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Genome-Wide identification of doublesex and Mab-3-Related transcription factor (DMRT) genes in nile tilapia (*oreochromis niloticus*)

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ABSTRACT

Doublesex and Mab-3-related transcription factor (DMRT) gene family is extensively known for its contribution in sex determination and differentiation across phyla. Here we report the identification of five DM (doublesex and mab-3) domain genes in the Nile tilapia which includes DMRT1, DMRTa2, DMRT2a, DMRT2b and DMRT3a. The full-length sequence of DMRT genes ranges from 3526 (DMRTA2) to 1471bp (DMRT1) which encode putative proteins series from 469 to 372 amino acids. All the DMRT proteins contained at least one conserved DNA-binding DM domain. Sub-cellular localization and gene ontology revealed DMRT1 protein is maximum localized in nuclear region and gene ontology analysis showed the molecular function of 48.2%, biological process 43.6% and cellular component 25%. Chromosomal location and synteny analysis displayed that DMRT genes mostly cluster linkage group 12. Altogether, our findings provide vital genomic information for future studies of biochemical, physiological, and phylogenetic studies on DMRT genes in teleost.

1. Introductions

Sex determination mechanisms and sex differentiation have high diversity among invertebrates, vertebrates and involve genetic factors, environmental factors or both [1–3]. The high variety of sex determination systems seen in fish is interconnected to the high turnover rate of their sex chromosomes. Due to this, most fish sex chromosomes are considered to be comparatively young and are frequently labelled as being homomorphics, i.e., with little discrepancy and no cytological alteration [4]. Sex chromosomes turnover is usually connected with the appearance of new master sex determination genes. Definitely, in therian mammals and birds, master sex determination (SD) genes are much conserved with the quasi-exclusive usage of sex determining region Y for mammals and DMRT1 for birds [4]. Teleosts comprise nearly half of all existing vertebrates [5] and display a wide variety of sex determination mechanisms [6]. A wide diversity of SD genes has been found in many teleost fish and this has significantly improved our knowledge of understanding of the SD mechanisms and SD evolution in fish [4,6]. In teleost fish, genes which has been reported in involving SD mechanisms are Sry-related HMG box (SOX), Doublesex and mab-3 related transcription factors (DMRT) transforming growth factors (TGF-b) family, Amhr2 (Anti-Mullerian hormone receptor type 2) and Gdf6 (Growth differentiation factor 6) [7,6]. Among them DMRT genes family play significant role in sexual determination and differentiation in animals including fish [8,6].

The DMRT gene family, which comprises multiple members encoding putative transcription factors with evolutionarily well-conserved DM (Doublesex and Mad-3) domain, which is involved in sexual development and differentiation in many phylogenetically distant groups from fruit fly (Drosophila melanogaster) to mammals [9–11]. DMRT protein has rare zinc finger DNA-binding motif known as the DM domain Erdman et al.,1993 which comprises six conserved cysteines and two histidines and binds into the minor groove of the target DNA [12].

In mammals, eight DMRT genes have been reported [13] with less number DMRT genes identified in non-mammalian species. However, due to whole genome duplication of DMRT genes has been also reported in teleosts [14]. In zebrafish (*Danio rerio),* fugu (*Takifugu rubripes*), Atlantic cod (*Gadus morhua*), Xenopus, anole lizard (*Anolis carolinensis*), zebra finch (*Taeniopygia guttata*), five, five, five, six, six, and four DMRT genes has been reported [8,14–16]. These studies recommended that the number of DMRT ortholog genes varies in different species in the teleosts. However, there is no report on how many members of DMRT genes are present in the genome of Nile tilapia (*Oreochromis niloticus*).

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Comparative genomics involves the investigation and evaluation of sequence, genes and regulatory regions between different organisms. Computational approaches for genome comparison have recently become a common research topic in biological science including fish biotechnology area. Sex determination in tilapia species is mainly genetic, although environmental factors also play a role [17,18]. Identifying of advantageous genes like growth-related genes, disease-related gene, sex determination, sex differentiation, reproductive gene and physiological gene is a key step in aquaculture that will optimized for greater yield, cost-efficiency, quality, and disease resistance [19–22]

Nile tilapia (*Oreochromis niloticus*), is a omnivorous fish, that feeds on phytoplankton, macrophytes, insects, detritus and zooplankton is one of the most important commercial species in aquaculture with a successful spread all over the world (Beveridge and Baird, 2000). Due to its high economic value, physiological and whole genome duplication of fish and evolutionary genomics, great efforts have been made to dig the potential value of Nile tilapia over the past decade [23–25].

The main goals of this study were to identify the abundance of DMRT genes in Nile tilapia (*Oreochromis niloticus*) relate the gene divergence among species with wide-ranging feeding habits and provide genomic resources for future studies on teleost DMRT genes. Here, utilizing all available genomic resources, we reported the genome-wide identification of DMRT genes family in Nile tilapia. Further, sequence structures and functional domains of DMRT genes family were predicted. Moreover, phylogenetic and syntenic analysis was performed. Our systematic study of DMRT genes may make available some fundamental genomic resources for better understanding the evolutionary and physiological aspects of post- whole-genome duplication (WGD) in Nile tilapia

2. Materials and methods

All available DMRT genes of zebrafish (*Danio rerio*) downloaded from Ensembl (http://asia.ensembl.org/index.html) were used as query sequences to search against the Nile tilapia (*Oreochromis niloticus*), available genomic resources (http://asia.ensembl.org/Oreochromis_niloticus/Info/Index) including whole genome sequences, and cDNAs by BLAST searches to acquire candidate genes with the E value set as 1e-10. Then, reciprocal BLAST searches were conducted using the candidate Nile tilapia DMRT genes as queries, to confirm the accuracy of the candidate genes. Furthermore, the coding sequences were confirmed by BLAST searches against the NCBI non-redundant protein sequence database (nr). The DMRT proteins from other organisms were retrieved from the Ensembl (https://asia.ensembl.org/index.html) and NCBI (https://www.ncbi.nlm.nih.gov/) genome databases.

