DM Domain Genes: Sexual and Somatic Development During Vertebrate Embryogenesis

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1. Introduction

Sex determination occurs during embryo development in Metazoans that appear as two morphologically distinct sexes. This means that there is a precise time point during embryogenesis when the initial signal starts to act and directs the development of the ambiguous embryo into male or female. What are these primary sex-determination signals? They are different in various vertebrates and can be either genetically or environmentally controlled. Once they appear, they activate the cascade of different genes that respond to these signals and regulate downstream sex-developmental events. Besides the existence of two sexes, which is virtually universal in the animal kingdom, sex-developmental strategies (both the initial signals and the cascade of regulatory genes) vary between phyla and are opposite to somatic-development strategies, which have been found to be more conservative.

Vertebrate sex determination occurs in the gonadal primordium (the genital ridge), and once it takes place, the gonads are differentiated into specific male (testes) and female (ovaries) structures that, mostly because of their hormone-secretion activity, conscript the body into further sexual differentiation (somatic sexual dimorphism).

The revolution in molecular biology technology that started over 50 years ago and continues today has allowed scientists to discover the molecular background of embryogenesis starting from the identification of single genes to the prediction of entire genomic and proteomic regulatory pathways involved in embryo development.

The group of genes that has been found as very important embryogenesis regulators encodes transcription factors, proteins that interact with DNA and regulate the expression of other genes below them in the regulatory hierarchy.

This chapter is dedicated to the fascinating story of one transcription factor family, the family of DM domain genes, which has been discovered in both vertebrate and invertebrate
genomes. They all encode the DM (doublesex and mab-3) domain, possess the highly conservative zing-finger DNA-binding motif and regulate not only sexual, but also somatic developmental pathways in animals. Here, the extensive knowledge of the biology of DM domain genes in vertebrates (from the history of their discovery in different animal genomes to their function in embryo development) is presented. Moreover, the very interesting and slightly contradictory evolutional aspect of DM domain genes is emphasised. So far, they represent the only exception during vertebrate sexual development due to their structural and functional conservation between phyla. On the other hand, the successive discovery of additional vertebrate genes with the DM domain (with their variations in number and function between species) shows how rapidly their evolution took place.

2. The discovery of DM domain genes: The chronological point of view

During the last 13 years, numerous studies of vertebrate DM domain genes have been extensively carried out. Structural analyses of these genes (their genomic organisation, sequence comparisons between species, chromosomal locations, mutational screenings of individuals with developmental abnormalities) as well as their expression profiles in both adult tissues and embryo sections together with functional studies in model organisms have been performed by different research groups all over the world. Here, I present the data that displays how our knowledge of this gene family has been increased over the past decade.

2.1 The DM domain, a link between invertebrates and vertebrates

The first report about the DM domain sequence in the vertebrate genome comes from the studies of Raymond and collaborators (Raymond et al., 1998), who have identified the human locus encoding a DM domain protein. Although the authors primarily named it DMT1 (for the first DM domain gene expressed in testis), it is now known as DMRT1 (doublesex and mab-3 related transcription factor 1). The name of the gene reveals its structural homology to sexual regulators: dsx (doublesex) in Drosophila melanogaster and mab-3 (male abnormal 3) in Caenorhabditis elegans. These two invertebrate homologs encode the conserved motif similar to the zing–finger DNA-binding domain, first described in both male DSX<sup>M</sup> and female DSX<sup>F</sup> isoforms of D. melanogaster (Erdman & Burtis, 1993) and later, simultaneously with its human homolog, in MAB-3 of C. elegans (Raymond et al., 1998). Raymond named this motif DM domain based on its occurrence in fly DSX and worm MAB-3 proteins.

The function of two invertebrate downstream sex regulators, dsx and mab-3, in somatic sex determination and differentiation was previously well characterised (Burtis & Baker, 1989; Shen & Hodgkin, 1988), and it was found that they are evolutionarily conserved. Both genes control analogous aspects of sexual development: direct regulation of yolk protein gene transcription (Yi & Zarkower, 1999), differentiation of male-specific sense organs (Baker & Ridge, 1980; Shen & Hodgkin, 1988; Yi et al., 2000) and mediation of male mating behaviour (Yi et al., 2000). The studies of Raymond (1998) have additionally emphasised the functional relation between these two evolutionally distinct proteins, showing that they can be functionally interchangeable in vivo: The fly dsx<sup>M</sup> but not dsx<sup>F</sup> could replace mab-3 during the development of a transgenic mab-3 mutant C. elegans male.
The report of Raymond and co-authors (1998) proved importance in the research field of animal sexual development by giving the first evidence of molecular evolutionary conservation within invertebrates as well as between invertebrate and vertebrate sexual-regulatory mechanisms.

2.2 DMRT – Vertebrate DM domain gene family

Although the function of the invertebrate DM domain genes dsx and mab-3 in somatic sexual development was described quite broadly, only little was known about the first vertebrate homolog, DMRT1, at the time when Raymond’s paper was published (Raymond et al., 1998). His group, however, has provided very convincing data about DMRT1 as a good candidate gene required in humans for male development. First, it was mapped to the autosomal locus (distal short arm of chromosome 9, band 9p24.3), which has been implicated in human XY sex reversal in numerous previously published reports (Crocker et al., 1988; Bennett et al., 1993; McDonald et al., 1997; Veitia et al., 1997; Veitia et al., 1998; Flejter et al., 1998). Second, DMRT1 was expressed exclusively in testes among 50 investigated human tissues. Further evidence for DMRT1 as a male sexual regulator came either from the later studies of its expression in human embryos (Moniot et al., 2000) or from additional reports describing sex-reversed patients with the monosomy of 9p (Raymond et al., 1999a; Calvari at al., 2000; Muroya et al., 2000; Ōunap et al., 2004; Privitera et al., 2005; Vinci et al., 2007). In the meantime, the group of Zarkower from the University of Minnesota (Raymond et al., 1999b) and the group of Sinclair from the University of Melbourne (Smith et al., 1999a) published very important data about DMRT1 expression during mouse, chicken and alligator embryogenesis. They consistently showed that DMRT1 is unique, in that it is expressed very early and sex specifically in the gonads of three investigated species, regardless of the sex-determining mechanism used (i.e., whether chromosomal (mouse, chicken) or environmental (alligator)). These findings suggested that DM domain genes may play a role in sexual development in a wide range of vertebrate phyla. Indeed, further studies extensively carried out in all vertebrate phyla (from mammals to fish) (Table 1) have supported this hypothesis. Moreover, they have shown the high structural similarity of DMRT1 across species (protein sequence identity within the DM domain with human DMRT1 ranges from 98% in mice to 87% in fish) as well as the conserved sexually dimorphic pattern of its expression both during early gonadogenesis and in adult tissues (Table 2). These studies, however, needed further confirmation through, for example, functional analyses of the gene (its artificial manipulation in a model organism). For the first time, functional studies were performed in 2000 by Zarkower’s group (Raymond et al., 2000), who showed that homozygous Dmrt1−/− mutant male mice fail to undergo normal postnatal testis differentiation. From this data, it was clear that Dmrt1 is a critical regulator of testis development in the mouse.

While Zarkower’s group was later mostly concentrated on mouse functional studies providing more and more interesting data about the role of DMRT1 in mammalian sex-developmental pathways (Fahriglu et al., 2007; Kim et al., 2007a; Krentz et al., 2009; Matson et al., 2010; Murphy et al., 2010; Krentz et al., 2011; Matson et al., 2011), Sinclair and his co-workers were focused on studies in the chicken (Smith et al., 1999b; Smith et al., 2003). They were constantly looking for strong evidence for Dmrt1 as a male dosage-sensitive sex-determination locus, previously shown to be linked to the Z chromosome (avian males are
homogametic ZZ) in the region highly homologous to human 9 chromosome bearing the DMRT1 locus (Nanda et al., 1999; Nanda et al., 2000). Their long-term studies were finally published in 2009, providing the convincing results that Dmrt1 is indeed required for testis determination in the chicken and supporting the Z dosage hypothesis for avian sex determination (Smith et al., 2009).

Although DMRT1 has been studied very intensively during the last decade and its function as the sex-determination/sex-differentiation locus in a wide range of vertebrate species has been very well documented in structural, expression and functional analyses, it has always been known that DMRT1 is not the only gene with the DM domain in the vertebrate genome. Thus, there was a strong need for further investigations.

| Gene Symbol | NCBI Reference mRNA Sequence | Chromosome Localisation | Organism | References |
|-------------|-----------------------------|-------------------------|----------|------------|
| DMRT1/DMT1  | AF130728                    | HSA 9p24.3              | Homo sapiens | Raymond et al., 1998; Raymond et al., 1999a |
| Dmrt1       | NM_015826.5                 | MMU 19C2-C3             | Mus musculus | Raymond et al., 1999b; De Grandi et al., 2000 |
| Dmrt1       | AF379608                    | RNO 1q51                | Rattus norvegicus | Chen & Heckert, 2001 |
| Dmrt1       | NM_001078060.1              | BSA 8q17                | Bos taurus | Bratus et al., 2009; Bratus & Slota, 2009 |
| Dmrt1       | AF216651                    | SSC 1q21                | Sus scrofa domestica | Bratus & Slota, 2009 |
| Dmrt1       | ENSMEUT00000011422*         | MEU 3p                  | Macropus eugenii | Fisk et al., 2003; El-Mogharbel et al., 2005 |
| Dmrt1       | AJ744848 (exon 1)           | OAN X5q                 | Ornithorhynchus anatinus | El-Mogharbel et al., 2007 |
| Dmrt1       | NM_001101831.1              | GGA Zp21                | Gallus gallus | Nanda et al., 1999 |
| Dmrt1       | -                           | DNO Zp                  | Dromaius novahollandaeae | Shetty et al., 2002 |
| Dmrt1       | AB272609                    | autosom                 | Rana rugosa | Shibata et al., 2002; Aoyama et al., 2003 |
| Dmrt1       | AB201112                    | autosom                 | Xenopus leavis | Osawa et al., 2005; Yoshimoto et al., 2006 |
| DM-W        | AB259777                    | XLE W                   | Xenopus leavis | Yoshimoto et al., 2008 |
| Dmrt1       | AY316537                    | -                       | Trachemys scripta | Murdoch & Wibbels, 2003 |
| Dmrt1       | AF335421                    | -                       | Lepidochelys olivacea | Torres-Maldonado et al., 2002 |
| Dmrt1       | -                           | -                       | Chelydra serpentina | Rhen et al., 2007 |
| Dmrt1       | AF464141                    | -                       | Calotes versicolor | Sreenivasulu et al., 2002 |
| Dmrt1       | AF192560                    | -                       | Alligator mississippiensis | Smith et al., 1999a |
| Dmrt1       | AF209095                    | Not Y-linked            | Oncorhynchus mykiss | Marchand et al., 2000; Alfaqih et al., 2009 |
| Dmrt1       | AY157562                    | DRE 5                   | Danio rerio | Guo et al., 2004a; Guo et al., 2005 |
| Dmrt1       | NM_001037949.1              | -                       | Takifugu rubripes | Brunner et al., 2001 |
| Dmrt1       | AAN65377                    | -                       | Xiphophorus maculatus | Veith et al., 2003 |
| Gene Symbol       | mRNA Reference Sequence | Chromosome Localisation | Organism                      | References                      |
|-------------------|-------------------------|-------------------------|-------------------------------|---------------------------------|
| Dmrt1             | AY319416                | -                       | Odontesthes bonariensis       | Fernandino et al., 2006        |
| Dmrt1             | AF421347                | -                       | Monopterus albus              | Huang et al., 2002              |
| tDmrt1            | AF203489                | Not Y-linked             | Oreochromis niloticus         | Guan et al., 2000               |
| tDMO              | AF203490                |                         | Oreochromis niloticus         | Guan et al., 2000               |
| DMY/Dmrt1bY       | AB071534                | OLA Y                    | Oryzias latipes               | Matsuda et al., 2002            |
| Dmrt1/Dmrt1a      |                         |                         | Oryzias latipes               | Nanda et al., 2002              |
| DMRT2             | NM_001130865.2          | HSA 9p24.3               | Homo sapiens                  | Raymond et al., 1999a           |
| Dmrt2             | NM_145831.3             | MMU 19C1                 | Mus musculus                  | Ottolenghi et al., 2000b        |
| Dmrt2             | NM_001192373            | BSA 8q17                 | Bos taurus                    | Bratuś & Słota, 2009            |
| Dmrt2             | XM_003480526            | SSC 1q21                 | Sus scrofa domestica          | Bratuś & Słota, 2009            |
| Dmrt2             | ENSOANT000000013       | OAN X5q                  | Ornithorhynchus anatinus      | El-Mogharbel et al., 2007       |
| Dmrt2             | AY960292                | -                       | Gallus gallus                 | Saúde et al., 2005              |
| Dmrt2             | AB264329                | -                       | Rana rugosa                   | Matsushita et al., 2007         |
| Dmrt2             | AF209096                | -                       | Oncorhynchus mykiss           | Marchand et al., 2000           |
| Dmrt2a            | AF319992                | OLA LG9                  | Oryzias latipes               | Brunner et al., 2001            |
| Dmrt2a            | NM_001037946.1          | -                       | Takifugu rubripes             | Brunner et al., 2001            |
| Dmrt2a            | AAL83920                | -                       | Xiphophorus maculatus         | Kondo et al., 2002              |
| Dmrt2a/terra      | NM_130952               | DRE 5                    | Danio rerio                   | Meng et al., 1999               |
| Dmrt2b            | NM_001079976            | DRE 6                    | Danio rerio                   | Guo et al., 2004a               |
| DMRT3/DMRTA3      | NM_021240.2             | HSA 9p24.3               | Homo sapiens                  | Ottolenghi et al., 2002         |
| Dmrt3             | NM_177360.3             | MMU 19C1                 | Mus musculus                  | Ottolenghi et al., 2002         |
| Dmrt3             | XM_001788026            | BSA 8q17                 | Bos taurus                    | Bratuś & Słota, 2009            |
| Dmrt3             | -                      | SSC 1q21                 | Sus scrofa domestica          | Bratuś & Słota, 2009            |
| Dmrt3             | XM_001507779.2          | OAN X5q                  | Ornithorhynchus anatinus      | El-Mogharbel et al., 2007       |
| Dmrt3             | XP_427822.1             | -                       | Gallus gallus                 | Smith et al., 2002              |
| Dmrt3             | AB264330                | -                       | Rana rugosa                   | Matsushita et al., 2007         |
| Dmrt3             | AF319993                | OLA LG9                  | Oryzias latipes               | Brunner et al., 2001            |
| Dmrt3             | AY621083                | DRE 5                    | Danio rerio                   | Guo et al., 2004a               |
| Dmrt3             | NM_001037945.1          | -                       | Takifugu rubripes             | Brunner et al., 2001            |
| DMRT4/DMRTA1      | NM_022160.2             | HSA 9p21-22              | Homo sapiens                  | Ottolenghi et al., 2002         |
| Dmrt4/Dmrt1a      | NM_175647.3             | MMU 4C4                  | Mus musculus                  | Ottolenghi et al., 2002         |
| Dmrt4             | AY648303                | -                       | Xenopus leavis                | Huang et al., 2005b             |
| Dmrt4             | AF209097                | -                       | Oncorhynchus mykiss           | Marchand et al., 2000           |
| Dmrt4             | AB201464.1              | -                       | Takifugu rubripes             | Yamauchi et al., 2006           |
| Dmrt4             | CAF90474                | -                       | Xiphophorus maculatus         | Kondo et al., 2002              |
| DMRT5/DMRTA2      | NM_032110.2             | HAS 1p32.3-33            | Homo sapiens                  | Ottolenghi et al., 2002         |
| Dmrt5/Dmrt2       | NM_172296.2             | MMU 4C7                  | Mus musculus                  | Ottolenghi et al., 2002         |

