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Dmrt the Sex Determination Gene in Fish

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ABSTRACT: Fish is considered one of the most varied aquatic groups of all animals. Fish possesses an incredible diversity of sex-determination processes compared to humans and birds. In fish, the female heterogametes (female WZ and male ZZ, as in birds) can be identified in both the identical fish genus and the same fish species. Genetic determination of sex in fish can be monogenic or polygenic. There are about nine types of sex determination in fish. Among vertebrates, fish stand as the sole category in which various species display inherent hermaphroditism—whether simultaneous or sequential—in their natural state. Among these sex determinants, *Dmrt* is a gene involved in gonadal development and sex differentiation from invertebrates to humans and is considered the primary conserved gene. The double sex- and Mab-3-related domain is a shared DNA-binding motif that sets the Dmrt family of molecules apart. Fish's genetic sex determination is influenced by either mild genetic or environmental factors or a combination. Temperature acts as an environmental influencer on sex determination, which has been connected to increased stress and induces changes in circulating cortisol levels. Understanding sexual development in terms of genetics and molecular mechanisms that control sex differentiation during embryonic development is important in order to understand disordered sexual development and comprehend the evolutionary background of sexual maturation and reproduction. In this paper, we have discussed the various genetic and environmental factors that influence the sex of fish. This review is dedicated to how *Dmrt* is related to sex determination in fish and its impact on environmental factors.

Keywords: Sex determination, *Dmrt,* DNA-binding motif, Stress, Fish

INTRODUCTION

Fish are known to be a very diverse aquatic group among all vertebrates. The role of an organism to multiply and reproduce allows the existence of life on earth; this process is complex and diversified. The existence of separate sexes, i.e., male and female, in the animal kingdom is almost ubiquitous. In fish, the mechanism of determining sex is exceptionally unpredictable and accountable. Devlin and Nagahama (2002) classified sex into two categories, autosomal or chromosome genes controlling the mechanism known as genetic sex determination and environmental sex determination. Both categories are influenced by several factors of the external environment like temperature, population density, nutrition, etc. Environmental effects can be viewed from two perspectives, deletion and induction of the somatic structure due to trauma and physiological changes. This physiological effect causes a biological state that is only "on" or "off" once during a person's lifespan about particular reproving stages (Pitman *et al*., 2013). The genetic differences between genders govern not only the sex-biased gene expression but also polygenic controls. It is also waged by the presence of sex chromosomes that can be male heterogamy (XY, XX) or (ZZ, ZW) female heterogamy (Small *et al*., 2009). Some genes that are linked to sex determination along with the process of chromosomal development are believed to continue the process (Zhang *et al*., 2009).

In vertebrates, eight isoforms (*Dmrt1* to *Dmrt8*) have been identified till now. However, *Dmrt7* and *Dmrt8* genes are exceptionally only in mammals (Dong *et al.,* 2020). Among fishes, D*mrt* was first discovered in Nile tilapia (*Oreochromis niloticus*) and rainbow trout (*Oncorhynchus mykiss*) (Guan *et al.,* 2000; Marchand *et al.,* 2000). *Dmrt1* and *Dmrt2* genes are sex-determination genes in *Taki fuguribicus, gadus morhua* (Picard *et al*., 2015). Isoforms of *Dmrt2, 3, 4, and 5* have also been characterized in many fishes like zebrafish, tilapia, flounder, fugu, medaka, and platyfish (Guo *et al*., 2004; Veith *et al*., 2006; Wen *et al*., 2009; Cao *et al*., 2010). Tissue analysis reveals that D*mrt*1 is expressed mainly in the testis, *Dmrt*2 is expressed in the ovary, and *Dmrt*3 is expressed in the heart, muscle, and gonad mandarin fish, *Siniperca chuatsi* (Han *et al.,* 2021). Kim *et al*. (2003) reported that *Dmrt3* and *Dmrt7* play an important role in sexual dimorphism in mouse embryo gonads. Moreover, *Dmrt2, Dmrt3,* and *Dmrt5* are also accountable for the differentiation of gonads in frogs (Matsushita *et al*., 2007).