2.1. Gene characterization and structure

To characterize the genes structures and compare them with their orthologs in the human (*Homo sapiens*), mouse (*Mus musculus*) and zebrafish (*Danio rerio*) genome, we first performed exon-intron structure analysis using the Gene Structure Display Server 2.0 online analysis tool The simple modular architecture research tool (SMART) was used to predict the conserved domains based on sequence homology, which were further confirmed by conserved domain prediction by BLAST.

2.2. Proteomics analysis of DMRT gene family

The protein size, molecular weight (MW) and theoretical isoelectric point (pI) of each DMRT protein were computed by using the proteome database and sequence analysis tools on the ExPASy Proteomics Server (http://expasy.org/). Protein sequence motifs were recognized by using Multiple EM for Motif Elicitation (MEME) 5.05 (http://meme-suite.org/tools/meme). Multiple Expectation-Maximization for Motif Elicitation is a suite of tools for motif discovery and searching. The analysis was performed with maximum number of motifs 10 and optimum width of motif 50. Discovered MEME motifs were searched in the Expasy-Prosite database with ScanProsite server (https:// prosite.expasy.org/scanprosite/).

2.3. Protein-protein and DNA-protein interaction and sub-cellular localization of DMRT protein

Here we have carried out protein-protein interaction and sub-cellular of only DMRT1 protein because it was difficult to handle such a huge date of all DMRT proteins. The network of protein-protein of DMRT1 was done with the help of String database (https://string-db.org/). DNA- protein interaction of DMRT1 was done using free online server HDOCK web server (http://hdock.phys.hust.edu.cn/.) A sub-cellular localization of DMRT1 protein was revealed using CELLO2GO tool (http://cello.life.nctu.edu.tw/cello2go/)

2.4. Chromosomal location and synteny analysis

The physical chromosome location data for each DMRT gene was downloaded from the

Ensembl database and mapped onto the 23 chromosomes of Nile tilapia by using Mapchart 2.32 software for the graphical presentation of linkage maps and QTLs. The syntenic analysis of DMRT paralogs pairs were identified by searching the gene duplication across all the species at Ensembl database (http://asia.ensembl.org/index.html) and NCBI database (https://www.ncbi.nlm.nih.gov/) and Map with map chart software individually.

2.5. Sequence alignment and phylogenetic analysis

Multiple protein sequences were aligned by T-Coffee (http://tcoffee.crg.cat/) consistency-based MSA tool that attempts to mitigate the pitfalls of progressive alignment methods with default parameters. Phylogenetic analysis was conducted with reference DMRT proteins from zebrafish (*Danio rerio*) GCA_000002035.4, Nile tilapia (*Oreochromis niloticus*) GCA_001858045.3, human (*Homo sapiens*) GCA_000001405.28, mouse (*Mus musculus*) GCA_000001635.8, chicken (*Gallus gallus*) GCA_000002315.5, common carp (*Cyprinus carpio*) GCA_000951615.2, goldfish (*Carassius auratus*) GCA_003368295.1, medaka (*Oryzias latipes*) GCA_002234675.1, rainbow trout (*Oncorhynchus mykiss*) GCA_002163495.1, guppy (*Poecilia reticulata*) GCA_000633615.2,

Table 1
Summary of DMRT genes in Nile tilapia.

Gene name	Genomic length(bp)	CDS (bp)	CDS (aa)	CDS status	No. of exons	Accession No.	Genome location
DMRT1	1471	1118	372	Completed	5	XP_013126366.1	LG12
DMRT3A	1923	1409	469	completed	2	XP_003444527.2	LG12
DMRT2A	1844	1409	469	Completed	3	NP_001266696.1	LG12
DMRTA2	3526	1346	448	Completed	2	XP_005479065.1	LG23
DMRT2B	1839	436	436	Completed	4	XP_005457139.1	LG17

Table 2
Comparative analysis of DMRT genes of Nile tilapia" with other vertebrates species.

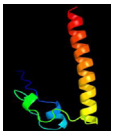
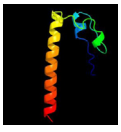
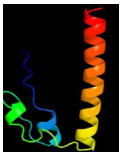
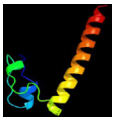
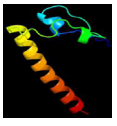
Gene name	Human	Mouse	*Dog*	Chicken	Zebra fish	Common carp	Goldfish	Medaka	Rainbow trout	Guppy	Bar-ramundi perch	Striped catfish	Torafugu (tiger pufferfish)	Chinook salmon	Atlantic salmon	Tongue sole	Mum-michog	Burton's mouth-brooder	Mexican tetra	channel catfish	Nile tilapia	Total
DMRT1	6	1	5	1	2	4	4	4	1	2	1	2	2	1	1	2	1	1	2	2	1	46
DMRT3A	1	1	1	1	1	3	3	1	1	2	1	1	1	2	2	1	2	1	1	1	1	28
DMRT2A	3	2	1	1	1	2	2	3	2	1	1	1	2	2	2	1	1	1	1	1	1	33
DMRTA2	1	1	1	1	1	1	2	1	2	1	1	1	2	3	3	2	1	2	1	1	1	31
DMRT2B	2	2	1	1	2	2	2	3	2*	0	2*	1	1*	2*	1	1*	0	2*	0	0	1	28

Uncharacterized (Proteins) presented as *.

Table 3
Detailed characteristics information of DMRT proteins in Nile tilapia.

Gene name	Molecular weight	Weight in Kilodaltons (kDa)	PI	Formula	Total number Atom	N-glycosylation sites
DMRT1	40387.32	40.39	9.01	$C_{1734}H_{2718}N_{512}O_{551}S_{26}$	5541	3
DMRT3A	50087.27	50.1	5.89	$C_{2196}H_{3461}N_{627}O_{687}S_{14}$	6985	2
DMRT2A	52156.55	52.17	9.52	$C_{2278}H_{3635}N_{677}O_{678}S_{25}$	7293	4
DMRTA2	47455.21	47.46	7.64	$C_{2047}H_{3262}N_{604}O_{657}S_{19}$	658	3
DMRT2B	48484.40	48.5	9.17	$C_{2099}H_{3371}N_{625}O_{637}S_{29}$	6761	1

Table 4
A secondary structure conformation of DMRT proteins in Nile tilapia.