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Table 1. DM-domain genes in representative vertebrates. The presented nomenclature of DM domain genes is adopted from Volff (Volff et al., 2003a) or described in given references. The DM domain genes chromosomal localisations linked to sex chromosomes are indicated in grey fields.

The second DM domain gene in humans, DMRT2, was first identified by Raymond and co-workers, who mapped it to the same chromosomal band (HSA 9p24.3) as DMRT1 (Raymond et al., 1999a). Both genes were shown to be deleted in the sex-reversing 9p monosomy, and therefore, DMRT2 was also considered to be partially responsible for the XY sex-reversal phenotype in humans. Further studies, however, have provided evidence of DMRT2 as a less likely sex-developmental candidate locus. First, it was mapped outside the deleted region in the newly refined 9p microdeletion in two XY sex-reversed females (Calvari et al., 2000). Second, its expression appeared to be widespread in adult human tissues (not restricted to testis) (Ottolenghi et al., 2000b). Third, DNA sequence analysis showed its high identity (100% in the DM domain) with the previously described DM domain gene in zebrafish, named terra, which was evidenced to be involved in somitogenesis but not sex development (Meng et al., 1999). Subsequent studies carried out in other vertebrates and based on both expression and functional analyses have indeed confirmed these preliminary presumptions (Tables 3 and 4).

Interestingly, further detailed screening of PAC/BAC clones overlapping the chromosomal region in humans associated with 46,XY gonadal dysgenesis and mapped to the tip of chromosome 9 (HSA 9p24.3) has revealed an additional (i.e., in addition to DMRT1 and DMRT2) locus with the DM domain named DMRT3 with a position proximal to DMRT1.
and distal to DMRT2 (Ottolenghi et al., 2000a). What is more, the newly described human cluster of DM domain genes, DMRT1-DMRT3-DMRT2, was later discovered to be a very conservative vertebrate locus. It was surprisingly found to be isolated from different fish species (i.e., medaka O. latipes, pufferfish F. rubripes (Brunner et al., 2001), zebrafish D. rerio (Guo et al., 2004a)) and from mice (Kim et al., 2003), rats (Guo et al., 2004a), platypus (El-Mogharbel et al., 2007), pigs and cattle. However, in these two last species, the order of DMRT genes was different (Bratuś & Slota, 2009).

It is now known that eight DMRT genes exist in human and mouse genomes (Ottolenghi et al., 2002; Kim et al., 2003; Veith et al., 2006b) (Table 1), which, compared to four and eleven DM domain loci previously isolated from invertebrates D. melanogaster and C. elegans respectively, is not surprising (reviewed by Volff and collaborators; Volff et al., 2003a). The subsequent expression and selected functional studies in numerous vertebrate species (Tables 3 and 4) have shown the variability in the expression profiles between both DM domain paralogs and homologs. Although the involvement of multiple DM domain genes in vertebrate sexual development was supported and might be considered a general phenomenon in developmental biology, it is obvious that DMRT genes also regulate the development of other organs during vertebrate embryogenesis (Tables 3 and 4). The recent data are discussed below in detail.

3. Sexual contra somatic embryo development: The involvement of DM domain genes

In order to determine the role of the genes in sexual development, both expression and functional studies have to be carried out. DM domain genes, as mentioned before, are molecular regulators of developmental processes that take place in the embryo. The embryo is, therefore, the main object used to study the function of DMRT genes. However, concerning humans, ethical issues arise. In this respect, performing studies in model organisms is often the only alternative. In the case of DM domain genes, extending investigations to all vertebrate phyla has brought new, interesting data about the evolution of this gene family.

Numerous DM domain genes were studied in different animal models employing various sex-determination strategies: genetic: (male or female heterogamety in XX/XY or ZZ/ZW systems, respectively), environmental (temperature, social factors) or a combination (Table 2). Different molecular biology methods were used to study the spatial and temporal expression of DM domain genes during embryogenesis. Both the mRNA and protein levels were measured either by very sensitive amplification methods (RT-PCR, quantitative RT-PCR) or less sensitive hybridisation techniques (Northern blot, Western-blot). In order to identify the cell type of the developing organ where the gene expression took place, the whole-mount in situ hybridisation (using gene-specific RNA probes) and/or immunohistochemistry methods (with specific antibodies) were applied to embryo sections. Since transcription factors, the proteins that regulate the expression of other genes by binding to the DNA sequence in their vicinity, are the final DMRT gene expression products, the chromatin immunoprecipitation (ChIP) method was employed to determine the upstream/downstream DMRT regulators in the embryo developmental pathways. What is more, both DMRT expression and ChIP techniques were supplemented by the next-generation technologies that currently provide tools for whole-genome investigations, such
as DNA microarrays (cDNA arrays and ChIP-chip, respectively). Moreover, functional studies, which provide the strongest evidence for gene-role determination, were carried out in different animal models (mostly in mice and in various fish species) and were based on artificial single-gene modifications like the loss of function mutation (e.g., knockout/knockdown of the gene) or the gain of function mutation (e.g., induced gene over-expression).

The function of DMRT genes in the developmental pathways of various vertebrate species is here broadly compared and summarised.

### 3.1 DMRT1, vertebrate sexual regulator

There is no doubt that among DM domain genes, DMRT1 has been the most extensively investigated. A careful on-line search of the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) provided the wide collection of data about DMRT1 expression during vertebrate embryogenesis and in postnatal/adult animal tissues (Table 2).

So far, DMRT1 appears to have a gonad-specific and sexually dimorphic expression profile during embryogenesis in all vertebrates tested (from mammals to fish). Besides this conservative status of DMRT1 as the universal vertebrate sexual regulator (which might be considered a new phenomenon in animal developmental biology), several lines of evidence supported its functional variability during vertebrate gonad development. Is this more of a sex determination or a sex-differentiation locus? Is it involved only in male gonad formation, or does it also play a role in ovary development? The expression and functional studies undertaken in a wide range of vertebrate species have resolved some of the above questions.

In most cases, DMRT1 is up-regulated either late during sex-determination or during the early testis-differentiation period. This subtle difference in its temporal expression during embryogenesis in various vertebrates makes its function vary significantly more among species.

**Dmrt1** may be considered a switch sex-determining gene in reptiles employing a temperature-dependent sex-determining strategy. In separate studies of different reptilian species (i.e., crocodiles (*Alligator mississippiensis*) and turtles (*Trachemys scripta*, *Lepidochelys olivacea*, *Chelydra serpentine*) (Table 2)), it has been shown that Dmrt1 is the earliest genetic factor whose expression is temperature sensitive: The mRNA level of the gene was higher in embryos incubated in a male-promoting temperature than in embryos incubated in a female-promoting temperature. If the hypothesis that Dmrt1 is more likely to be itself temperature sensitive and auto-regulatory than to be regulated by another unidentified sensitive-temperature genetic factor is supported, Dmrt1 may primarily play a male-determining role (Zarkower, 2001). However, no functional studies have been carried out in this vertebrate phylum. That is not the case in birds, where both expression (Table 2) and functional analyses (Table 3) have confirmed the sex-determination status of avian Dmrt1. Sex is chromosomally based (ZZ males/ZW females) in birds, but sex determination had been a long-standing mystery. The bird homolog of the previously identified mammalian master-determining Sry (Sinclair et al., 1990; Koopman et al., 1991) has not been isolated from the avian genome. Thus, two hypotheses have been proposed.
regarding the mechanism of sex determination in birds. The primary switch gene may be either a W-linked female dominant factor or a dosage-sensitive gene residing on the Z chromosome and triggering testis development. *Dmrt1*, which has been shown to be Z-linked in different bird species (Nanda et al., 2000; Shetty et al., 2002), is transcribed specifically during chick embryogenesis. Its expression becomes sexually dimorphic before the onset of sex differentiation: It is stronger in developing male than female gonads (Table 2). The elevated expression of *Dmrt1* from two Z chromosomes (unlike the mammalian X chromosome, there is no dosage compensation in birds) in the genital ridge at the time of sex determination may initiate testis differentiation, whereas one gene dosage is insufficient and lets ZW gonads follow a default female pathway. The *Dmrt1* Z dosage hypothesis for chicken sex determination was finally confirmed by the latest functional studies (Table 3), in which *Dmrt1* knockdown ZZ embryos successfully showed significant gonad feminisation (Smith et al., 2009). Although this spectacular finding closes the large gap in the bird sex-determination pathway, further studies of other avian species have to be undertaken in order to confirm/exclude the universal *Dmrt1* status as the bird sex-determining gene.

