous taurine availability in fish species. Our literature review suggests that the lack or null expression of the main key genes in the synthesis or transportation of taurine could affect fish physiologically, particularly when a disruption, silencing, or elimination of *cdo* or *taut* occurs. Additionally, our in

silico approach to determining putative TFs suggests that the following are shared among the promoter region of all study species in genes implicated in taurine transportation and biosynthesis: homeobox protein BarH-like 1 (BARX1), brain-specific homeobox protein homolog (BSX), helicase-like transcription factor (HLTF), homeobox protein Hox-A7 (HOXA7), homeobox protein Hox-B3 (HOXB3), homeobox protein Hox-B6 (HOXB6), homeobox protein Meis1 (MEIS1), homeobox protein Meis3 (MEIS3), nuclear factor of activated T cells 1 (NFATC1), and homeobox protein Nkx-6.2 (NKX6-2). However, it is necessary to recall that it has also been found that each species has its regulatory elements and that further work regarding how these TFs regulated taurine synthesis needs to be further investigated.

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SUPPLEMENTARY MATERIAL

Supplementary Material 1. Complete CiiiDER analysis results of transcription factors and transcription factor binding sites in promoter region of the genes cysteine dioxygenase (*cdo*), cysteine sulfonate decarboxylase (*csad*) promoters, glutamate decarboxylase (*gad*), 2-amino ethanethiol dioxygenase (*ado*), taurine transporter (*taut*) of different fish species.