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Review Article

# THE EFFECT OF GENES AND THE ENVIRONMENT ON DETERMINING SEX

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Sex is determined in several ways through evolution. Among the influences on sex determination (SD) are genes, hormone levels, the ratio of sex chromosomes to autosomes and the environment. Genes involved in SD in various species contribute their effects by acting on the Anti-Mullerian Hormone (AMH) encoded by the *Amh* gene. The AMH inhibits development of mullerian ducts in males, whereas in female development reduced levels of P450 aromatase results in ovarian development. Sex determination involves reconciliation of various factors including both genetic and environmental influences, mediated by hormonal levels regulated by the products of these genes.

**Keywords:** Sex differentiation, Genetic Sex Determination, Temperature-Dependent Sex Determination, Sex Chromosome, Sex change, Hermaphroditism, P450Aromatase,

## INTRODUCTION

The principle of having two sexes, or many types, in each organism is a problem that has been addressed in many ways through evolution. Systems for distinguishing sex have included sex determination (SD) by chromosome complement, gene complement, environmental influence, hormonal influence, and temporal effects. In some systems, sex is determined by chromosomal makeup. Mammals and plants have an XX/XY SD system with heterogametic males, whereas birds, some amphibians, and reptiles have a WZ/ZZ system, with heterogametic females. The X types of chromosomes do not resemble the W

types, and the Y types do not resemble the Z types. SD genes have been described in humans following investigation of cases of disorders of sexual development (Pearlman *et al.*, 2010). In order to fully understand the role of genes in SD, it will be necessary to examine how these genes interact with each other, and how these interactions may be superseded by environmental or hormonal influences on sex determination.

There are systems in which the determining factor is the X autosome ratio. There are SD systems that are entirely environmental. There are also systems in which SD is based on temperature or the pH during egg incubation or

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hatching (Morehead and Hart, 2003; Goodman, 2008; Brown *et al.*, 2011). There are SD systems that are temporal in fish, where one sex is present in the early stages and the other sex develops in the hermaphroditic individual over the course of time. There are examples, where the male occurs first (protandrous), and there are examples where the female appears first (protogynous) in fish with this type of SD. Also, it is possible to override other determinants with the application of hormones such as the Anti-Mullerian Hormone (AMH). There are some organisms with no evidence of genes or chromosomes being involved in SD (Roughgarden, 2004). An entire chromosome may be involved in SD or it may pertain to a single gene, translocated from a sex chromosome to an autosome.

## **ENVIRONMENTAL SEX DETERMINATION**

The environment in which the egg matures or hatches may determine sex. For example, SD in alligators depends upon the temperature in which the eggs are incubated (Ferguson and Joanen, 1982). In European sea bass and other fishes, warmer temperatures are associated with female development (Roemer and Beisenherz, 1996; Piferrer *et al.*, 2005). However, higher temperatures during development may result in male SD in the blue tilapia, *Oreochromis aureus* (Desprez and Melard, 1998). Crocodylians, *Alligator mississippiensis*, and Southern flounder, *Paralichthys lethostigma*, give maleness at higher temperatures whereas in red-eared slider turtles, *Trachemys scripta*, higher incubation temperatures result in female development (Luckenbach *et al.*, 2003; Yao and Capel, 2005; Shoemaker *et al.*, 2007). pH may also influence SD in some fish (Roemer and Beisenherz, 1996).

There is evidence to support the notion that species, which respond to temperature differences during development by choosing the sex of the developing individual, mediate sex determination via hormonal influences. Temperatures that result in elevated expression of aromatase and other ovary developing hormones result in female SD (Ramsey *et al.*, 2007).

## **CHROMOSOMAL SEX DETERMINATION**

There is an XX/XY system of sex determination in most mammals, and a ZZ/ZW system of sex determination in avians, amphibians, and reptiles. Monotremes seem to comprise a special case of chromosomal SD in mammals. To date, no testes-determining factor has been found in monotremes (Ayush *et al.*, 2012). Monotremes have a distinctive system, in which sex chromosomes are composed of ancient sex chromosomes and autosomes; there are 5 X chromosomes and 5 Y-derivative chromosomes (Rens *et al.*, 2004). All ten align in a complex figure during meiosis (Rens *et al.*, 2007). Although no testes-determining-factor has been described in monotremes, the Y chromosomes do have some areas of homology with avian Z chromosomes (Ferguson-Smith and Rens, 2010). Chromosomal SD may reflect our lack of knowledge about the genes involved, and may reflect differential expression of these genes, as in the SD by sex chromosome:autosome ratio, seen in *Drosophila melanogaster* and *Caenorhabditis elegans* (Wilkins 1994).

## **GENETIC SEX DETERMINATION**

The master gene in most mammals with an XX/

XY SD determining system is SRY, the testes-determining-factor (Jost *et al.*, 1973; Sinclair *et al.*, 1990). However, this “master gene” can be overwritten by the effects of specific SD genes. *Sox9*, SRY (sex determining region Y)-box 9; a transcription factor, encodes a zinc-finger protein, which is an activator of SRY. In the XX/XY SD system, AMH normally represses the development of Mullerian ducts, giving a male phenotype. AMH is a member of the TGF  $\beta$  superfamily of genes. SOX9 up-regulates *Amh* *in vitro* and *in vivo* (de Santa Barbara *et al.*, 1998; Arango *et al.*, 1999; Lasala *et al.*, 2004). SOX 9 also activates Mullerian Inhibiting Substance (*Mis*; *Amh*), *Sox8* and inactivates *Sry* as seen in *Sox9* knock-out mice (Chaboissier *et al.*, 2004). SOX9 acts synergistically with SF-1 (steroidogenic factor 1) to enhance *Amh* expression (Nachtigal *et al.*, 1998; de Santa Barbara *et al.*, 1998). *WT1* (-KTS; Wilms Tumor 1), which functions as a tumor suppressor gene, induces *Sry* activity, represses *Mis*, and downregulates the androgen receptor (AR) gene (Shimamura *et al.*, 1997). There are four different isoforms of the WT1 protein, and this observation applies to the isoform missing the three amino acids (Leucine-Threonine-Serine; KTS). WT1 (-KTS) could be considered a “master gene” in sexual development in XX/XY SD systems. This notion is supported by the observation in humans in which WT1 (-KTS) mutations in the male can result in pseudohermaphroditism (Nachtigal *et al.*, 1998). WT1 (-KTS) is necessary for expression of SOX9, SOX8 and AMH. This is known because WT1 mutant male mice appeared to have an intersex phenotype (Gao *et al.*, 2006).