| Phylum      | Species                  | Sex-determination strategy | Expression (placement/molecular level/methods)                  | References                                  |
|-------------|--------------------------|----------------------------|-----------------------------------------------------------------|---------------------------------------------|
| Mammals     | Human (H. sapiens)       | GSD, XX females XY males  | T/mRNA/ISH                                                      | Raymond et al., 1998                       |
|             |                          | Dominant Y                 | T/mRNA/DB                                                       | Moniot et al., 2000                        |
|             | Mouse (M. musculus)      |                            | T+O/mRNA/ISH                                                    | Smith et al., 1999a                        |
|             |                          |                            | T+O/mRNA/ISH & RT-PCR                                           | Raymond et al., 1999b                      |
|             |                          |                            | T+O/mRNA/ISH & RT-PCR & qRT-PCR                                  | De Grandi et al., 2000                     |
|             | Rat (R. norvegicus)      |                            | T+O/mRNA/ISH & RT-PCR & qRT-PCR                                  | Lu et al., 2007                             |
|             | Pig (S. scrofa)          |                            | T+O/mRNA/ISH & RT-PCR                                           | Pask et al., 2003                          |
|             | Cattle (B. taurus)       |                            | T+O/mRNA/RT-PCR                                                 | Pask & Slota, 2009                         |
|             | Tammar wallaby (M. eugenii) |                            | T+O/mRNA/RT-PCR                                                 | Bratu & Slota, 2009                        |
|             | Platypus (O. anatinus)   |                            | T+O/mRNA/RT-PCR & qRT-PCR; T+O/protein/IHC                      | El-Mogharbel et al., 2007; Tsend-Ayush et al., 2009 |
|             | Chicken (G. gallus)      | GSD, ZZ males ZW females  | T+O/mRNA/ISH                                                    | Smith et al., 1999a                        |
|             |                          | Dosage Z                   | T+O/mRNA/ISH                                                    | Raymond et al., 1999b                      |
|             |                          |                            | T+O/mRNA/ISH & qRT-PCR                                           | Shan et al., 2000                          |

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| Phylum     | Species               | Sex-determination strategy | Expression (placement/molecular level/methods)                                                                 | References                |
|-----------|-----------------------|----------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------|
| Embryogenesis | Phylum Species Sex-determination strategy | Embryo | Postnatal/Adult Tissue |
|           |                       |                             | T+O/protein/IHC | T+O/mRNA/RT-PCR |
|           |                       | Embryos of both sexes/mRNA/RT-PCR|
|           |                       |                              | T+H/mRNA/RT-PCR |
|           |                       |                              | T/mRNA/NB |
|           |                       | GSD, Dosage Z? | T+O/mRNA/RT-PCR; T+O/mRNA/RT-PCR & ISH |
|           | Embryo Postnatal/Adult Tissue |
|           |                       | Embryo Postnatal/Adult Tissue |
|           |                       | Embryos of both sexes/mRNA/RT-PCR | Zhao et al., 2007 |
|           |                       | T+O/mRNA/RT-PCR | Shetty et al., 2002 |
|           |                       | T+O/mRNA/RT-PCR | Smith et al., 1999a |
|           |                       | T+O/mRNA/RT-PCR | Kettlewell et al., 2000 |
|           |                       | T+O/mRNA/RT-PCR | Murdock & Wibbels, 2003 |
|           |                       | T+O/mRNA/RT-PCR | Torres-Maldonado et al., 2002 |
|           |                       | T+O/mRNA/RT-PCR | Rhen et al., 2007 |
|           |                       | T+O/mRNA/RT-PCR | Sreenivasulu et al., 2002 |
|           |                       | T+O/mRNA/RT-PCR | Shibata et al., 2002 |
|           |                       | T+O/mRNA/RT-PCR | Aoyama et al., 2003 |
|           |                       | T+O/mRNA/RT-PCR | Osawa et al., 2005 |
|           |                       | T+O/mRNA/RT-PCR | Yoshimoto et al., 2006 |
|           |                       | T+O/mRNA/RT-PCR | Yoshimoto et al., 2008 |
|           |                       | T+O/mRNA/RT-PCR | Marchand et al., 2000 |
|           |                       | T+O/mRNA/RT-PCR | Guan et al., 2000 |
|           |                       | T+O/mRNA/RT-PCR | Brunner et al., 2001 |
|           |                       | T+O/mRNA/RT-PCR | Nanda et al., 2002 |
|           |                       | T+O/mRNA/RT-PCR | Winkler et al., 2004 |
|           |                       | T+O/mRNA/RT-PCR | Kobayashi et al., 2004 |
|           |                       | T+O/mRNA/RT-PCR | Nanda et al., 2002 |
|           |                       | T+O/mRNA/RT-PCR | Kobayashi et al., 2004 |
|           |                       | T+O/mRNA/RT-PCR | Yamaguchi et al., 2006 |
|           |                       | T+O/mRNA/RT-PCR | Brunner et al., 2001 |
|           |                       | T+O/mRNA/RT-PCR & qRT-PCR & NB & ISH | Guo et al., 2005 |
|           |                       | T+O/mRNA/RT-PCR & ISH | Veith et al., 2006a |

**Phylum**
- Embryogenesis

**Species**
- Emu 
  (D. novaehollandiae)
- Alligator
  (A. mississippiensis)
- Red-eared slider turtle
  (T. scripta)
- Sea turtle
  (L. olivacea)
- Snapping turtle
  (C. serpentine)
- Indian garden lizard
  (C. versicolor)
- Frog
  (R. rugosa)
- Clawed frog
  (X. laevis)
- Rainbow trout
  (O. mykiss)
- Nile tilapia
  (O. niloticus)
- Medaka
  (O. latipes)
- Japanese pufferfish
  (T. rubripes)
- Green spotted puffer
  (T. nigrospilus)
- Zebrfish
  (D. rerio)
- Platyfish
  (X. maculatus)

**Sex-determination strategy**
- GSD, Dosage Z?
- TDS
- T+O/mRNA/RT-PCR
- T+O/mRNA/RT-PCR & ISH
- T+O/mRNA/ISH & RT-PCR
- T+O/mRNA/qRT-PCR
- T+O/mRNA/ISH & RT-PCR
- T/mRNA/RT-PCR
- T/mRNA/RT-PCR & ISH
- T/mRNA/RT-PCR
- T/mRNA/RT-PCR
- T/mRNA/NB
- T/mRNA/RT-PCR
- T/mRNA/RT-PCR
- T/mRNA/RT-PCR
- T/mRNA/RT-PCR
- T/mRNA/RT-PCR
- T+O/mRNA/RT-PCR
- T+O/mRNA/RT-PCR
- T+O/mRNA/RT-PCR
- T+O/mRNA/RT-PCR
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- T+O/mRNA/RT-PCR
- T+O/mRNA/RT-PCR

**Expression (placement/molecular level/methods)**
- T+O/protein/IHC
- T+O/mRNA/RT-PCR
- T+O/mRNA/RT-PCR & ISH
- T+O/mRNA/ISH & RT-PCR
- T+O/mRNA/qRT-PCR
- T+O/mRNA/ISH & RT-PCR
- T+O/mRNA/ISH & RT-PCR
- T+O/mRNA/ISH & RT-PCR
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- T+O/mRNA/ISH & RT-PCR
- T+O/mRNA/ISH & RT-PCR
- T+O/mRNA/ISH & RT-PCR
- T+O/mRNA/ISH & RT-PCR

**References**
- Zhao et al., 2007
- Shetty et al., 2002
- Smith et al., 1999a
- Kettlewell et al., 2000
- Murdock & Wibbels, 2003
- Torres-Maldonado et al., 2002
- Rhen et al., 2007
- Sreenivasulu et al., 2002
- Shibata et al., 2002
- Aoyama et al., 2003
- Osawa et al., 2005
- Yoshimoto et al., 2006
- Yoshimoto et al., 2008
- Marchand et al., 2000
- Guan et al., 2000
- Brunner et al., 2001
- Nanda et al., 2002
- Winkler et al., 2004
- Kobayashi et al., 2004
- Nanda et al., 2002
- Kobayashi et al., 2004
- Yamaguchi et al., 2006
- Brunner et al., 2001
- Guo et al., 2005
- Veith et al., 2006a
In fish, it is already known that \textit{Dmrt1} is the unique male sex-determination locus, exclusively identified in a single fish species, medaka \textit{O. latipes}. Medaka, unlike many other fish, uses a simple genetic mechanism similar to that found in mammals, with XX females and XY males. Surprisingly, two research groups simultaneously but independently found that the duplicated copy of previously isolated autosomal \textit{Dmrt1}/\textit{Dmrt1a} locus (Brunner et al., 2001) is located on the Y chromosome in its sex-determination region. This new paralog was named after the authors: \textit{Dmrt1bY} (Nanda et al., 2002) or \textit{DMY} (Matsuda et al., 2002). Its specific expression pattern during embryogenesis (it is transcribed early and exclusively in XY embryos) (Table 2) and the molecular analysis of XY \textit{DMY} mutants that appeared to be male-to-female sex reversed (Matsuda et al., 2002) are consistent with its sex-determination function. Thus, medaka \textit{Dmrt1bY/DMY} represents the unique non-mammalian vertebrate equivalent of \textit{Sry}; however, it is not described in any other fish species, regardless of their relation to medaka (i.e., whether close or distant) (Kondo et al., 2003; Volff et al., 2003b; Veith et al., 2003).

What is, then, the role of \textit{Dmrt1} in mammals that exhibit a genetic sex-determining mechanism (XX females/XY males) with the well-described Y-borne male-dominant locus of \textit{Sry}? Intriguingly, the latest detailed studies have presented some functional diversity.

The data from humans, similar to that from chicken and medaka, are consistent with the hypothesis that \textit{DMRT1} dosage is crucial for sex determination. Male-to-female sex reversal in XY individuals with monosomic deletion of 9p (bearing \textit{DMRT1}) may be due to haploinsufficiency for expression of this male regulatory factor (either by itself or with nearby genes) (Raymond et al., 1999a). Furthermore, the report of Moniot and others (Moniot et al., 2000) showed co-expression of \textit{SRY} and \textit{DMRT1} in the genital ridge of the human male but not in the female embryo at the time when gonads appear morphologically undifferentiated. This male-specific expression of \textit{DMRT1} in early gonadogenesis prior to sex differentiation suggests a partial (shared with \textit{SRY}) role in

| Phylum | Species | Sex-determination strategy | Expression (placement/molecular level/methods) | References |
|--------|---------|---------------------------|---------------------------------------------|------------|
|        | Pejerrey, \((O. bonariensis)\) | TDS | T\+O?mRNA/qRT-PCR | Fernandino et al., 2006 |
|        | Atlantic cod \((G. morhua L.)\) | T\+O/mRNA/RT-PCR & qRT-PCR & ISH | Johnsen et al., 2010 |
|        | Rice field eel \((M. albus)\) | T\+O+B/mRNA/RT-PCR & qRT-PCR; O\+T/mRNA/NB | Huang et al., 2005a |

Table 2. \textit{DMRT1} expression in vertebrates. GSD-genetic sex determination, TDS-temperature dependence sex determination, T-testis/genital ridge in male embryo, O-ovary/genital ridge in female embryo, K-kidney, L-liver, H-heart, M-muscle, LU-lung, S-spleen, ISH-\textit{in situ} hybridisation, RT-PCR-reverse transcription-polymerase chain reaction, qRT-PCR-quantitative RT-PCR, NB-Northern blot, DB-Dot blot, IHC-immunohistochemistry, WB-Western blot, RPA-RNase protection assay.
human sex determination. Unlike human homolog, murine Dmrt1, which has been extensively examined during embryogenesis (Table 2) and in genetically modified mouse models (Table 3), appeared to play an essential role in male gonad differentiation but not sex determination. Its early expression in the genital ridges of both sexes became XY-specific (up-regulated in developing male gonads) after the activation of the Sry gene (Smith et al., 1999a; De Grandi et al., 2000). Furthermore, male Dmrt1 knockout mice were found to have postnatal affected testes but were not sex reversed (Raymond et al., 2000). Murine Dmrt1, however, through its expression in premeiotic germ cells and in Sertoli cells of both foetal and postnatal gonads, controls many aspects of testicular development, including differentiation, proliferation, migration and pluripotency of germ cells as well as proliferation and differentiation of Sertoli cells (Fahrioglu et al., 2007; Kim et al., 2007; Krentz et al., 2009).