Sr.No	Name of Protein	Alpha helix Alpha helix	Beta strand Beta strand	Disordered	Structure
1.	DMRT1	15%	10%	70%	
2.	DMRT2A	43%	1%	63%	
3.	DMRT2B	30%	2%	66%	
4.	DMRT3A	15%	1%	81%	
5.	DMRTA2	17%	1%	77%	

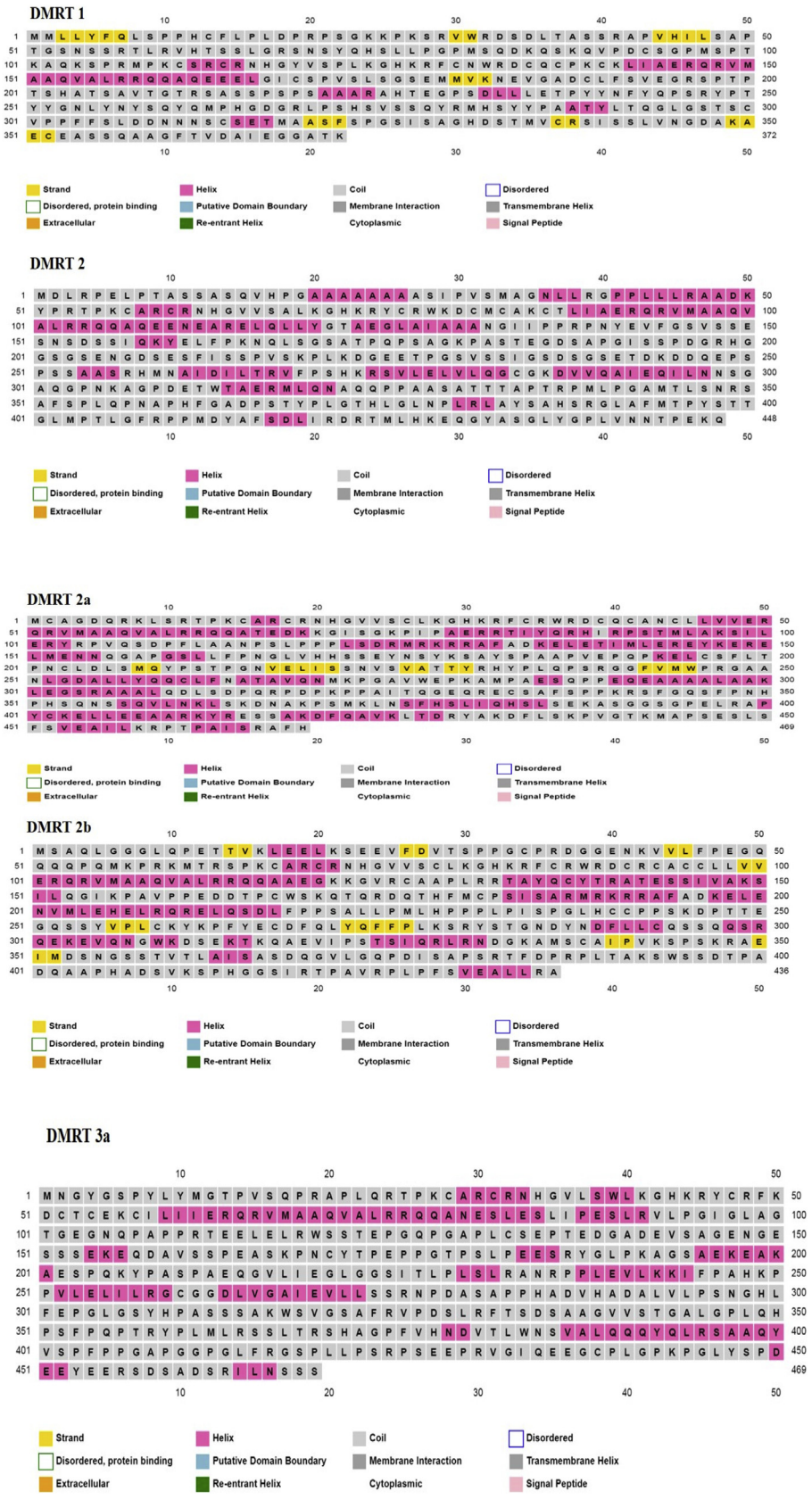


Fig. 1. DMRT proteins annotation of Nile tilapia.

barramundi perch (*Lates calcarifer*) GCA_001640805.1, striped catfish (*Platydoras armatulus*) GCA_003671635.1, torafugu (*Takifugu rubripes*) GCA_901000725.2, chinook salmon (*Oncorhynchus tshawytscha*) GCA_002872995.1, atlantic salmon (*Salmo salar*) GCA_000233375.4, tongue sole (*Cynoglossus sp*) GCA_000523025.1, mummichog (*Fundulus heteroclitus*) GCA_000826765.1, burton's mouthbrooder (*Astatotilapia burtoni*) GCA_000239415.1, mexican tetra (*Astyanax mexicanus*) GCA_000372685.2 and channel catfish (*Ictalurus punctatus*) GCA_001660625.1. We performed maximum likelihood analysis in MEGA7 [26] with bootstrap test of 1000 replicates. The tree was displayed by using the interactive Tree Of Life platform (iTOL).

3. Results

3.1. Identification and characterization DMRT genes in Oreochromis niloticus

We identified a total of 5 DMRT genes in the *Oreochromis niloticus* (Nile tilapia) genome using all available genomic resources, including DMRT1, DMRT3A, DMRT2A DMRTA2, DMRT2B (Table 1**).** Detailed information on their corresponding genomic sequences, coding sequences and number of exons is summarized in Tables 1. A coding region of DMRT2A and DMRT3A were similar and maximum i.e 1409 bp which encodes 469 amine acids followed by DMRTA2. The DMRT1 has 5 exons, DMRT2B has 4 exons, DMRT2A has 3, DMRT3A and DMRTA2 have same exon number i.e 2. Genes DMRT1, DMRT3A, DMRT2A, were located on same linkage group i.e 12 L G and DMRTA2 and DMRT2B located on 23 and 17 linkage group. The comparative analysis of DMRT genes of higher vertebrates and fish are given in Table 2.