Dmrt (Doublesex and Mab-3 Related Transcription factor) gene is associated with sex differentiation from invertebrate to human. Double sex showed alternative splicing and produced two isoforms, in female Dsx^f and in male Dsx^m. Dsx isoforms are responsible for differential behavior and brain structure in males and females. In humans, *Dmrt1* is located at the 9p chromosome with two genes from the same family named *Dmrt2* and *Dmrt3*. *Dmrt2* and *Dmrt3* are responsible for feminization and abnormal testicular formation (Veitia *et al*., 1997; Raymond *et al*., 1999). DMY (Domain Y specific chromosome) is an autosomal copy of *Dmrt1a*. In an organism, the male characteristic is revealed and expressed by the DMY prior to gonad differentiation. However, there will be sex reversal (male to female) if the natural mutation occurs. Similarly, in medaka (*Oryzias latipes*), the DMY is recognized as the sex-determining gene, and the XY system is for sex determination of the fish, where X is for the female sex, and Y is for the male sex (Veith *et al*., 2003). Contrastingly, the administration of hormones like estrogens or androgens in diets during the juvenile stage may alter the sex of the fish (Piferrer *et al*., 1993; Nagahama *et al*., 2004).

The *Dmrt1* is found to be expressed only in vertebrate gonads and is involved in the development of male gonads (Hong *et al.,* 2007). It also found that upregulation in XX male tilapia causes partial to complete sex reversal and abnormal development of follicle degeneration and ovarian cavity (Wang *et al*., 2010). Wu *et al*. (2010) found that a deficiency in protandrous *Acanthopagrus schlegelii* causes germ cell reduction in the testis and arouses male-to-female sex reversal, *Dmrt1* absent mutant mice cause largely cocogenic testis, where after birth, proper differentiation of Sertoli and germ cell fails (Kim *et al*., 2007).

The process of spermatogenesis in air-breathing catfish (*C. gariepinus*) was found to be higher in the preparatory and pre-spawning phase, which indicates the *Dmrt1* gene has a significant role in spermatogenesis (Raghuveer and Senthilkumaran 2009). Throughout a vertebrate's evolution, the *Dmrt1* gene's structure and function have changed during the development and differentiation of the male gonad. There is a need for a solid foundation for a more systematic understanding of the structural characteristics of these members in the fish dart family and a need for further investigations into the different functions of fish dart family members in sex determination or differentiation along with their underlying mechanisms.

FISH SEX DETERMINATION

The determination of a fish's genetic sex is influenced by both mild genetic and environmental factors. Temperature sensitivity involves genetic and environmental interaction (Baroiller and Dcotta 2001). Species with a dominant or strong influence on genetic sex determination, like trout, medaka, carp, etc., were found to have environmental and minor genetic factors (Quillet *et al*., 2002). Seabass and zebrafish have polyfunctional systems with minor or straightforward genetic sex determination, while *Menidia menedia* have stern or harsh genetic and environmental interaction (Conover, 2004). Among vertebrates, fish is the only species that show natural hermaphroditism, simultaneous or sequential. Fish exhibit a variety of sex-determining systems, such as temperature-dependent, heterogametic male and female systems. Fish's sex-determining system seems to be at a very rudimentary evolutionary stage (Solari, 1993).

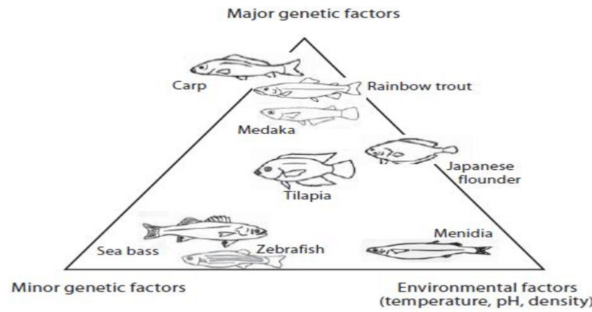

Fig. 1. The schematic triangle of three factors representing sex influencing in fish, major genetic factors, minor genetic factors, and environmental factors (Baroiller *et al*., 2009).

A. Fish sex determination on the basis of genetic factors

There are five master genes that have been reported in fish till now, which are considered as the genetic factors. They are *gsdf, amhy, amhr2, sdY,* and *dmY* (DM-domain gene on the Y chromosome). These genes cause high genetic variation between fish species. In medaka fish the *SDg* transcription factor is expressed in somatic cells which surround the germ cells before the sex is differentiate. It also further takes part in germ cell proliferation and development of Sertoli cells. TGF-ß superfamily members SDF, *amhy*, and *amhr2* are involved in cell signaling and proliferation (Heule *et al.,* 2014). In *T. rubipre, amhr2* (antimullerian hormone receptor type 2) is expressed in somatic cells surrounding germ cells (Kamiya *et al*., 2012). The gene included a unique SNP variant in the *amhr2* kinase domain on the X chromosome, which causes a reduced affinity for the *amh* hormone and specifies the female pathway.