Despite the well-evidenced redundant function of Dmrt1 in ovary development due to fully fertile Dmrt1+/− XX mouse mutants (Raymond et al., 2000), the latest studies provide some unexpected data suggesting the involvement of mammalian Dmrt1 in female gonad differentiation. In contrast to humans, both DMRT1 proteins (mouse, tammar wallaby) and Dmrt1 transcripts (pig, cattle)—together with their expression in testes—were detected in adult ovaries (Table 2). What is more, the latest genome-wide studies have revealed that murine Dmrt1 is a bi-functional transcriptional regulator that activates some genes and represses others. This not only occurs in juvenile testes, where Dmrt1 acts differently depending on the testis cell line (Murphy et al., 2010). Dmrt1 also can regulate the same gene target sex-specifically. Stra8 (Stimulated by retinoic acid 8), the well-known meiotic inducer, is directly activated by Dmrt1 in foetal ovary germ cells, which results in oogenesis initiation, whereas in adult testes, Stra8 is transcriptionally repressed, showing Dmrt1-dependant control of spermatogenesis (Krentz et al., 2011). Although Dmrt1+/− mutant females were fertile (having reduced but enough functional ovarian follicles), the latest report of Krentz’s group has finally demonstrated that Dmrt1 does indeed function in the foetal ovary (Krentz et al., 2011).

In lower vertebrates, as in mammals, Dmrt1 mRNA was also expressed in adult ovarian tissue of several fish species (Table 2). Moreover, in addition to the testis-specific tdMrt1, the other DM domain gene (tdMO) was isolated from one teleost fish, the tilapia (Guan et al., 2000). tdMO (tilapia DM domain gene in Ovary), the expression of which is limited to the ovary in adult animals, is the first-described female-specific DM domain gene in vertebrates. In contrast to the alternatively spliced male and female invertebrate doublesex (Burtis & Baker, 1989), tdMrt1 and tdMO cDNAs appear to be encoded by two different genes that share little homology outside the DM domain.

However, more spectacular were functional studies carried out by Yoshimoto and co-workers (Yoshimoto et al., 2008; Yoshimoto et al., 2010), who isolated a W-linked DM-W. This is a paralog of Dmrt1 in a single amphibian species, the African clawed frog Xenopus leavis, which has a ZZ/ZW-type sex-determining system. Both the DM-W transient expression in ZW tadpoles in the period of sex determination and the functional analysis of ZZ transgenic tadpoles carrying a DM-W expression vector and showing ovarian cavities and primary oocytes has suggested that DM-W is a likely sex (ovary)-determining locus in X. leavis, probably acting by antagonising Dmrt1 (Yoshimoto et al., 2010).
| Function                  | Gene     | Species                | References                                      |
|---------------------------|----------|------------------------|------------------------------------------------|
| **Male sex determination**| Dmrt1    | Gallus gallus          | Smith et al., 2003, Smith et al., 2009         |
|                           | DMY/Dmrt1bY | Oryzias latipes      | Matsuda et al., 2002                           |
| **Male sex differentiation**| Dmrt1    | Mus musculus           | Raymond et al., 2000, Boyer et al., 2002, Fahrioglu et al., 2007, Kim et al., 2007a, Krentz et al., 2009, Matson et al., 2010, Matson et al., 2011, Lei et al., 2009 |
|                           | Dmrt7    | Mus musculus           | Kawamata & Nishimori, 2006, Kim et al., 2007b |
|                           | Dmrt4    | Mus musculus           | Balcuniene et al., 2006                        |
| **Female sex determination**| DM-W     | Xenopus laevis         | Yoshimoto et al., 2008, Yoshimoto et al., 2010 |
| **Female sex differentiation** | Dmrt1    | Mus musculus           | Krentz et al., 2011                           |
|                           | Dmrt4    | Mus musculus           | Balcuniene et al., 2006                        |
| **Muscle development**    | Dmrt2    | Mus musculus           | Seo et al., 2006, Seo, 2007, Sato et al., 2010, Lourenço et al., 2010 |
|                           | terra/Dmrt2a | Danio rerio            | Meng et al., 1999, Saúde et al., 2005          |
|                           | Dmrt2b   | Danio rerio            | Liu et al., 2009                              |
| **Neurogenesis**          | Dmrt4    | Xenopus laevis         | Huang et al., 2005b                           |

Table 3. Functional studies of DM domain genes in vertebrates.

Summarising the presented data, the vertebrate DM domain gene Dmrt1 and its close paralogs act as primary-sex determining genes in different vertebrate phyla, including fish (DMY/Dmrt1bY), amphibians (DM-W) and birds (Z-linked Dmrt1), each with an independently evolved chromosomal sex-determination mechanism. Unlike sex chromosome-linked Dmrt1 orthologs, autosomal Dmrt1 genes appear as critical sex-differentiating (but not sex-determining) factors acting in developing embryonic/postnatal gonads in mammals (mouse), amphibians (frog Rana rugosa) and fish (medaka, Nile tilapia).
In species not having sex chromosomes with temperature-dependant sex-determination mechanisms (some reptiles), \textit{Dmrt1} is a likely genetic factor that may play a primary sex-determination role.

From an evolutionary point of view, \textit{Dmrt1} homologs are thought to be frequently recruited or retained to determine/differentiate sex as new sex-determination mechanisms arise.

Despite the wide knowledge about \textit{Dmrt1} as the vertebrate sex-developmental locus, new studies, especially based on recently available high-throughput genome-wide technologies, are being performed in order to better understand its transcriptional regulation in testis/ovary differentiation pathways. Still, little is known about the \textit{Dmrt1} targets or the manner in which their expression is regulated. What is more, the newest intriguing data about the \textit{DMRT1} association with the testicular germ cell tumour (TGCT) in humans also requires further explanation (Kanetsky, et al., 2011; Turnbull et al., 2011).

### 3.2 DM domain genes, not just a sex issue

It is now well known that besides \textit{Dmrt1}, seven other DM domain genes exist in the vertebrate genome (Table 1) (however, the numbers vary across species). Although they have not been studied as intensively as \textit{Dmrt1}, recent findings provide a great deal of data about their embryonic expression pattern in different vertebrate clades, including mammals (mouse), birds (chicken), amphibians (frogs \textit{R. rugosa}, \textit{X. leavis}) and broadly investigated fish (medaka, zebrafish, platyfish, Japanese pufferfish). Following the extensive database search (as was done for \textit{Dmrt1}), the newest knowledge about \textit{DMRT} expression in both embryos and adult tissues in a variety of vertebrate species is summarised in Table 4.

A number of general statements can be deduced from this table. In addition to \textit{Dmrt1}, most \textit{Dmrt} genes are expressed in developing gonads during early embryogenesis, and in many cases, their expression is subsequently maintained at higher levels in male than in female gonads. However, in contrast to \textit{Dmrt1}, many \textit{Dmrt} genes are activated in other developing tissues/organs, either before or after the onset of their expression in gonads. This suggests that they may control a broader range of developmental processes. This non-gonad-restricted embryonic expression pattern was observed for \textit{Dmrt2}, \textit{Dmrt3}, \textit{Dmrt4}, \textit{Dmrt5}, \textit{Dmrt6} and \textit{Dmrt8.1}. In most species, \textit{Dmrt} genes have been detected in mesodermally derived somites (mouse, chick and fish \textit{terra}/\textit{Dmrt2a} and chick \textit{Dmrt3}), ectodermally derived olfactory placodes (mouse and chick \textit{Dmrt3}; \textit{Xenopus}, platyfish and medaka \textit{Dmrt4}; and platyfish \textit{Dmrt5}) and neuroectodermally derived developing brain (\textit{Dmrt3}, \textit{Dmrt4}, \textit{Dmrt5} and \textit{Dmrt6} in mouse, chicken, \textit{Xenopus} and fish). It is important to emphasise that the expression of some \textit{Dmrt} genes has not been carefully studied besides forming gonads, and therefore, their activation in other tissues may have been overlooked. For example, most murine \textit{Dmrt} genes were analysed in a variety of organs but only at one developmental stage (E 14.5), and subsequent detailed investigations were carried out only in dissected embryonic gonads (Kim at al., 2003). Similarly, the data from the embryonic expression of some \textit{Dmrt} genes in frog \textit{Rana rugosa} were based on cDNA preparations from either whole embryos or gonads of tadpoles (Matsushita et al., 2007). Moreover, the choice of method is also crucial. It was often noticed that transcripts detectable by more sensitive RT-PCR are not visible in embryo sections following the less sensitive \textit{in situ} hybridisation.
| Gene          | Organism | Expression in embryos | Expression in adult tissues | References                                      |
|--------------|----------|-----------------------|-----------------------------|------------------------------------------------|
| **DMRT2**    | **H. sapiens** | embryos aged 4-7 weeks of both sexes$^1$ | K, SM, Th, L, I, T          | Ottolenghi et al., 2000a, Ottolenghi et al., 2000b |
| Dmrt2        | **M. musculus** | at E9.5 PSM, somites at E14.5 B, T, H, O, K, BL, K, L, S, Li | T$^2$                        | Meng et al., 1999, Kim et al., 2003 |
|              | S. scrofa  | -                     | SM, B, K, T, O, Sp          | Ottolenghi et al., 2000a, Ottolenghi et al., 2000b |
|              | B. taurus  | -                     | SM, K, T                    | Ottolenghi et al., 2000a, Ottolenghi et al., 2000b |
|              | O. anatinus | -                     | K, T, O                     | El-Mogharbel et al., 2007, Tseng-Ayush et al., 2009 |
|              | G. gallus  | PSM, somites$^3$      | -                           | Saúde et al., 2005 |
|              | R. rugosa  | T, O$^4$              | K, T, B                     | Matsushita et al., 2007 |
|              | O. latipes | since day 2, somites, PSM, day 4, somites, B | T, O, G                     | Brunner et al., 2001, Winkler et al., 2004, Kim et al., 2003 |
|              | T. rubripes | -                     | T, O, G, I, E, M            | Veith et al., 2006a |
|              | X. maculatus | since day 3, somites, head | G                           | Veith et al., 2006a |
| terra/Dmrt2a | **D. rerio** | somites, PSM         | M, T, O, B                  | Meng et al., 1999, Zhou et al., 2008 |
| **DMRT3/DMRTA3** | **D. rerio** | branchial arches     | M, Li, O, T, B              | Meng et al., 2000a, Ottolenghi et al., 2000b, Ottolenghi et al., 2000b |
| Dmrt3        | **H. sapiens** | -                     | T, B, L, SM                 | Ottolenghi et al., 2000a, Ottolenghi et al., 2000b |
|              | **M. musculus** | at E9.5 forebrain, nasal placodes at E14.5 B, L, S, T, K, I | not expressed in T          | Smith et al., 2002, Kim et al., 2003 |
|              | S. scrofa  | -                     | T                           | Ottolenghi et al., 2000a, Ottolenghi et al., 2000b |
|              | B. taurus  | -                     | T                           | Ottolenghi et al., 2000a, Ottolenghi et al., 2000b |
|              | O. anatinus | -                     | T                           | Ottolenghi et al., 2000a, Ottolenghi et al., 2000b |
|              | G. gallus  | since E1 PSM, somites, at E2.1 telencephalon, olfactory placodes at E7.5 Müllerian duct | -                           | Ottolenghi et al., 2000a, Ottolenghi et al., 2000b |
|              | R. rugosa  | T, O                  | B, T                        | Matsushita et al., 2007 |
|              | O. latipes | since day 3, hindbrain, neural tube | T                           | Brunner et al., 2001, Winkler et al., 2004, Kim et al., 2003 |
|              | D. rerio   | olfactory placodes, neural tube | T, O                        | Li et al., 2008 |
|              | T. rubripes | at 115 days after hatching | T, O, G, B, Li, M           | Yamaguchi et al., 2006 |
| **DMRT4/DMRTA1** | **D. rerio** | branchial arches     | M, Li, O, T, B              | Meng et al., 2000a, Ottolenghi et al., 2000b, Ottolenghi et al., 2000b |
| Dmrt4        | **H. sapiens** | -                     | Li, K, P, Pr, L, T, O       | Ottolenghi et al., 2000a, Ottolenghi et al., 2000b, Ottolenghi et al., 2000b |
|              | **M. musculus** | at E14.5 B, H, O, T, BL, K, L, S | O,T, PG, Li, H, K, Sp, Th, L, I | Kim et al., 2003, Balciuniene et al., 2006 |
|              | **X. laevis** | since stage 17, olfactory placodes, forebrain, telencephalon | -                           | Huang et al., 2005b |
|              | **O. latipes** | since day 1, olfactory placodes, telencephalon | T, K, G, O, E, B            | Kondo et al., 2002, Winkler et al., 2004 |
|              | T. rubripes | -                     | T, O, Sp                    | Yamaguchi et al., 2006 |
| Species       | DMRT5/DMRTA2 | Expression                                                                 | Tissues                | Authors                     |
|--------------|--------------|---------------------------------------------------------------------------|------------------------|----------------------------|
| *X. maculatus* | since day 3, olfactory placodes; day 5: olfactory placodes, branchial arches, B | G                      | Veith et al., 2006a       |
| *M. musculus* | at E13.5 B   | T                                                                      |                        | Ottolenghi et al., 2002    |
| *H. sapiens*  | at E14.5 B   | T                                                                      |                        | Kim et al., 2003           |
| *R. rugosa*   | T, O         | B, H, T, O, P, K                                                        | Matsushita et al., 2007|
| *D. rerio*    | B            | B, T, O                                                                | Guo et al., 2004b      |
| *T. rubripes* | since day 3, olfactory placodes; B, lenses, day 5: olfactory epithelium, B | B, E                    | Veith et al., 2006a       |