3.2. Physiochemical properties of DMRT proteins

To better understand the biological function of DMRT protein, we looked into the characteristics of proteins, including the molecular mass, theoretical PI, potential N-glycosylation sites, and the functional domains. The molecular weight of DMRT proteins ranged from 40.39–52.17 kDa (Table 3). The theoretical PI of most DMRT proteins were within 7.0∼9.5. The number of potential N-glycosylation sites varied in *Oreochromis niloticus* DMRT proteins, ranging from 4 to 1(Table 3). A secondary structure of DMRT proteins consists of disordered (63 to 81%) followed by alpha helix 43% to 15 % beta sheet, transmembrane, cysteine residues signal peptide (Table 4 and Fig. 1**).**The functional domains and motifs of DMRT proteins were predicted based on their protein sequences Figs. 2 and 3. As shown in Fig. 2 all DMRT proteins have DM (Doublesex and Mad-3) domain

3.3. Protein-protein and DNA-Protein interaction and sub-cellular localization of DMRT1 protein

The network of DMRT1 was downloaded from String database. Having numbers of nodes is 41, number of edges is 182, the averages nodes 8.88, the average local cluster coefficient is 0.763 and expected no of edges is 44. To studied better the interaction network was divided into 9 clusters by using K-mean cluster. The cluster was composed of closely connected proteins interaction,

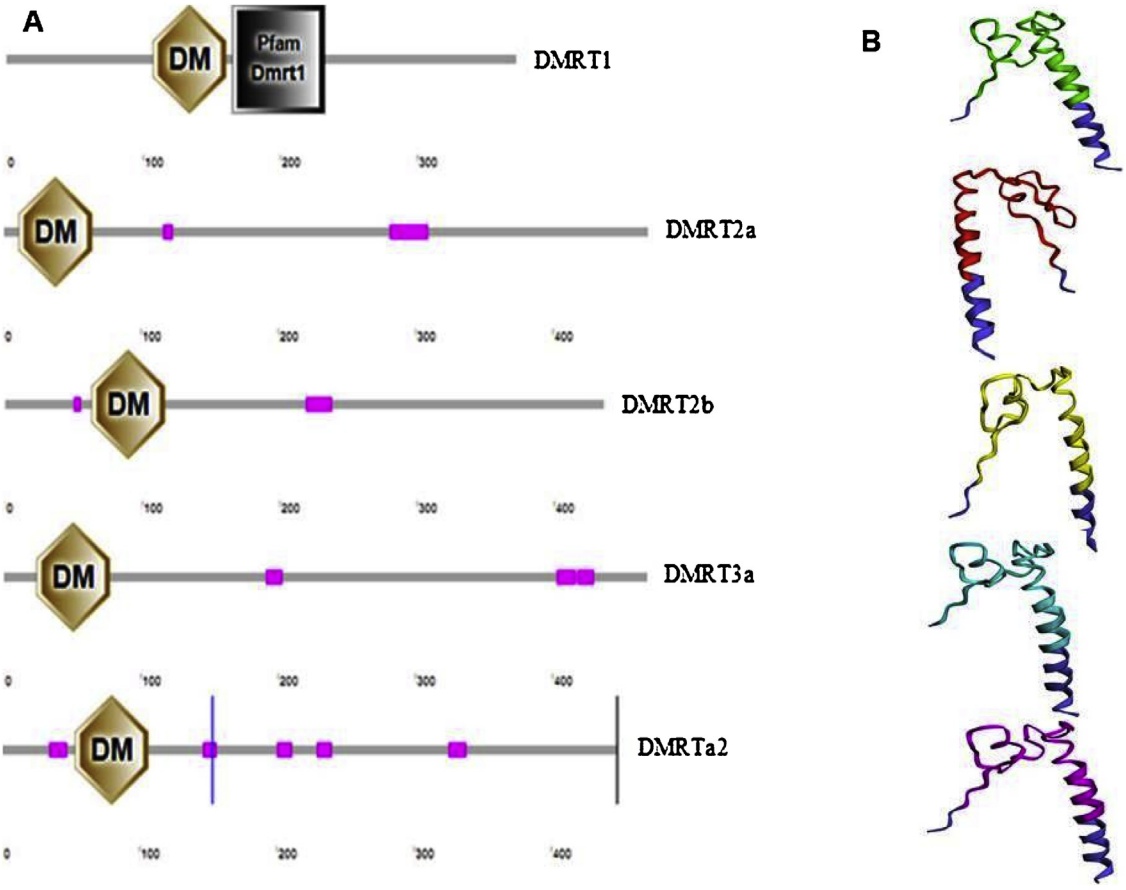


Fig. 2. The conserved DM domain of all DMRT members.