SDgs evolution has been described in either closely related species like *O. Latipes* dmY and *Oryzias luzonensis* gsdf1 (Myosho *et al*., 2012) or divergent in *Oncorhynchus mykiss sdY* (Yano *et al.,* 2012) and *fugu* amhr2 (Kamiya *et al.,* 2012). The diversity of *SDg* in fish is highlighted during the undifferentiated stage of gonads to switch and drive gonad fate (Graves and Peichel 2010; Heule *et al*., 2014). Dmrt1 and related genes discovered in medaka have also been detected in birds and amphibians (Smith and Sinclair, 2004; Yoshimoto *et al.,* 2008). Understanding the evolutionary link between morphogenetic effects and the underlying genetic network will also require gene expression studies in conjunction with next-generation sequencing technologies. Microarrays have assessed gene expression profiles (Gardner *et al*., 2012; Sreenivasan *et al.,* 2014). Furthermore, newer approaches such as RNA-Seq are being used due to their increased sensitivity and accuracy and the fact that they provide additional information on genetic variants associated with expression alterations (Sun *et al.,* 2013; Tao *et al.,* 2013).

B. The environmental factors on sex determination

Menidia menidia was the first fish species to have temperature-dependent sex determination described (Conover and Kynard, 1981). Many research findings indicated the influence of environmental elements in laboratory circumstances, which can be dramatic in certain cases but do not always mirror species' conditions in the wild (Ospina-Alvarez and Piferrer 2008). The occurrence of temperature-dependent sex determination in fish, however, illustrates the plasticity of gonad development (Baroiller *et al.,* 2009). Although this is not a process that determines gonad fate at the start of development, it is an outstanding example of the plasticity of gonad development in fish, as well as proof of the presence of bipotential primordium cells in adult fish differentiated gonads (Zhou and Gui, 2010). High temperatures usually result in more males, while low temperatures may have little effect or result in more females (Ospina-Alvarez and Piferrer 2008). The ultimate mechanism linking temperature and sex ratio is unknown, while various hypotheses have been advanced.

The effect of temperature on sex determination has been linked to increased stress, which causes alterations in circulating cortisol levels. In fact, dietary cortisol administration has dramatically affected the sex ratio (Mankiewicz *et al.,* 2013). Hayashi *et al.* (2010) postulated that the follicle-stimulating hormone receptor, which is linked to germ cell proliferation, is directly up-regulated. Fernandino *et al.* (2013) also proposed an increase in *hsd11b2*, a steroidogenic enzyme involved in both the metabolism of cortisol into cortisone and the creation of physiologically active androgens, such as *11-ketotestosterone*. Navarro-Martin *et al.* (2011) found that hyper-methylation of the aromatase promoter correlates with high temperature during the thermosensitive period in *Dicentrarchus labrax* (European sea bass), strongly implying that epigenetic factors control sex differentiation in this species.

C. Role of Dmrt1 in Sex Determination

The *Dmrt1* molecule series is distinguished by a conserved DNA-binding motif called the doublesex- and Mab-3-related domains. This domain is a non-canonical cysteine-rich DNA binding motif with two heavily interwoven finger structures that chelate one zinc ion each while binding to the DNA's minor groove (Zhu *et al.*, 2000). *Dmrt1* was reported to express in testis differentiation of Siberian sturgeon (Marchand *et al.*, 2000). The *Dmrt1* gene is crucial for the development and differentiation of gonads. The other members of the *Dmrt* gene family are likewise involved in testis formation, regulation of reproduction, and embryonic development, according to a number of recent findings. Notwithstanding the crucial functions of *Dmrt* genes, there is a paucity of thorough teleost *Dmrt* gene discovery and study. These investigations will yield vital genomic resources for teleost *Dmrt* gene research in the future and improve our knowledge of the roles these genes play in gonad development and sex determination/differentiation. In rainbow trout, *rtDmrt1,* which is homologous to *Dmrt1*, is cloned and found in testicular differentiation but not ovarian differentiation. After treatment with steroids for ten days, it was observed that down-regulation in estrogens treated male gonads and could not restore the expression in female gonads. It supports the proposal of vertebrates for *Dmrt1* in testicular differentiation (Marchand *et al*., 2000; Berbejillo *et al*., 2012).