| Species       | DMRT6/DMRTB1 | Expression                                                                 | Tissues                | Authors                     |
|--------------|--------------|---------------------------------------------------------------------------|------------------------|----------------------------|
| *X. maculatus* | since day 3, olfactory placodes; B, lenses, day 5: olfactory epithelium, B | T                      | Veith et al., 2006a       |
| *H. sapiens*  | at E14.5 B   | T                                                                      |                        | Ottolenghi et al., 2002    |
| *M. musculus* | at E14.5 O, T| T                                                                      |                        | Kim et al., 2003           |
| *O. anatinus* | -            | T                                                                      | Tsend-Ayush et al., 2009|

| Species       | DMRT7/DMRTC2 | Expression                                                                 | Tissues                | Authors                     |
|--------------|--------------|---------------------------------------------------------------------------|------------------------|----------------------------|
| *X. maculatus* | since day 3, olfactory placodes; B, lenses, day 5: olfactory epithelium, B | T                      | Veith et al., 2006a       |
| *H. sapiens*  | at E14.5 O   | T                                                                      |                        | Ottolenghi et al., 2002    |
| *M. musculus* | at E14.5 O   | T                                                                      |                        | Kim et al., 2003           |
| *Kawamata & Nishimori, 2006* | -            | T                                                                      |                        | Kawamata et al., 2007      |
| *Kawamata et al., Tsend-Ayush et al., 2009* | -            | T                                                                      |                        | Tsend-Ayush et al., 2009   |
| *O. anatinus* | -            | T                                                                      |                        | Tsend-Ayush et al., 2009   |

| Species       | DMRT8/DMRTC1 | Expression                                                                 | Tissues                | Authors                     |
|--------------|--------------|---------------------------------------------------------------------------|------------------------|----------------------------|
| *X. maculatus* | since day 3, olfactory placodes; B, lenses, day 5: olfactory epithelium, B | T                      | Veith et al., 2006b       |
| *H. sapiens*  | at E13.5 S, Me, I, O, T, L, K, H, head, neural tube | T                      | Veith et al., 2006b       |
| *Kawamata & Nishimori, 2006* | -            | T                                                                      |                        | Kawamata et al., 2007      |

Table 4. Spatial and temporal expression of DMRT2-3-4-5-6-7-8 genes during embryogenesis and in adult animals across different vertebrate species. The order of the indicated tissues in the row correlates with the decreasing level of the detected expression (e.g., the murine DMRT7 at the E14.5 was enriched in ovaries). B-brain, BL-bladder, E-embryonic day, E-eye, G-gills, H-heart, I-intestine, K-kidney, L-lung, Li-liver, M-muscle, M-mesonephros, O-ovary, P-pancreas, PG-preputial gland, Pr-prostate, T-testis, PSM-Presomitic mesoderm, S-stomach, SM-skeletal muscle, Sp-spleen, Th-thymus,’-’ not reported.

However, based on available data, further observations can be made. While the expression patterns for various Dmrt genes have appeared to be conserved across species, there are also some clear differences. For instance, the specific for Dmrt4 expression profile in nasal placode and in telencephalon in Xenopus, medaka and platyfish appears to be Dmrt3 characteristic in mouse and chicken. What is more, chick Dmrt3 is additionally expressed in presomitic mesoderm, which is not true for its mouse and fish orthologs but typical for Dmrt2 is mouse, zebrafish, platyfish and medaka. Additionally, Dmrt1, which has been
found to be exclusively expressed in developing and adult gonads of all vertebrate phyla, surprisingly appears to be expressed in extragonadal adult tissues in cattle (heart, spleen, skeletal muscle, kidney, lung, liver) and in pig (kidney) (Bratuś & Słota, 2009; Table 2). The bovine Dmrt1 widespread tissue-expression profile closely resembles the transcription patterns described for DMRT2, DMRT4 and DMRT8 in adult human tissues (Table 4).

The above observations indicate that the expression patterns and presumably the function of some vertebrate members of the DM-domain gene family may have shifted during evolution (Hong et al., 2007).

It is obvious, however, that in addition to Dmrt1, some other DM domain genes are involved in sexual development. This statement was already suggested after the observation of a relatively mild Dmrt1 mutant phenotype in mice (Raymond et al., 2000). No defects outside the gonads were observed in the Dmrt1/- males, while Dmrt1/- females were not affected. The lack of Dmrt1, thus, might have been compensated for by the activation of other DM domain genes during sexual differentiation. Mouse Dmrt3, Dmrt5 and Dmrt7 exhibit sex-specific expression in the early embryonic gonads (their expression becomes enriched either in developing testes (Dmrt3) or in developing ovaries (Dmrt5, Dmrt7) (Kim et al., 2003).

Unlike Dmrt3 and Dmrt5, but similar to Dmrt1, Dmrt7 expression is restricted only to embryonic mouse gonads of both sexes and becomes postnatally testis specific. Although the early XX-enriched expression of Dmrt7 makes this gene a candidate for a role in early ovarian differentiation, further functional studies have shown that it is essential for male fertility (Kawamata & Nishimori, 2006; Kim et al., 2007b; Table 3). While Dmrt7-deficient female mice were fertile, adult null males were infertile due to the affected functioning of testicular germ cells. It has been found that the lack of Dmrt7 in mice is associated with an arrest of spermatogenesis at the late pachyten stage and with abnormal sex chromatin modifications normally required for male meiotic progression (Kim et al., 2007b).

Like Dmrt7, another DM domain gene, Dmrt8 seems to be mammalian specific (so far not described in other vertebrates) and exclusively expressed in the embryonic gonads of both sexes as well as in the testes of adult mice (Veith et al., 2006b). However, unlike Dmrt7, its function as a sex regulator is now highly speculated because of at least three reasons: 1) It is widely expressed in human adult tissues including brain, lung, kidney, pancreas and gonads, 2) One of its copy found in mice, Dmrt8.1, is expressed in multiple embryonic organs in a non-sex-specific manner, and 3) No functional studies have yet been carried out in order to determine its role in mammalian development.

Conversely, functional studies of another murine Dmrt gene, Dmrt4, have revealed its involvement in some aspects of sexual development (Balciuniene et al., 2006). Despite its widespread expression in both embryos and adults, Dmrt4 mutant mice appear to be viable and fertile. However, two potential mutant phenotypes have been observed: 1) Dmrt4-deficient females have elevated numbers of polyovular follicles due to affected folliculogenesis, and 2) 25% of mutant males attempt to copulate with other males, suggesting a possible behavioural abnormality. This potential involvement of Dmrt4 in proper ovary development and male sexual behaviour has not been found in previous functional studies carried out in frog Xenopus, suggesting that Dmrt4 orthologs are not functionally conserved (Huang et al., 2005b). The effects of Dmrt4 depletion in frog embryos have been shown to be consistent with its early embryonic expression pattern (Table 4). The
Embryogenesis

Dmrt4-deficient embryos showed specific disruption of the expression of known neuronal differentiation factor (Xebf2) in the olfactory placode. Later, during embryogenesis, mutants exhibited impaired neurogenesis in the olfactory epithelium. Moreover, the forced expression of Dmrt4 was sufficient to activate neurogenic markers in cultured Xenopus explants. Therefore, it was proposed that Xenopus Dmrt4 is a key regulator in neurogenesis but not in gonad development. Moreover, the maintained activity of some neuronal gene markers in the Dmrt4 mutant nasal placode may suggest the compensatory activity of other DM domain genes, such as Dmrt3 and Dmrt5.

Similarly, Dmrt6 and Dmrt2 have also been shown to be less likely sexual regulators. In contrast to the poorly investigated Dmrt6, the expression of which was found to be restricted to the developing brain in mouse embryos (Kim et al., 2003), Dmrt2 has been extensively studied during vertebrate embryogenesis as well as in genetically modified model organisms (Tables 3 and 4). Dmrt2 shows a conserved expression pattern during embryogenesis. Dmrt2 is expressed primarily in the presomitic mesoderm and newly formed somites in various vertebrate clades, including mammals (mouse), birds (chicken) and fish (medaka, platyfish and zebrafish) (Table 4). This suggests its involvement in muscle development across species. The detailed functional analyses, however, performed only in mouse and zebrafish, have indeed confirmed this hypothesis, but they have also revealed that type of developmental processes regulated by Dmrt2 can differ in these two organisms. In zebrafish, overexpression of terra/Dmrt2a (homolog of human and mouse Dmrt2) induced rapid apoptosis in the somitic mesoderm both in vitro and in vivo, suggesting that the terra activity needs to be strictly regulated for proper mesoderm development (Meng et al., 1999). Moreover, the depletion of terra activity in zebrafish embryos has revealed two important roles of this DM domain gene: 1) It is involved in the active mechanism responsible for the left-right asymmetry formation, fundamental to vertebrate body-plan creation, and 2) It is responsible for proper bilateral synchronisation of the segmentation clock in the somatic mesoderm, essential for the normal development of bilateral structures such as skeletal muscles (Saúde et al., 2005). What is more, it was recently reported that due to a genome duplication event, zebrafish terra/Dmrt2a has a paralog named Dmrt2b (Zhou et al., 2008). Contrary to terra/Dmrt2a, which is present in all vertebrates, Dmrt2b duplication exists only in the fish genome. Dmrt2b, like terra/Dmrt2a, also showed a left-right asymmetry establishment function in zebrafish embryos. However, unlike its paralog, it regulates other aspects of somite differentiation affecting slow muscle development (Liu et al., 2009). Surprisingly, neither the regulation of left-right patterning in the mesoderm nor the involvement in symmetric somite formation has been observed for murine Dmrt2 (Lourenço et al., 2010). Instead, mouse embryos lacking the Dmrt2 function showed early somite patterning defects, perturbed somite maturation, abnormal skeletal muscle in myotome and affected onset of myogenesis (Seo et al., 2006; Sato et al., 2010). Thus, murine Dmrt2 and both zebrafish paralogs, terra/Dmrt2a and Dmrt2b, appear to be Dmrt family members with a well-evidenced role in vertebrate muscle development and not sex determination/differentiation.

4. Conclusion

Summarising the presented story about DM domain genes in vertebrates, it is a privilege for me to adopt one conclusion that has been proposed by professor Zarkower in his excellent
review paper about sexual development. “Conservation amidst diversity?” Ten years of further extensive investigations have brought the wide, fascinating knowledge about the DM domain gene family that perfectly reflects the cited conclusion. However, there has been one minor change: The question mark is not needed anymore.

5. Acknowledgment

I would like to thank Stefan for his patience and constant support.