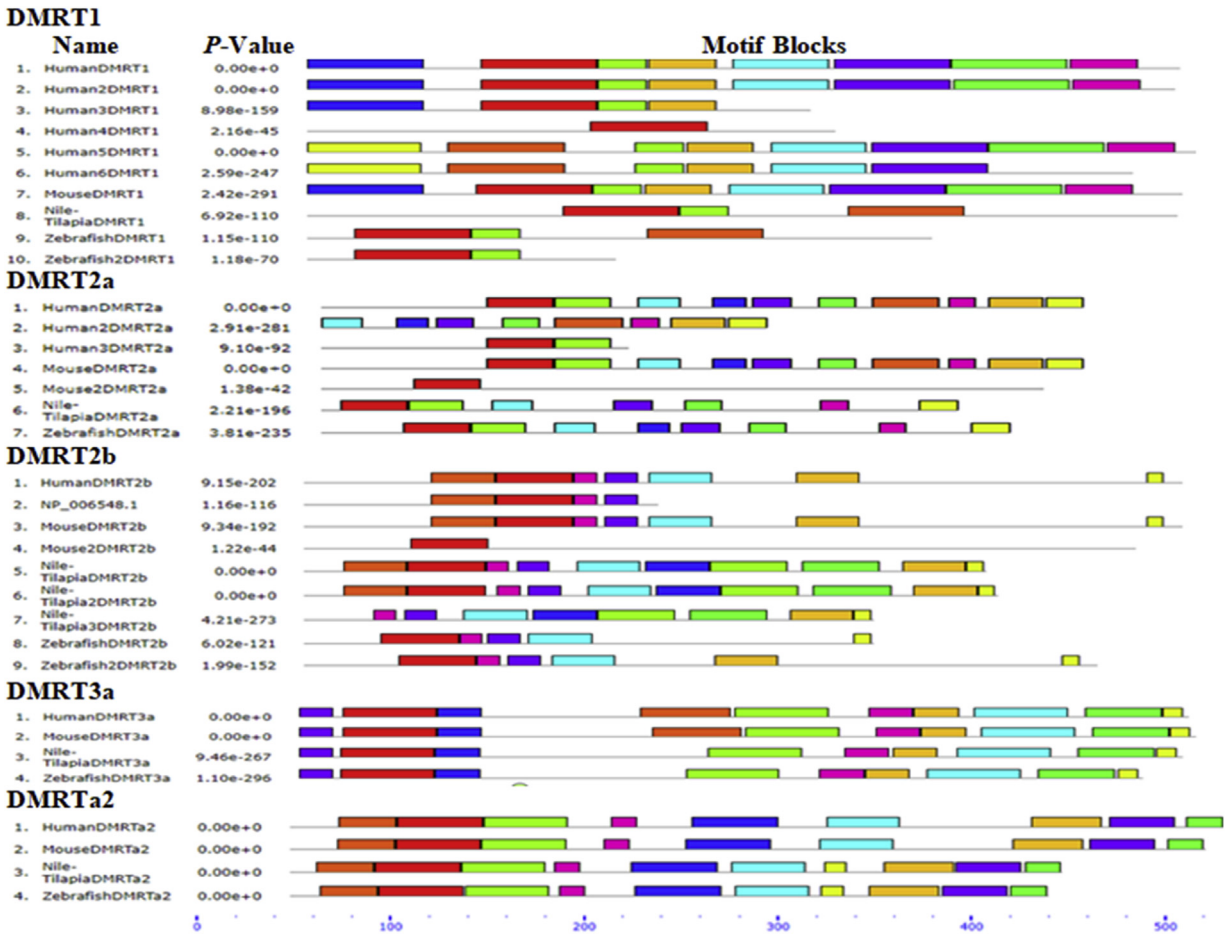


Fig. 3. A motif blocks of all DMRT protein of Nile tilapia with other vertebrates.

the balls giving unspecified effects in the interaction network. The arrows shows positive action effect and one is show negative effects. The networks were divided into different colours clusters shown in Fig. 4. DMRT1 is interacting with protein like FOXL2, SOX9, CYP19A1 WNT4 STRA8, SOX3 etc. The localization probability revealed DMRT1 is maximum localised at nuclear region of cell with score 4.117. DMRT1 is involved in biological functions (43.6%), 48.2 % molecular functions and 25% cellular functions as given in Fig. 5. DNA-Protein interaction of DMRT1 as displayed in Fig. 6

3.4. Phylogenetic analysis of DMRT genes

The phylogenetic analysis revealed all the DMRT genes of Nile tilapia were clustered with their respective homologs from other species as shown in Fig. 7 indicating all genes in DMRT gene family are highly conserved. The teleost, higher vertebrates and other DMRT gene were grouped into distinct clades. Among the teleost cluster Nile tilapia close to *Haplochromis burtoni, Lates calcarifer, Danio rerio* as given in Fig. 7. The multiple alignment of all DMRT proteins are given in **supplementary file 1**

3.5. Synteny analysis of DMRT genes

All the DMRT genes were physically mapped on the chromosomes of Nile tilapia as per data received from public database. Among all chromosomes, linkage group 12 of Nile tilapia contains the highest number of DMRT genes (3) and linkage group 12 and 23 contain one each DMRT gene. The distribution pattern of DMRT genes on chromosomes also specified certain physical areas with a relatively higher accumulation of DMRT genes gene clusters. i.e submetacentric (Fig. 8)

4. Discussion

The aim of the present study was to find out genome wide identification of Doublesex and Mab-3-related transcription factor (DMRT) genes in Nile tilapia, in-silico structural insight into the predicted protein, phylogenetic and syntenic analysis of DMRT genes. In Nile tilapia, totally five DMRT genes have been located in available whole genome of Nile tilapia based on E-value and coverage of gene. In vertebrate, DMRT genes is divided into numerous diverse subfamilies based on conserved exon–intron structures and protein domains DMRT1, DMRTA2, DMRT5, DMRT4 and DMRTA3 (DMRT3) genes [27]. A number of DMRT genes have been recognized in different teleost species [28], and no fish orthologs could be identified for DMRT 6, 7, and 8. Due to evolutionary whole genome duplication of DMRT genes have been reported in teleosts [14]. In zebrafish (*Danio rerio),* fugu (*Takifugu rubripes*), Atlantic cod (*Gadus morhua*), Xenopus, anole lizard (*Anolis carolinensis*), zebra finch (*Taeniopygia guttata*), five, five, five, six, six, and four DMRT genes has been reported [14,16] DMRT2a and DMRT2b detected in the genome of both freshwater and Japanese pufferfish [28] Nile tilapia [29], Zebrafish [14] may be due to result of whole genome duplication of the in the teleost fish lineage [30]. In the present work totally full–length of DMRT1 gene