In Medaka, the Y chromosome-specific region contains an autosomal *Dmrt1* duplicate copy that is *Dmrt1*Y, which is the functional gene in this chromosome segment for the sex determination of males. *Dmrt1*Y is expressed only during male larval and embryonic development and in the adult testis of Sertoli cells. Therefore, it makes *Dmrt1*Y a male sex-determining gene in medaka (Nanda *et al*., 2002).

Different *Dmrt1s* were cloned, and it was found that two alternatives were spliced and a full length from adult testis of *Clarias gariepinus*. Amino acid-residues predicted proteins of 287 for *Dmrt1a*, 253 for *Dmrt1b*, and 233 for *Dmrt1c*. DM domain was found lacking in *Dmrt1c*. In *Clarias batrachus Dmrt1a* and *Dmrt1c* are procured. *Dmrt1b* and *Dmrt1*c were apparent in the male gonads developing stage, while *Dmrt1c* could not be seen in female developing gonads. *Dmrt1a* transcript was higher in the preparatory phase testis than in the *Dmrt1b* and *Dmrt1c* transcript of spawning and post-spawning. In catfish, gonadal sex differentiation initiates around 40-50 days after hatching. Treatment with methyl testosterone in the early stage of gonad sex differentiation also showed sex reversal results in male sex. Immunofluorescence staining and immunocytochemical study showed that *Dmrt1* was found in spermatocytes and spermatogonia (Raghuveer and Senthilkumaran 2009).

D. Expression of Dmrt 1 gene in fish

In *Clarias fuscus*, cDNA cloning and expression analysis of *Dmrt1* was reported in different tissues like muscles, intestine, heart, ovaries, testis, gills, etc., and it was found to have an amino acids sequence of 83.3% - 96.1% similar to *Clarias gariepinus*, *Clarias batrachus* and *Pelteobragras fulvidraco*. *Clarias fuscus* shared 100% DM domain identity with the three Siluriformes. With 91.9% -97.3% in *Danio rerio*, *O. mykiss* shared 80% with chicken, rats and humans. Expression of *Dmrt1* was found only in the testis but not in ovaries, intestines, hearts, etc. *Dmrt1* in testis spermatogenesis stage (II) is found to be higher than stage (III) to stage (V). Hence, it is indicated as the sex-determining gene in *Clarias fuscus* (Deng *et al*., 2012). Webster *et al*. (2017) findings on zebrafish revealed that *Dmrt1* functions as male sex determination and testis development. It was also found that *Dmrt1* (double sex and mab-3 related transcription factor 1) is necessary for normal transcriptional regulation of *foxl2* (forkhead box L2) and *amh* (anti-Mullerian hormone) genes. They are responsible for male and female sexual development. In Medaka, the master sex-determining gene is DMY. Its expression exhibits constancy in *Silurus meridionalis*, *Danio rerio*, and *Clarias gariepinus*, showing its importance during testis differentiation (Liu *et al*., 2010).

Expression of *Dmrt1* in pejerrey (*Odontesthes bonariensis*) was found to be comparatively high during sex differentiation of gonads. When comparing male-producing temperature (MPT) and female-producing temperature (FPT), *Dmrt1* expression was found to be higher during male-producing temperature (MPT). The results showed that *Dmrt1* and *Cyp19* are all involved in the gonad differentiation process of *O. bonariensis* (Fernandino *et al*., 2008). In mammals, birds, reptiles, and fish, *Dmrt1* is an essential gene involved in testicular differentiation but not in ovary differentiation (Shibata *et al*., 2002).