6. References

Alfaqih, M.A.; Brunelli, J.P.; Drew, R.E. & Thorgaard, G.H. (2009). Mapping of five candidate sex-determining loci in rainbow trout (Oncorhynchus mykiss). BMC genetics (electronic resources), Vol.10, pp.2, ISSN 1471-2156

Aoyama, S.; Shibata, K.; Tokunada, S.; Takase, M.; Matsui, K. & Nakamura, M. (2003). Expression of Dmrt1 protein in developing and in sex-reversed gonads in amphibians. Cytogenetic and Genome Research, Vol.101, No.3-4, pp. 295-301, ISSN 0301-0171

Baker, B.S. & Ridge, K.A.(1980). Sex and the single cell. I. On the action of major loci affecting sex determination in Drosophila melanogaster. Genetics, Vol.94, No.2, pp.383-423, ISSN 0016-6731

Balciuniene, J.; Bardwell, V.J. & Zarkower, D. (2006). Mice mutant in the DM domain gene DMRT4 are viable and fertile but have polyovular follicles. Molecular and Cellular Biology, Vol.26, No.23, pp. 8984-8991, ISSN 0270-7306

Bennett, C.P.; Docherty, Z.; Robb, S.A.; Ramani, P.; Hawkins, J.R. & Grant, D. (1993). Deletion 9p and sex reversal. Journal of Medical Genetics, Vol.30, No.6, pp. 518-520, ISSN 0022-2593

Boyer, A.; Dornan, S.; Daneau, I.; Lussier, J. & Silversides, W. (2002). Conservation of the function of DMRT1 regulatory sequences in mammalian sex differentiation. Genesis, Vol.34, No.4, pp. 236-243, ISSN 1526-954X

Bratuś, A.; Bugno, M.; Klukowska-Röttler, J.; Sawińska, M.; Eggen, A. & Ślota, E.(2009). Chromosomal homology between the human and the bovine DMRT1 genes. Folia biologica (Krakow), Vol.57, No.1-2, pp. 29-32, ISSN 0015-5497

Bratuś, A. & Ślota, E. (2009). Comparative cytogenetic and molecular studies of DM domain genes in pig and cattle. Cytogenetic and Genome Research, Vol.126, No.1-2, pp. 180-185, ISSN 1424-8581

Brunner, B.; Hornung, U.; Shan, Z.; Nanda, I.; Kondo, M.; Zend-Ajusch, E.; Haaf, T.; Ropers, H-H.; Shima, A.; Schmid, M.; Kalscheuer, V.M. & Schartl, M. (2001). Genomic organization and expression of the doublesex-related gene cluster in vertebrates and detection of putative regulatory regions for DMRT1. Genomics, Vol.77, No.1-2, pp. 8-17, ISSN 0888-7543

Burtis, K.C. & Baker, B.S. (1989). Drosophila doublesex gene controls somatic sexual differentiation by producing alternatively spliced mRNAs encoding related sex-specific polypeptides. Cell, Vol.56, No.6, pp. 997-1010, ISSN 0092-8674
Calvari, V.; Bertini, V.; De Grandi, A.; Peverali, G.; Zuffardi, O.; Furguson-Smith, M.; Knudtzon, J.; Camerino, G.; Borsani, G. & Guioli, S. (2000). A new submicroscopic deletion that refines the 9p region for sex reversal. *Genomics*, Vol.65, No.3, pp. 203-212, ISSN 0888-7543

Chen, J.K. & Heckert, L.L. (2001). *Dmrt1* expression is regulated by follicle-stimulating hormone and phorbol esters in postnatal Sertoli cells. *Endocrinology*, Vol.142, No.3, pp. 1167-1178, ISSN 0013-7227

Cheng, H.H.; Ying, M.; Tian, Y.H.; Guo, Y.; McElreavey, K. & Zhou, R.J. (2006). Transcriptional diversity of *DMRT1* (*dsx-*and *mab3*-related transcription factor 1) in human testis. *Cell Research*, Vol.16, No.4, pp. 389-393, ISSN 1001-0602

Crocker, M.; Coghill, S.B. & Cortinho, R. (1988). An unbalanced autosomal translocation (7;9) associated with feminization. *Clinical Genetics*, Vol.34, No.1, pp. 70-73, ISSN 0009-9163

De Grandi, A.D.; Calvari, V.; Bertini, V.; Bulfone, A.; Peverali, G.; Camerino, G.; Borsani, G. & Guioli, S. (2000). The expression pattern of a mouse doublesex-related gene is consistent with a role in gonadal differentiation. *Mechanisms of Development*, Vol.90, No.2, pp. 323-326, ISSN 0925-4773

El-Mogharbel, N.; Deakin, J.; Tsend-Ayush, E.; Pask, A. & Graves, J.A.M. (2005). Assignment of the *DMRT1* gene to tammar wallaby chromosome 3p by fluorescence in situ hybridization. *Cytogenetic and Genome Research*, Vol.108, No.4, pp. 362E, ISSN 1424-8581

El-Mogharbel, N.; Wakefield, M.; Deakin, J.E.; Tsend-Ayush, T.; Grützner, F.; Alsop, A.; Ezaz, T. & Graves, J.A.M. (2007). DMRT1 gene cluster analysis in the platypus: New insights into genomic organization and regulatory regions. *Genomics*, Vol.89, No.1, pp. 10-121, ISSN

Erdman, S.E. & Burtis, K.C. (1993). The *Drosophila* doublesex proteins share a novel zinc finger related DNA binding domain. *The EMBO Journal*, Vol.12, No.2, pp. 527-535, ISSN 0261-4189

Fahrioglu, U.; Murphy, M.W.; Zarkower, D. & Bardwell, V.J. (2007). mRNA expression analysis and the molecular basis of neonatal testis defects in Dmrt1 mutant mice. *Sexual Development*, Vol.1, No.1, pp. 42-58, ISSN 1661-5425

Fernandino, J.I.; Guilgur, L.G. & Somoza, G.M. (2006). *Dmrt1* expression analysis during spermatogenesis in pejerrey, *Odontesthes bonariensis*. *Fish Physiology and Biochemistry*, Vol.32, No.3, pp. 231-240, ISSN 0920-1742

Fernandino, J.I.; Hattori, R.S.; Shinoda, T.; Kimura, H.; Strobl-Mazzulla, P.H.; Strüssmann, C.A. & Somoza, G.M. (2008). Dimorphic expression of *dmrt1* and *cyp19a1* (ovarian aromatase) during early gonadal development in pejerrey, *Odontesthes bonariensis*. *Sexual Development*, Vol.2, No.6, pp. 316-324, ISSN 1661-5425

Flejter, W.L.; Fergestad, J.; Gorski, J.; Varvill, T. & Chandrasekharappa, S. (1998). A gene involved in XY sex reversal is located on chromosome 9, distal to marker D9S1779. *American Journal of Human Genetics*, Vol.63, No.3, pp. 794-802, ISSN 0002-9297

Guan, G.; Kobayashi, T. & Nagahama, Y. (2000). Sexually dimorphic expression of two types of DM (Doublesex/Mab-3)-domain genes in a teleost fish, the tilapia (*Oreochromis*...
niloticus). Biochemical and Biophysical Research Communications, Vol.272, No.3, pp. 662-666, ISSN 0006-291X
Guo, Y.; Gao, S.; Cheng, H. & Zhou, R. (2004a). Phylogenetic tree and synteny of dmrt genes family of vertebrates. Acta Genetica Sinica, Vol.10, pp. 1103-1108, ISSN 0379-4172
Guo, Y.; Li, Q.; Gao, S.; Zhou, X.; He, Y.; Shang, X.; Cheng, H. & Zhou, R. (2004b). Molecular cloning, characterization, and expression in brain and gonad of DMRT5 of zebrafish. Biochemical and Biophysical Research Communications, Vol.324, No.2, pp. 569-575, ISSN 0006-291X
Guo, Y.; Cheng, H.; Huang, X.; Gao, S.; Yu, H. & Zhou, R. (2005). Gene structure, multiple alternative splicing, and expression in gonads of zebrafish Dmrt1. Biochemical and Biophysical Research Communications, Vol.330, No.3, pp. 950-957, ISSN 0006-291X
Hong, C-S.; Park, B-Y. & Saint-Jeanne, J-P. (2007). The function of Dmrt genes in vertebrate development: it is not just about sex. Developmental Biology, Vol.310, No.1, pp. 1-9, ISSN 0012-1606
Huang, X.; Cheng, H.; Guo, Y.; Liu, L.; Gui, J. & Zhou, R. (2002). A conserved family of doublesex-related genes from fishes. Journal of Experimental Zoology, Vol.294, No.1, pp. 63-67, ISSN 0022-104X
Huang, X.; Guo, Y.Q.; Shui, Y.; Gao, S.; Yu, H.S.; Cheng, H.H. & Zhou, R.J. (2005a). Multiple alternative splicing and differential expression of dmr1 during gonad transformation of the rice field eel. Biology of Reproduction., Vol.73, No.5, pp. 1017-1024, ISSN 0006-3363
Huang, X.; Hong, C.S.; O'Donnell, M. & Saint-Jeannet, J.P. (2005b). The doublesex-related gene, XDMRT4, is required for neurogenesis in the olfactory system. Proceedings of the National Academy of Sciences of the United States of America, Vol.102, No.(32), pp. 11349-11354, ISSN 0027-8424
Johnsen, H.; Seppola, M.; Torgersen, J.S.; Delgandhi, M. & Andersen, Ø. (2010). Sexually dimorphic expression of dmrt1 in immature and mature Atlantic cod (Gadus morhua L.). Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology, Vol.156, No.3, pp.197-205, ISSN 1096-4959
Kanetsky, P.A.; Mitra, N.; Vardhanabhuti, S.; Vaughn, D.J.; Li, M.; Ciosek, S.L.; Letrero, R.; D'Andrea, K.; Vaddi, M.; Doody, D.R.; Weaver, J.; Chen, C.; Starr, J.R.; Håkonarson, H.; Rader, D.J.; Godwin, A.K.; Reilly, M.P.; Schwartz, S.M. & Nathanson, K.L. (2011). A second independent locus within DMRT1 is associated with testicular germ cell tumor susceptibility. Human Molecular Genetics, Vol.20, No.15, pp. 3109-3117, ISSN 0964-6906
Kawamata, M. & Nishimori, K (2006). Mice deficient in DMRT7 show infertility with spermatogenic arrest at pachytene stage. FEBS letters, Vol.580, No.27, pp. 6442-6446, ISSN 0014-5793
Kawamata, M.; Inoue, H. & Nishimori, K. (2007). Male-specific function of DMRT7 by sexually dimorphic translation in mouse testis. Sexual Development, Vol.1, No.5, pp. 297-304, ISSN 1661-5425
Kettlewell, J.R.; Raymond, C.S. & Zarkower, D. (2000). Temperature-dependent expression of turtle Dmrt1 prior to sexual differentiation. Genesis, Vol.26, No.3 pp. 174-178, ISSN 1526-954X
Kim, S.; Kettlewell, J.R.; Anderson, R.C.; Bardwell, V.J. & Zarkower, D. (2003). Sexually dimorphic expression of multiple doublesex-related genes in the embryonic mouse gonad. *Gene Expression Patterns*, Vol.3, No.1, pp. 77-82, ISSN 1567-133X

Kim, S.; Bardwell, V.J. & Zarkower, D. (2007a). Cell type-autonomous and non-autonomous requirements for Dmrt1 in postnatal testis differentiation. *Developmental Biology*, Vol.307, No.2, pp. 314-327, ISSN 0012-1606

Kim S.; Namekawa, S.H.; Niswander, L.M.; Ward, J.; Lee, J.T.; Bardwell, V.J. & Zarkower, D. (2007b). A mammal-specific Doublesex homolog associates with male sex chromatin and is required for male meiosis. *PLoS Genetics*, Vol.3 No.4, pp. 559-571, ISSN 1553-7390

Kobayashi, T.; Matsuda, M.; Kajiura-Kobayashi, H.; Suzuki, A.; Saito, N.; Nakamoto, M.; Shibata, N. & Nagahama, Y. (2004). Two DM domain genes, DMY and DMRT1, involved in testicular differentiation and development in the medaka, Oryzias latipes. *Developmental Dynamics*, Vol.231, No.3, pp. 518-526, ISSN 1058-8388

Kondo, M.; Froschauer, A.; Kitano, A.; Nanda, I.; Hornung, U.; Volf, J.N.; Asakawa, S.; Mitani, H.; Naruse, K.; Tanaka, M.; Schmid, M.; Shimizu, N.; Schartl, M. & Shima, A. (2002). Molecular cloning and characterization of DMRT genes from the medaka *Oryzias latipes* and the platyfish *Xiphophorus maculatus*. *Gene*, Vol.295, No.2, pp. 213-222, ISSN 0378-1119

Kondo, M.; Nanda, I.; Hornung, U.; Asakawa, S.; Shimizu, N.; Mitani, H.; Schmid, M.; Shima, A. & Schartl, M. (2003). Absence of the candidate male sex-determining gene *dmrt1b(Y)* of medaka from other fish species. *Current Biology*, Vol.13, No.5, pp. 416-420, ISSN 0960-9822

Koopman, P.; Gubbay, J.; Vivian, N.; Goodfellow, P. & Lovell-Badge, R. (1991). Male development of chromosomally female mice transgenic for *Sry*. *Nature*, Vol.351, No.6322, pp. 117-121, ISSN 0028-0836

