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Paper report

Sex determination in fish

An excellent candidate for the master sex-determining gene on the Y chromosome of the medaka fish is not related to the mammalian *SRY* gene

***DMY* is a Y-specific DM-domain gene required for male development in the medaka fish.**

M Matsuda, Y Nagahama, A Shinomiya, T Sato, C Matsuda, T Kobayashi, CE Morrey, N Shibata, S Asakawa, N Shimizu, *et al.* *Nature* 2002, **417**:559-563 [[Read the abstract on PubMed](#)]

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In contrast to mammals and birds, teleost fish display an amazing diversity of sex-determination systems. Male heterogamety (males are XY and females XX, as is generally the rule in mammals) and female heterogamety (females are WZ and males ZZ, the system at work in birds) are sometimes observed within the same fish genus and even the same fish species. More complicated systems can involve multiple sex chromosomes and multiple gene loci (influence from autosomal loci on sex determination and polyfactorial sex determination). Hermaphroditism has been observed in fish; environmental factors (for example temperature) can also influence their sex-determination systems. Almost nothing is known about the mechanisms driving the diversity of sex determination in fish, and the evolutionary significance of the various mechanisms remains almost completely obscure.

In most mammalian species, the male-inducing master sex-determining gene, *SRY*, is located on the Y chromosome and is therefore absent from XX females. *SRY* is presumed to be specific to mammals. No master sex-determination gene has yet been unambiguously identified in fish or other nonmammalian vertebrates. Matsuda *et al.* have described an outstanding candidate for the first master sex-determining gene in

fish, from *Oryzias latipes*.

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Sex determination in the teleost fish *O. latipes* (medaka) involves simple male heterogamety. In contrast to the situation observed in humans, the medaka Y chromosome is very similar to the X; there is no cytogenetic difference between X and Y, and X-Y pairing occurs along almost the complete chromosome length. This suggests that the male-determining region on the Y chromosome should be relatively small. Using a positional cloning strategy, Matsuda *et al.* restricted this region to 530 kb encompassed by four bacterial artificial chromosome genomic clones. Sequencing of about 422 kb from this region led to the identification of 52 putative genes. Deletion analysis of the Y chromosome of an XY congenic female further shortened the region to 250 kb, containing 27 candidate genes. Only three of these were expressed in embryos; and only one gene, called *DMY*, was expressed exclusively in XY embryos and was present on the Y but not on the X chromosome. The *DMY* gene spans six exons and encodes a putative protein of 267 amino acids containing a DNA-binding domain called DM, which is also present in some proteins involved in sex determination in nematodes and flies. Interestingly, *DMY* is very similar to *DMRT1*, a transcription factor that is also involved in male development in other vertebrates, including humans. *DMY* was shown to be essential for male medaka development, as a spontaneous XY female (sex reversal) produced a truncated *DMY* protein as a result of a single insertion in exon 3. A second XY female presented a very low level of expression of *DMY*. And *DMY* expression was detected only in the somatic cells surrounding the germ cells in XY embryos. Taken together, the results of Matsuda *et al.* indicate that *DMY* is a Y-specific gene required for male development in the medaka fish.

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Although more work is required to define the Y-specific gene identified by Matsuda *et al.* as the master sex-determining gene, *DMY* is without doubt the leading candidate for this function in the medaka. The phylogenetic relationship between *DMY* and *DMRT1*, as well as the molecular mechanism of formation and the age of the *DMY* gene on the Y chromosome, remain to be determined. Transcription factors containing the DM domain are involved in sex determination in animals as different as nematodes, flies and mammals, but do not by themselves determine the sex. In these organisms they are under the control of upstream sex-deciding signals (for example, the X-chromosome:autosome ratio in the fruit fly, or the presence or absence of *SRY* in most mammals) that are generally poorly conserved between divergent animal lineages. Two possibilities have then to be considered for the medaka *DMY*: either upstream sex-determining signals are simply not present in this fish, or *DMY* acquired a new function at the top of the cascade, controlling or replacing the pre-existing upstream sex-determining signals. Could *DMY* be the master sex-determining gene in fish? This appears possible, as even in birds the best candidate for such a function is the *DMY*-related *DMRT1* gene, which is located on the Z but not on the W chromosome in chickens. Nevertheless, the role of *DMY* in the numerous sex-determination systems found in fish remains to be determined. Alternatively, the diversity of sex-determination systems in fish might be related to the use of different master sex-determining genes, and the quest for such genes in different fish species might uncover currently unknown vertebrate sex-determining genes. Because of the absence of obvious sex-linked markers and heteromorphic sex chromosomes, pufferfish and zebrafish do not appear to be suitable for performing studies on genetic sex determination. Comparison of the medaka with alternative models, such as the platyfish *Xiphophorus maculatus* and the

tilapia *Oreochromis niloticus*, will probably contribute considerably to our understanding of the molecular and evolutionary mechanisms driving the variability of sex determination in fish.

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