The expression of *Sebastes schlegelii* (Korean rockfish) *Dmrt1* in all the larval stages of the development period from 1-35 days (inspected larval) after the birth decreased gradually. *S. schlegelii Dmrt1* (*SsDmrt1*) full cDNA length was 1,587 bp. In adult male gonads, *Dmrt1* was found to be extremely high compared to the ovary, which is very low, but it is explicitly expressed in both the ovary and testis cells. The total length of cDNA for *S. schlegelii* (*ssDmrt1*) was found to have 1,587 bp. Phylogenetics studies have also found similar to many other known *Dmrt1* fish. Thus, *SsDmrt1* may have a significant role in the ovary and testis differentiation (Ma *et al*., 2014). In another study, the testicular *Dmrt1* was found differently expressed in Black porgy (*Acanthopagrus schegelii*) and fish treated with *in vitro* gonadotropin as well as *in vivo* with (*GnRh*) gonadotropin-releasing hormone had higher expression of *Dmrt1* in testis. The endocrine factor may also affect the sex change of male to female. In hermaphroditic fish brain pituitary-gonadal axis via the *GnRh-Gth-Dmrt1* axis regulate the maintenance of the male phase also, in Sertoli cells, *Dmrt1* is required for testis differentiation (Wu *et al*., 2012). *Dmrt1* transcript and functional testis were found lower in 3-year-old fish than in the 1-year- and 2-year-old fish. Less *Dmrt1* in the test is at 3 years old may be the low production of sperm compared to 1 and 2 years old. This finding assumes that sex change in black porgy is due to *Dmrt1* (He *et al*., 2003).

In medaka, before and after the hatching. DMY high expression was clearly seen in male embryos. A male-related gene, i.e., *Dmrt1* expression, was not seen in both female or male embryos within 20 days of hatching, but it was clearly seen when tested in 30 days of hatching in testis. DMY expression in mature medaka males is found to be similar to the sexually maturing males, but a higher level of expression was seen in the spleen of mature medaka fish. In several other male tissues of the brain, liver, testis, eyes and muscle, *Dmrt1* is seen but expressed more in the male testis (Ohmuro-Matsuyama *et al*., 2003).

In Atlantic cod, *Dmrt1, Dmrt2a, Dmrt3, Dmrt4* and *Dmrt5* were found present. Chromosomal synteny gene and expression patterns of *Dmrt1, Dmrt2a, Dmrt3, Dmrt4,* and *Dmrt5* in larvae as well as in embryos were also disclosed to be expressed distinctly and found to preserve extragonadal role in premature growth and development. Dmrt1 was found to express very low during embryogenesis until it reached 35 days of hatching. At seven days old, larvae *Dmrt2a* expression showed a very high peak in the head compared to the abdomen and was found gradually decreased (Johnsen and Andersen 2012).

In *Micropterus salmoides* (largemouth bass), *Dmrt1* from gonads was cloned and sequenced. In mature testis, *Dmrt1* is highly expressed compared to other tissue like the brain, heart, liver, etc., which showed the differentiation between males and females in different stages of gonads. The study indicates that *Dmrt1* is particularly conserved in *Micropterus salmoides* for sex determination (Yan *et al*., 2019). Whereas, in the case of protogynous hermaphroditic groupers, sex reversal expression of *Dmrt1* was found only in some stages of spermatogenesis. *Dmrt1* protein is not present in Sertoli cells but only in spermatogonia and primary and secondary spermatocytes. *Dmrt1* in grouper is intron-less, with no detection of duplicated genes. Its ability to undergo transcriptional turnover may make it possible for spermatogenesis to stimulate protogynous hermaphroditic groupers' gonads (Xia *et al*., 2007).

DISCUSSION

Fish are regarded to be one of the most diverse aquatic animal groups. Fish have an incredible diversity of sex-determination systems compared to humans and birds. Many fish species have natural hermaphroditism, either concurrently or sequentially. Sex determination in fish is a very varied process in terms of evolutionary trends observed throughout genera and families, and it is prone to change by external stimuli within individuals. Genetic, environmental (e.g., temperature), behavioral, and physiological factors can all influence the destiny of somatic and germ cells inside the primordial gonad. Exogenous sex steroids administered during gonad determination can significantly affect the course of sex differentiation in fish, showing that they play an important role in gonad determination and subsequent differentiation. The most conserved gene, *Dmrt*1, involves sex differentiation from invertebrates to humans. The *Dmrt* 1 gene is involved in the transition of invertebrates to humans. The double sex identifies the *Dmrt*1 molecular family- and Mab-3-related domain, a DNA-binding motif.

CONCLUSIONS

Dmrt (Doublesex and Mab-3 Related Transcription factor) is an important gene involved in fish sex determination. This function of *Dmrt* genes is conserved regardless of mating system and sex determination method. It plays an important role in regulating the development of male characteristics such as testis formation, and its absence usually results in female development. Understanding the function of *Dmrt* is important for understanding the molecular mechanisms underlying sex determination in fish species.

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Conflict of Interest. None.

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