Krentz, A.D.; Murphy, M.W.; Kim, S.; Cook, M.S.; Capel, B.; Zhu, R.; Matin, A.; Sarver, A.L.; Parker, K.L.; Griswold, M.D.; Looijenga, L.H.; Bardwell, V.J. & Zarkower, D. (2009). The DM domain protein DMRT1 is a dose-sensitive regulator of fetal germ cell proliferation and pluripotency. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.106, No.52, pp. 22323-22328, ISSN 0027-8424

Krentz, A.D.; Murphy, M.W.; Sarver, A.L.; Griswold, M.D.; Bardwell, V.J. & Zarkower, D. (2011). DMRT1 promotes oogenesis by transcriptional activation of Stra8 in the mammalian fetal ovary. *Developmental Biology*, Vol.356, No.1, pp. 63-70, ISSN 0022-3870

Lei, N.; Hornbaker, K.I.; Rice, D.A.; Karpova, T.; Agbor, V.A. & Heckert, L.L. (2007). Sex-specific differences in mouse DMRT1 expression are both cell type- and stage-dependent during gonadal development. *Biology of Reproduction*, Vol.77, No.3, pp. 466-475, ISSN 0006-3363

Lei, N.; Karpova, T.; Hornbaker, K.I.; Rice, D.A. & Heckert L.L. (2009). Distinct transcriptional mechanisms direct expression of the rat Dmrt1 promoter in Sertoli cells and germ cells of transgenic mice. *Biology of Reproduction*, Vol.81, No.1, pp. 118-125, ISSN 0006-3363
Li, Q.; Zhou, X.; Guo, Y.; Shang, X.; Chen, H.; Lu, H.; Cheng, H. & Zhou, R. (2008). Nuclear localization, DNA binding and restricted expression in neural and germ cells of zebrafish DMRT3. *Biology of the Cell*, Vol.100, No.8, pp. 453-63, ISSN 0248-4900

Liu, S.; Li, Z. & Gui, J.F. (2009). Fish-specific duplicated DMRT2B contributes to a divergent function through Hedgehog pathway and maintains left-right asymmetry establishment function. *PLoS One*, Vol.4, No.9, pp. e7261, ISSN 1932-6203

Lourenço, R.; Lopes, S.S. & Saúde, L. (2010). Left-right function of DMRT2 genes is not conserved between zebrafish and mouse. *PLoS One*, Vol.5, No.12, pp. e14438, ISSN 1932-6203

Lu, H.; Huang, X.; Zhang, L.; Guo, Y.; Cheng, H. & Zhou, R. (2007). Multiple alternative splicing of mouse Dmrt1 during gonadal differentiation. *Biochemical and Biophysical Research Communications*, Vol.353, No.3, pp. 630-634, ISSN 0006-291X

Murphy, M.W.; Sarver, A.L.; Rice, D.; Hatzì, K.; Ye, K.; Melnick, A.; Heckert, L.L.; Zarkower, D. & Bardwell, V.J. (2010). Genome-wide analysis of DNA binding and transcriptional regulation by the mammalian doublesex homolog DMRT1 in the juvenile testis. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.107, No.30, pp. 13360-13365, ISSN 0027-8424

Marchand, O.; Govoroun, M.; D’cotta, H.; McMeel, O.; Lareyre, J-J.; Bernot, A.; Laudet, V. & Guiguen, Y. (2000). DMRT1 expression during gonadal differentiation and spermatogenesis in the rainbow trout, Oncorhynchus mykiss. *Biochimica et Biophysica Acta*, Vol.1493, No.1-2, pp. 180-187, ISSN 0006-3002

Matson, C.K.; Murphy, M.W.; Griswold, M.D.; Yoshida, S.; Bardwell, V.J. & Zarkower, D. (2010). The mammalian doublesex homolog DMRT1 is a transcriptional gatekeeper that controls the mitosis versus meiosis decision in male germ cells. *Developmental Cell*, Vol.19, No.4, pp. 612-624, ISSN 1534-5807

Matson, C.K.; Murphy, M.W.; Sarver, A.L.; Griswold, M.D.; Bardwell, V.J. & Zarkower, D. (2011). DMRT1 prevents female reprogramming in the postnatal mammalian testis. *Nature*, Vol.467, No.7358, pp. 101-104, ISSN 0028-0836

Matsuda, M.; Nagahama, Y.; Shinomiya, A.I.; Sato, T.; Matsuda, C.; Kobayashi, T.; Morrey, C.E.; Shibata, N.; Asakawa, S.; Shimizu, N.; Hori, H.; Hamaguchi, S. & Sakaizumi, M. (2002). DMY is a Y-specific DM-domain gene required for male development in the medaka fish. *Nature*, Vol.417, No.6888, pp. 559-563. ISSN 0028-0836

Matsushita, Y.; Oshima, Y. & Nakamura, M. (2007). Expression of DMRT genes in the gonads of Rana rugosa during sex determination. *Zoological Science*, Vol.24, No.1, pp. 95-99, ISSN0289-0003

McDonald, M.T.; Flejter, W.; Sheldon, S.; Putzi, M.J. & Gorski, J.L. (1997). XY sex reversal and gonadal dysgenesis due to 9p24 monosomy. *American Journal of Medical Genetics*, Vol.73, No.3, pp. 321-326, ISSN 0148-7299

Meng, A.; Moore, B.; Tang, H.; Yuan, B. & Lin, S. (1999). A Drosophila doublesex-related gene, terra, is involved in somitogenesis in vertebrates. *Development*, Vol.126, No.6, pp.1259-1268, ISSN 0950-1991

Moniot, B.; Berta, P.; Scherer, G.; Südbeck, P. & Poulat, F. (2000). Male specific expression suggests role of DMRT1 in human sex determination. *Mechanisms of Development*, Vol.91, No.1-2, pp. 323-325, ISSN 0925-4773

www.intechopen.com
Murdock, C. & Wibbels, T. (2003). Expression of Dmrt1 in a turtle with temperature-dependent sex determination. *Cytogenetic and Genome Research*, Vol.101, No.3-4, pp. 302-308, ISSN 1424-8581

Muroya, K.; Okuyama, T.; Goishi, K.; Ogiso, Y.; Fukuda, S.; Kameyama, J.; Sato, H.; Suzuki, Y.; Terasaki, H.; Gomyo, H.; Wakui, K.; Fukushima, Y. & Ogata, T. (2000). Sex-determining gene(s) on distal 9p: clinical and molecular studies in six cases. *The Journal of Clinical Endocrinology & Metabolism*, Vol.85, No.9, pp. 3094-3100, ISSN 0021-972X

Nanda, I.; Shan, Z.; Schartl, M.; Burt, D.W.; Koehler, M.; Nothwang, H.; Grützner, F.; Paton, I.R.; Windsor, D.; Dunn, I.; Engel, W.; Staeheli, P.; Mizuno, S.; Haaf, T. & Schmid, M. (1999). 300 million years of conserved synteny between chicken Z and human chromosome 9. *Nature Genetics*, Vol.21, No.3, pp. 258-259. ISSN 1061-4036

Nanda, I.; Zend-Ajusch, E.; Shan, Z.; Grützner, F.; Schartl, M.; Burt, D.W.; Koehler, M.; Fowler, V.M.; Goodwin, G.; Schneider, W.J.; Mizuno, S.; Dechant, G.; Haaf, T. & Schmid, M. (2000). Conserved synteny between the chicken Z sex chromosome and human chromosome 9 includes the male regulatory gene DMRT1: a comparative (re)view on avian sex determination. *Cytogenetics and Cell Genetics*, Vol.89, No.1-2, pp. 67-78, ISSN 0301-0171

Nanda, I.; Kondo, M.; Hornung, U.; Asakawa, S.; Winkler, C.; Shimizu, A.; Shan, Z.; Haaf, T.; Shimizu, N.; Shima, A.; Schmid, M. & Schartl, M. (2002). A duplicated copy of DMRT1 in the sex-determining region of the Y chromosome of the medaka, *Oryzias latipes*. *Proceedings of the National Academy of Sciences of the United States of America*, Vol.99, No.18, pp. 11778-11783, ISSN 0027-8424

Osawa, N.; Oshima, Y. & Nakamura, M. (2005). Molecular cloning of Dmrt1 and its expression in the gonad of Xenopus. *Zoological Science*, Vol.22, No.6, pp.681-687, ISSN 0289-0003

Ottolenghi, C.; Veitia, R.; Quintana-Murci, L.; Torchard, D.; Scapoli, L. & Souleyreau-Therville, N. (2000a). The region on 9p associated with 46,XY sex reversal contains several transcripts expressed in the urogenital system and a novel doublesex-related domain. *Genomics*, Vol.64, No2, pp. 170-178, ISSN 0888-7543

Ottolenghi, C.; Veitia, R.; Barbieri, M.; Fellous, M. & McElreavey, K. (2000b). The human doublesex-related gene, DMRT2, is homologous to a gene involved in somitogenesis and encodes a potential bicistronic transcript. *Genomics*, Vol.64, No. 2, pp. 179-186, ISSN 0888-7543

Ottolenghi, C.; Fellous, M.; Barbieri, M. & McElreavey, K. (2002). Novel paralogy relations among human chromosomes support a link between the phylogeny of doublesex-related genes and the evolution of sex determination. *Genomics*, Vol. 79, No.3, pp. 333-343, ISSN 0888-7543

Öunap, K.; Uibo, O.; Zordania, R.; Kiho, L.; Ilus, T.; Öiglane-Shlik, E. & Bartsch, O. (2004). Three patients with 9p deletions including DMRT1 and DMRT2: a girl with XY complement, bilateral ovotestes, and extreme growth retardation, and two XX females with normal pubertal development. *American Journal of Medical Genetics*, Vol.130A, No.4, pp. 415-423, ISSN 1552-4825
Pask, A.J.; Behringer, R.R. & Renfree, M.B. (2003). Expression of DMRT1 in the mammalian ovary and testis – from marsupials to mice. *Cytogenetic and Genome Research*, Vol.101, No.3-4, pp. 229-236, ISSN 0301-0171

Privitera, O.; Vessechia, G.; Bernasconi, B.; Bettio, D.; Stioui, S. & Giordano, G. (2005). Prenatal diagnosis of del(9)(p24): a sex reverse case. *Prenatal Diagnosis*, Vol.25, No.10, pp. 945-948, ISSN 0197-3851

Raymond, C.S.; Shamu, C.E.; Shen, M.M.; Seifert, K.J.; Hirsch, B.; Hodgkin, J. & Zarkower, D. (1998). Evidence for evolutionary conservation of sex-determining genes. *Nature*, Vol.391, No.6668, pp. 691-695, ISSN 0028-0836

Raymond, C.S.; Parker, E.D.; Kettlewell, J.R.; Brown L.G.; Page, D.C.; Kusz, K.; Jaruzelska, J.; Reinberg, Y.; Flejter, W.L.; Bardwell, V.J.; Hirsch, B. & Zarkower, D. (1999a). A region of human chromosome 9p required testis development contains genes related to known sexual regulators. *Human Molecular Genetics*, Vol.8, No.6, pp. 989-996, ISSN 0964-6906

Raymond, C.S.; Kettlewell, J.R.; Hirsch, B.; Bardwell, V.J. & Zarkower, D. (1999b). Expression of Dmrt1 in the genital ridge of mouse and chicken embryos suggests a role in vertebrate sexual development. *Developmental Biology*, Vol.215, No.2, pp. 208-220., ISSN 0012-1606

Raymond, C.S.; Murphy, M.W.; O’sullivan, M.G.; Bardwell, V.J. & Zarkower, D. (2000). Dmrt1, a gene related to warm and fly sexual regulators, is required for mammalian testis differentiation. *Genes & Development*, Vol.14, No.20, pp. 2587-2595, ISSN 0890-9369

Rhen, T.; Metzger, K.; Schroeder, A. & Woodward, R. (2007). Expression of putative sex-determining genes during the thermosensitive period of gonad development in the snapping turtle, *Chelydra serpentine*. *Sexual Development*, Vol.1, No.4, pp. 255-270, ISSN 1661-5425

Sato, T.; Rocancourt, D.; Marques, L.; Thorsteinsdóttir, S. & Buckingham, M. (2010). A Pax3/DMRT2/Myf5 regulatory cascade functions at the onset of myogenesis. *PLoS Genetics*, Vol.6, No.4, pp. e1000897, ISSN 1553-7390