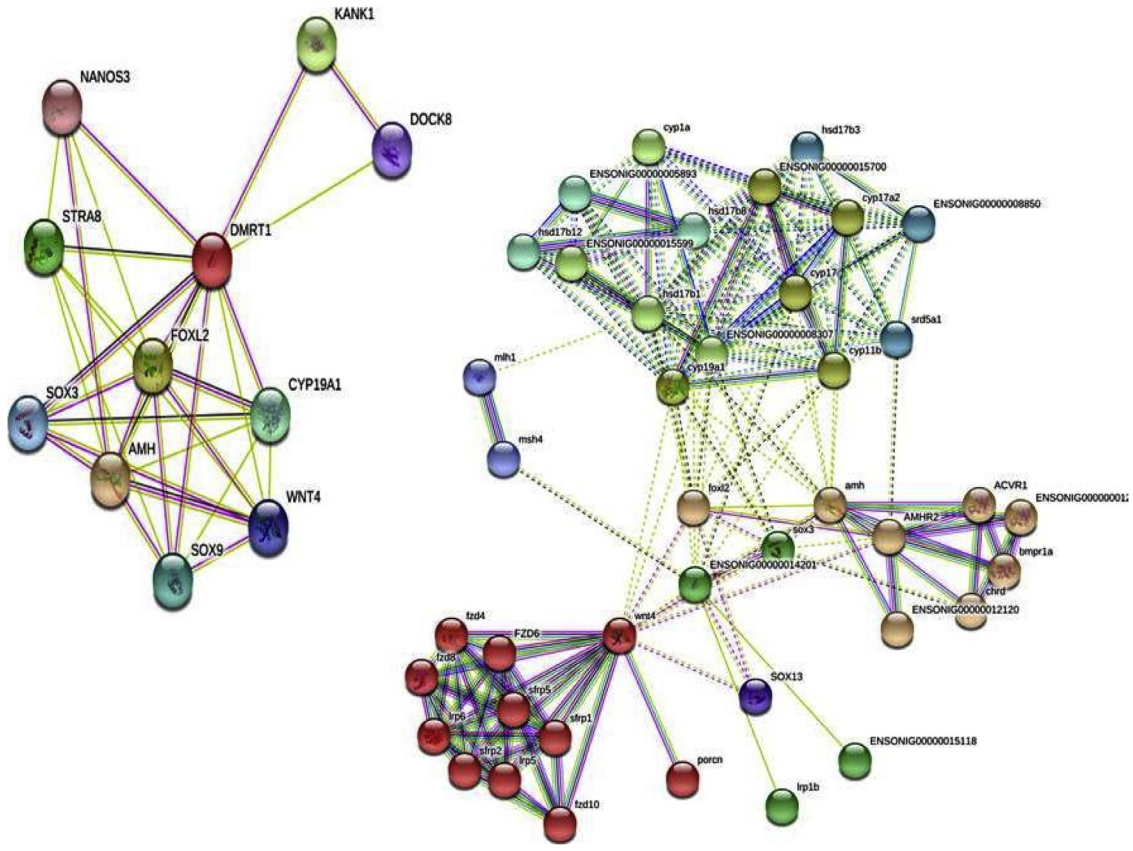


Fig. 4. Protein DMRT1 interaction (Protein-protein interaction) with other proteins.

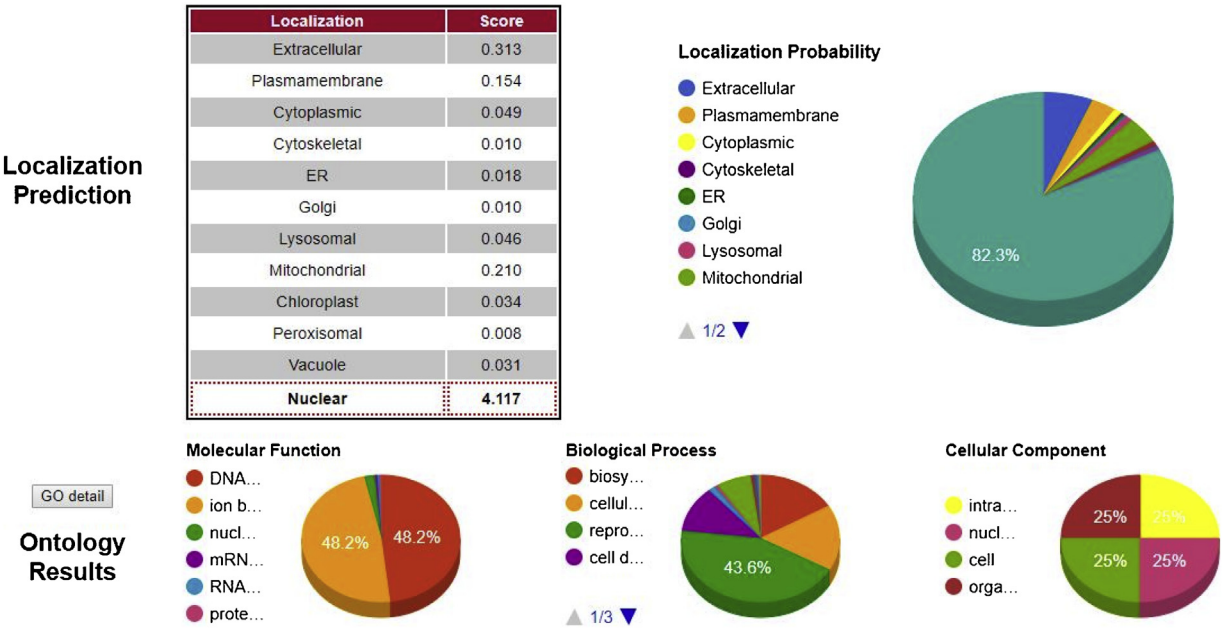


Fig. 5. A localization probability of DMRT1 in Nile tilapia.

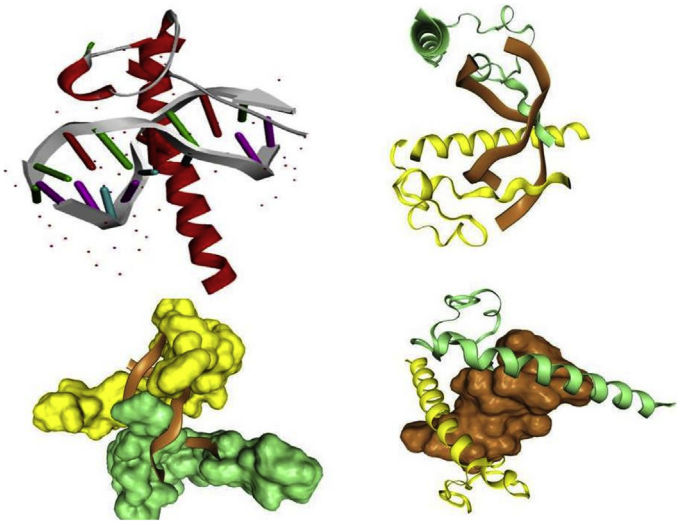


Fig. 6. Protein DMRT1 and DNA interaction (Protein-DNA interaction).