Saúde, L.; Lourenço, R.; Gonçalves, A. & Palmeirim, I. (2005). *Terra* is a left-right asymmetry gene required for left-right synchronization of the segmentation clock. *Nature Cell Biology*, Vol.7, No.9, pp. 918-920, ISSN 1465-7392

Seo, K.W.; Wang, Y.; Kokubo, H.; Kettlewell, J.R.; Zarkower, D.A. & Johnson, R.L. (2006). Targeted disruption of the DM domain containing transcription factor DMRT2 reveals an essential role in somite patterning. *Developmental Biology*, Vol.290, No.1, pp. 200-210, ISSN 0012-1606

Seo, K.W. (2007). DMRT2 and Pax3 double-knockout mice show severe defects in embryonic myogenesis. *Comparative Medicine*, Vol.57, No.5, pp. 460-468, ISSN 1532-0820

Shan, Z.; Nanda, I.; Wang, Y.; Schmid, M.; Vortkamp, A. & Haaf, T. (2000). Sex-specific expression of an evolutionarily conserved male regulatory gene, *DMRT1*, in birds. *Cytogenetics and Cell Genetics*, Vol.89, No.3-4, pp. 252-257, ISSN 0301-0171

Shen, M.M. & Hodgkin, J. (1988). *Mab-3*, a gene required for sex-specific yolk protein expression and a male-specific lineage in C. elegans. *Cell*, Vol.54, No.7, pp. 1019-1031, ISSN 0092-8674
Shetty, S.; Kirby, P.; Zarkower, D. & Graves, J.A.M. (2002). DMRT1 in a ratite bird: evidence for a role in sex determination and discovery of a putative regulatory element. *Cytogenetic and Genome Research*, Vol.99, No.1-4, pp. 245-251, ISSN 1424-8581

Shibata, K.; Takase, M. & Nakamura, M. (2002). The Dmrt1 expression in sex-reversed gonads of amphibians. *General and Comparative Endocrinology*, Vol.127, No.3, pp. 232-241, ISSN 0016-6480

Sinclair, A.H.; Berta, P.; Palmer, M.S.; Hawkins, J.R.; Griffiths, B.L.; Smith, M.J.; Foster, J.W.; Frischauf, A-M.; Lovell-Badge, R. & Goodfellow, P.N. (1990). A gene from the human sex- determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature*, Vol.346, No.6281, pp. 240-244, ISSN 0028-0836

Shibata, K.; Takase, M. & Nakamura, M. (2002). The Dmrt1 expression in sex-reversed gonads of amphibians. *General and Comparative Endocrinology*, Vol.127, No.3, pp. 232-241, ISSN 0016-6480

Sinclair, A.H.; Berta, P.; Palmer, M.S.; Hawkins, J.R.; Griffiths, B.L.; Smith, M.J.; Foster, J.W.; Frischauf, A-M.; Lovell-Badge, R. & Goodfellow, P.N. (1990). A gene from the human sex- determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature*, Vol.346, No.6281, pp. 240-244, ISSN 0028-0836

Smith, C.A.; McClive, P.J.; Western, P.S.; Reed, K.J. & Sinclair, A.H. (1999a). Conservation of a sex-determining gene. *Nature*, Vol.402, No.6762, pp. 601-602, ISSN 0028-0836

Smith, C.A.; Smith, M.J. & Sinclair, A.H. (1999b). Gene expression during gonadogenesis in the chicken embryo. *Gene*, Vol.234, No.2, pp. 395-402, ISSN 0378-1119

Smith, C.A.; Hurley, T.M.; McClive, P.J. & Sinclair, A.H. (2002). Restricted expression of DMRT3 in chicken and mouse embryos. *Mechanisms of Development*, Vol.119, Suppl 1, pp. S73-S76, ISSN 0925-4773

Smith, C.A.; Katz, M. & Sinclair, A.H. (2003). DMRT1 is upregulated in the gonads during female-to-male sex reversal in ZW chicken embryos. *Biology of Reproduction*, Vol.68, No.2, pp. 560-570, ISSN 0006-3363

Smith C.A.; Roeszler, K.N.; Ohnesorg, T.; Cummins, D.M.; Farlie, P.G.; Doran, T.J. & Sinclair, A.H. (2009). The avian Z-linked gene DMRT1 is required for male sex determination in the chicken. *Nature*, Vol.461, No.7261, pp. 267-271, ISSN 0028-0836

Sreenivasulu, K.; Ganesh, S. & Raman, R. (2002). Evolutionarily conserved, DMRT1, encodes alternatively spliced transcripts and shows dimorphic expression during gonadal differentiation in the lizard, Calotes versicolor. *Gene Expression Patterns*, Vol.2, No.1-2, pp. 51-60, ISSN 1567-133X

Torres-Maldonado, L.C.; Landa-Piedra, A.; Moreno-Mendoza, N.; Marmolejo-Valencia, A.; Meza-Martines, A. & Merchant-Larios, H. (2002). Expression profiles of Dax1, Dmrtl, and Sox9 during temperature sex determination in gonads of the sea turtle *Lepidochelys olivacea*. *General and Comparative Endocrinology*, Vol.129, No.1, pp. 20-26, ISSN 0016-6480

Tsend-Ayush, E.; Lim, S.L.; Pask, A.J.; Hamdan, D.D.; Renfree, M.B. & Grützner, F. (2009). Characterisation of ATRX, DMRT1, DMRT7 and WT1 in the platypus (*Ornithorhynchus anatinus*). *Reproduction, Fertility, and Development*, Vol.21, No.8, pp.985-991, ISSN 1031-3613

Turnbull, C.; Rapley, E.A.; Seal, S.; Pernet, D.; Renwick, A.; Hughes, D.; Ricketts, M.; Linger, R.; Ng, S.; Deloukas, P.; Huddart, R.A.; Bishop, D.T.; Easton, D.F.; Stratton, M.R.; Rahman, N. & UK Testicular Cancer Collaboration. (2011). Variants near DMRT1, TERT and ATF7IP are associated with testicular germ cell cancer. *Nature Genetics*, Vol.42, No.7, pp.604-607, ISSN 1061-4036

Veith, A.M.; Froschauer, A.; Körtig, C.; Nanda, I; Hanel, R.; Schmid, M.; Schartl, M. & Volff, J.N. (2003). Cloning of the dmrt1 gene of *Xiphophorus maculatus*: www.intechopen.com
dmY/dmrt1Y is not the master sex-determining gene in the platyfish. Gene, Vol.317, No.1-2, pp. 59-66, ISSN 0378-1119

Veith, A.M.; Schäfer, M.; Klüver, N.; Schmidt, C.; Schultheis, C.; Schartl, M.; Winkler, C. & Volff, J.N. (2006a). Tissue-specific expression of dmrt genes in embryos and adults of the platyfish Xiphophorus maculatus. Zebrafish, Vol.3, No.3, pp. 325-37, ISSN 1545-8547

Veith, A.M.; Klattig, J.; Dettaï, A.; Schmidt, C.; Englert, C. & Volff, J.N. (2006b). Male-biased expression of X-chromosomal DM domain-less Dmrt8 genes in the mouse. Genomics, Vol.88, No.2, pp. 185-195, ISSN 0888-7543

Veitia, R.; Nunes, M.; Brauner, R.; Doco-Fenzy, M.; Joanny-Flinois, O.; Jaubert, F.; Lortat-Jacob, S.; Fellous, M. & McElreavey, K. (1997). Deletions of distal 9p associated with 46,XY male to female sex reversal: definition of the breakpoints at 9p23.3-p24.1. Genomics, Vol.41, No.2, pp. 271-274, ISSN 0888-7543

Veitia, R.A.; Nunes, M.; Quintana-Murci, L.; Rappaport, R.; Thibaude, E.; Jaubert, F.; Fellous, M.; McElreavey, K.; Gonçalves, J.; Silva, M.; Rodrigues, J.C.; Caspuro, M.; Boieiro, F.; Marques, R. & Lavinha, J. (1998). Swyer syndrome and 46,XY partial gonadal dysgenesis associated with 9p deletions in the absence of monosomy-9p syndrome. American Journal of Human Genetics, Vol.63, No.3, pp. 901-905, ISSN 0002-9297

Vinci, G.; Chantot-Bastaraud, S.; El Houate, B.; Lortat-Jacob, S.; Brauner, R. & McElreavey, K. (2007). Association of deletion 9p, 46,XY gonadal dysgenesis and autistic spectrum disorder. Molecular Human Reproduction, Vol.13, No.9, pp. 685-689, ISSN 1360-9947

Volff, J-N.; Zarkower, D.; Bardwell, V.J. & Schartl, M. (2003a). Evolutionary dynamics of the DM domain gene family in metazoans. Journal of Molecular Evolution, Vol.57, Suppl.1, pp. S241-S249, ISSN 0022-2844

Volff, J-N.; Kondo, M. & Schartl, M. (2003b). Medaka dmY/dmrt1Y is not the universal primary sex-determining gene in fish. Trends in Genetics, Vol.19, No.4, pp. 196-199, ISSN 0168-9525

Winkler, C.; Hornung, U.; Kondo, M.; Neuner, C.; Duschl, J.; Shima, A. & Schartl, M. (2004). Developmentally regulated and non-sex-specific expression of autosomal dmrt genes in embryos of Medaka fish (Oryzias latipes). Mechanism of Development, Vol.121, No.7-8, pp. 997-1005, ISSN 0925-4773

Yamaguchi, A.; Lee, K.H.; Fujimoto, H.; Kadomura, K.; Yasumoto, S. & Matsuyama, M. (2006). Expression of the DMRT gene and its roles in early gonadal development of the Japanese pufferfish Takifugu rubripes. Comparative Biochemistry and Physiology Part D: Genomics and Proteomics, Vol.1, No.1, pp. 59-68, ISSN 1744-117X

Yoshimoto, S.; Okada, E.; Oishi, T.; Numagami, R.; Umemoto, H.; Tamura, K.; Kanda, H.; Shiba, T.; Takamatsu, N. & Ito, M. (2006). Expression and promoter analysis of Xenopus DMRT1 and functional characterization of the transactivation property of its protein. Development, Growth & Differentiation, Vol.48, No.9, pp. 597-603, ISSN 0012-1592

Yoshimoto, S.; Okada, E.; Umemoto, H.; Tamura, K.; Uno, Y.; Nashida-Umehara, C.; Matsuda, Y.; Takamatsu, N.; Shiba, T. & Ito, M. (2008). A W-linked DM-domain gene, DM-W, participates in primary ovary development in Xenopus laevis.
Yoshimoto, S.; Ikeda, N.; Izutsu, Y.; Shiba, T.; Takamatsu, N. & Ito, M. (2010). Opposite roles of DMRT1 and its W-linked parologue, DM-W, in sexual dimorphism of Xenopus laevis: implications of a ZZ/ZW-type sex-determining system. *Development*, Vol.137, No.15, pp. 2519-2526, ISSN 0950-1991

Yi, W. & Zarkower, D. (1999). Similarity of DNA binding and transcriptional regulation by *Caenorhabditis elegans* MAB-3 and *Drosophila melanogaster* DSX suggest conservation of sex determining mechanisms. *Development*, Vol.126, No.5, pp. 873-881, ISSN 0950-1991

Yi, W.; Ross, J.M. & Zarkower, D. (2000). Mab-3 is a direct *tra-1* target gene regulating diverse aspects of *C. elegans* male sexual development and behavior. *Development*, Vol.127, No.20, pp. 4469-4480, ISSN 0950-1991

Zarkower, D. (2001). Establishing sexual dimorphism: conservation amidst diversity? *Nature Reviews. Genetics*, Vol.2, No.3, pp. 175-185, ISSN 1471-0056

Zhao, Y.; Lu, H.; Yu, H.; Cheng, H. & Zhou, R. (2007). Multiple alternative splicing in gonads of chicken DMRT1. *Development Genes and Evolution*, Vol.217, No.2, pp. 119-126, ISSN 0949-944X

Zhou, X.; Li, Q.; Lu, H.; Chen, H.; Guo, Y.; Cheng, H. & Zhou, R. (2008). Fish specific duplication of DMRT2: characterization of zebrafish Dmrt2b. *Biochimie*, Vol.90, No.6, pp. 878-887, ISSN 0300-9084
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