is 1471bp with open reading frame (ORF) OF 1118 bp which encode 372 amine acids. In zebrafish, full –length of DMRT1 is 1390 bp which encode 267 amine acids [31]. DMRT1 cDNA is 1855 bp long, with ORF of 864 bp, encoding a 287 amine acids in lambari fish [32]. DMRT1 has been already reported in various like African catfish, rare minnow, medaka, rare minnow, olive flounder, Atlantic cod and rainbow trout [33–37]. In Nile tilapia, DMRT1 has 5 exons, however in case of zebrafish it has 7 exons [31]. Human DMRT1 has five exons and in the similar range as the five to seven exons noted for all other species [38,39]. In the present work DMRT2a and DMRT2a genes encode 469 and 436 amine acides with 3 and 4 exons in their gene. Zhou et al. [14] reported fish specific duplication of DMRT2 i.e DMRT2a and DMRT2a which have 364 and 507 amine acids with 3 and 4 exons.

The protein encoded by Nile tilapia DMRT family was analogous to DMRT of other species. It contains the conserved DM domain, featured structural motif present in the DSX protein of the model fly Drosophila. This domain is well conserved across vertebrates as revealed by multiple protein analysis. The present observation is in agreement with the earlier reports confirming that the DM domain of DMRT is highly conserved [8,40]. This plays a vital role in sex determination and sex differentiation regulatory downstream gene expression via uniting specific DNA sequences with a zinc finger [41,42]. The DM domain is detected in a range of species starting from the model organisms to mammals including teleost fish species [43,44]. The DMRT gene family is comprised of proteins encoded DM domain, not only plays an essential role in determining but also involved in maintaining the development and function of certain organs [45,46]. In Nile tilapia DMRT protein family encoded well conserved DM domain.

Protein–protein interaction showed that DMRT1 is interact with other transcription factors like FOXL2, SOX9, CYP19A1 WNT4 STRA8, SOX3 etc. All these proteins are directly or indirectly involved in the Sex determination, sex differentiation and steroidogenesis processes. Barrionuevo et al. [47] reported that *Sox9* coordinately with DMRT1responsible for adult testis maintenance. Several *in-vivo* studies suggested that DMRT1 along with SOX9 plays a key role in testis development [48,49]. Wei et al. [50] revealed male sex-differentiation factor Dmrt1 positively controls the transcription of the Nile tilapia Sox9b gene by straight binding to exact cis-regulatory elements within the Sox9b promoter. Two genes DMRT1 and FOXL2 sustain male and female gonadal sex phenotypes by stimulating their own signalling networks and also by hindering the other [51]. Krentz et al. [11] shown expression of DMRT1 in germ cells of fetal ovary may be an essential factor in producing primordial follicles by initiating expression of the meiotic inducer stimulated by retinoic acid 8 (STRA8). DMRT1 has been localized in nuclear region of cell. In amphioxus DMRT domains contain the putative nuclear localization signal (NLS) Wang et al. [52] Hornung et al. [53] and Herpin et al. [54] reported the nuclear localization of Dmrt1 protein in animals. Immunocytochemical and immunofluorescence technique shown that DMRT1 was confined in germ cell i.e primary spermatogonia, secondary spermatogonia and spermatocytes, although spermatid and spermatozoa did not show any immunoreactivity Raghuveer, et al., 2009. In zebrafish DMRT1 has been localized and gene expression is measured both in testis and ovary [55,56]. However, Lei et al. (2007) revealed DMRT1 is localized both in somatic and germ cell. DMRT protein has rare zinc finger DNA-binding motif known as the DM domain Erdman et al., 1993 which comprises conserved cysteines and histidines and binds into the minor groove of the target DNA [12]. In Nile tilapia Kobayashi et al. [57] reported DMRT1 a superior testicular differentiation marker than the Sox9a. In another report showed Foxl2 and Dmrt1 show antagonistic roles in sex differentiation in Nile tilapia through regulating cyp19a1a expression and estrogen production [58].

In the present work synteny and chromosomal analysis showed all DMRT genes present in different linkage group with maximum at linkage group 12. In the same fish i.e Nile tilapia, Shirak et al. [29] already reported DMRTA2 is localized at linkage group 23 which is similar with present observation. Guo et al. [31] reported in zebrafish DMRT1, DMRT2, and DMRT3 genes were revealed to form a gene cluster, which was located on chromosome linkage group5 (LG5). Similar type of gene cluster DMRT1, DMRT2, and DMRT3 was observed in Nile tilapia. Phylogenetic analysis was done to properly describe the evolution history of DMRT genes family in mammals and fish species. All the genes of DMRT family have been cluster in their respective clade. Nile tilapia shown close association or similarity with *Haplochromis burtoni* due to having same family i.e Cichlidae.

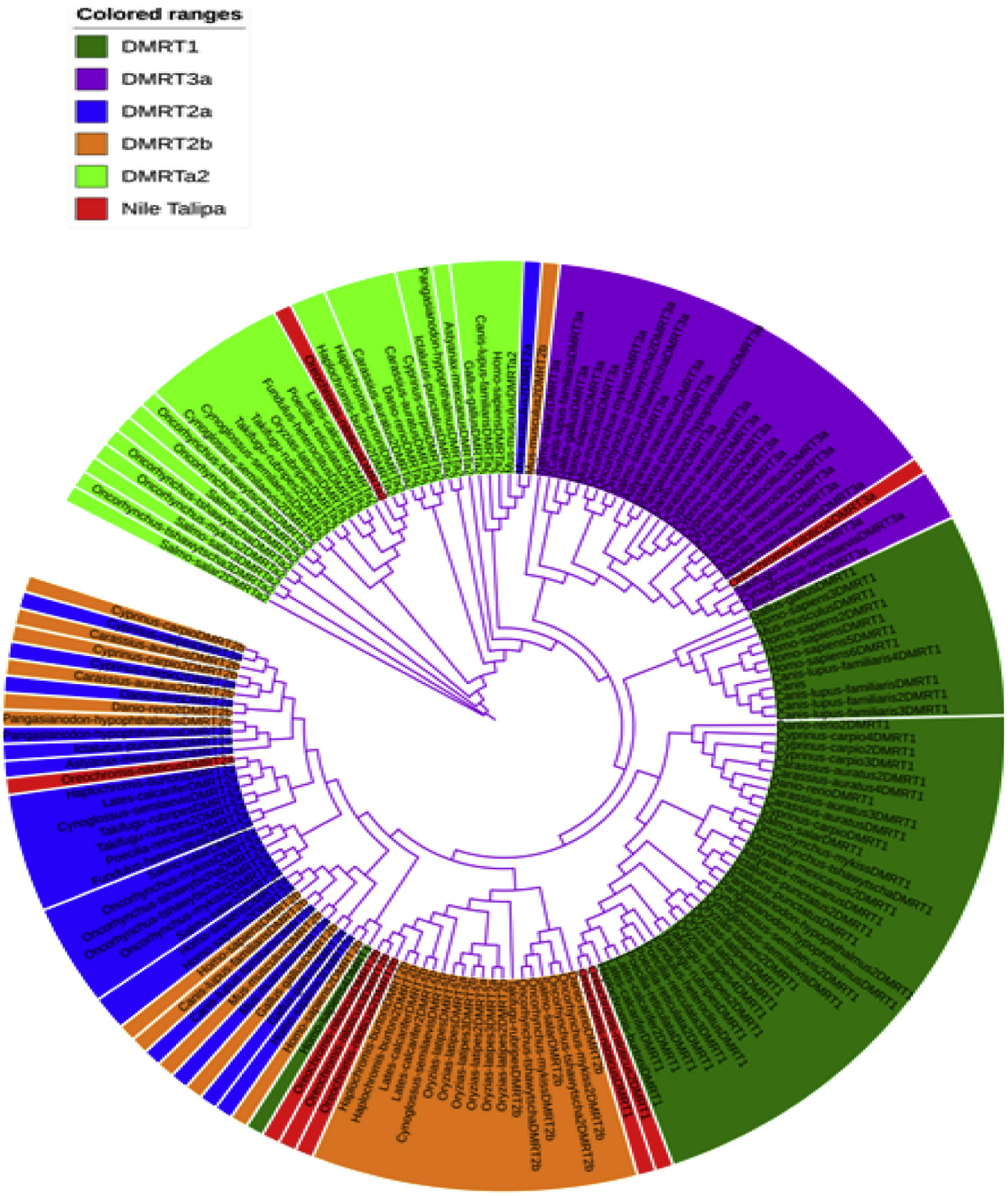


Fig. 7. Neighbor-joining-based phylogenetic tree of DMRT proteins sequences of Nile tilapia with other vertebrates.

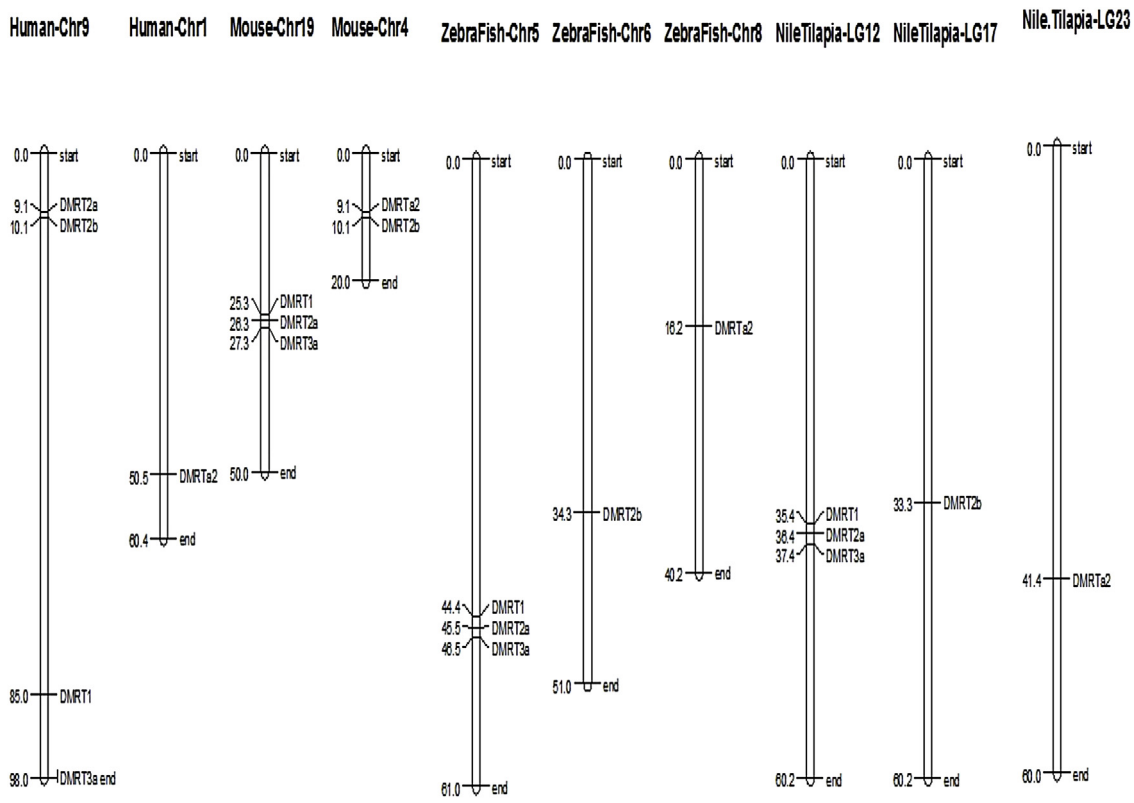


Fig. 8. Analysis of conserved synteny blocks harboring DMRT genes in several vertebrates.

5. Conclusion

In conclusion, we identified a diversified set of 5 DMRT genes of Nile tilapia. The five DMRTs can be divided DMRT1 DMRT3A DMRT2A DMRTA2 and DMRT2B. All DMRT proteins have conserved DM domain. DMRT gene mainly located at linkage group 12. The present information will be helpful for further understanding of structural and functional properties of DMRT gene family in fish

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Declaration of Competing Interest

All authors reported that there is no conflict of interest related with this work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.btre.2019.e00398.

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