What is known about SD in XX/XY systems, has been explored in the mouse rather than in

the human, except as noted. The products of three genes, *CITED2* and *LHX9*, in concert with *WT1* stimulate the expression of *SF1* to promote *MIS* expression (Nachtigal *et al.*, 1998; Wilhelm and Englert, 2002; Buaas *et al.*, 2009). The product of *SF1* regulates the expression of genes including but not limited to *Cytochrome P-450 aromatase*, *Mis*, and *Dax-1* (Parker *et al.*, 1999). Testes development is initiated by SRY, which is activated by *Cited2*. *Cited2* is activated by the combination of *WT1* and *SF1* (Buaas *et al.*, 2009). There is expression of *SF-1* when *WT1* is deleted in mice although there is no expression of *Sox8*, *Sox 9* or *Amh* (Oryzias Gao *et al.*, 2006). Other genes in SD include *Dmrt* and the recently described *Gsdfy* in Medaka, *Oryzias luzonensis* (*O. luzonensis*), and the SDY gene in Rainbow Trout, *Oncorhynchus mykiss* (Myosho *et al.*, 2012; Yano *et al.*, 2012).

Other mammalian SD genes that have been identified in various animals include *Map3k1*, *Rspo1*, *Nr5a1*, *Wt1*, *Nr0b1*, and *Wnt4* (Perlman *et al.*, 2010). Mutations in *Map3k1* in humans or in *Map3k4* in mice are known to be associated with Male to Female sex reversal, presumably by interfering with either the p38 or the ERK1/ERK2 pathways (Perlman *et al.*, 2010; Warr *et al.*, 2012). *Rspo1* in humans is not known to be responsible for male development in the XX/XY system of SD, however mutations in this gene cause maleness in XX females lacking *Sry* (Parma *et al.*, 2006; Tomaselli *et al.*, 2008). Additionally, *Rspo1* allows female development in the presence of *Wnt4* expression (Parma *et al.*, 2006). The effects of the *Sry* master gene may be overcome by overexpression of *Wnt4*, which causes upregulation of the downstream double dosage sex reversal gene (*DAX1*). This

may result in an individual with a female phenotype and an XY chromosome complement (Jordan *et al.*, 2001). It has been noted that WNT interferes with SF1 activation of Sox9 in ovarian development via the Tesco enhancer (Bernard *et al.*, 2012). It seems that DAX1 acts as an antagonist of SRY in XX/XY sex determining systems, since duplication of the *Dax1* region leads to repression of *Sox9* through its SF-1 transcriptional regulator and its synergistic relationship with WT1 as shown in mice (Ludbrook *et al.*, 2012). The synergistic relationship of SF1 and WT1 along with cAMP acts to promote male development through inhibin proteins, which inhibit Follicle Stimulating Hormone in mice (FSH; Ji *et al.*, 2013). The testis produces hormones, which induce the development of the male phenotype (Pearlman *et al.*, 2010). Sertoli cells secrete AMH, reducing femaleness whereas Leydig cells promote maleness by differentiating Wolffian ducts into seminal vesicles, epididymis, and vas deferens as shown by studying *Wt1* knock-out mice (Gao *et al.*, 2006). However, the relationship between SF1 and WT1 is rather complicated, because WT1 is also a regulator of *Dax1* in mice (Wilhem and Englert, 2002). LHX9, LIM Homeobox 9, and WT1 activate SF1 which in turn upregulates transcription of *Sox9* in mice (Wilhelm and Englert, 2002; Ludbrook *et al.*, 2012). An example of a gene that promotes femaleness in mammals is *Fog2*, which represses *Gata4* in cells from mouse and African green monkey (Svenson *et al.*, 2000; Antonnen *et al.*, 2003). It appears that WT1 expression is increased by the activity of another gene, SF1.

It may be difficult to determine whether SD in mice or in other model systems represent SD in

humans, because there could be functional redundancies with other pathways or a pathway could be missed if it is active early in SD (Bogani *et al.*, 2009). Despite 90 million years of separation, evolutionarily the laboratory mouse is an excellent animal model for the study of human disorders or characters (Murphy *et al.*, 2007). Other genes may control the genes involved in the SD cascade. For example, hTES, the human testi-enhancers sequence, controls the expression of SOX9, SRY, and SF1 (Kowner *et al.*, 2011). It is possible that SRY and SF1 increase expression of *Sox9* by acting on a specific enhancer (Sekido 2008). It is not always clear what the important pathway is in developing ovaries vs. testes, but it is known that DM-W expression may induce expression of p450 aromatase in *Xenopus laevis*, and that this leads to the development of ovaries (Okada, 2009). There is known to be redundancy in the GSD systems for example SOX8 can replace SOX9 in sex determination in XX/XY systems, such as in the mouse (Sock *et al.*, 2001; Chaboissier *et al.*, 2004; hang *et al.*, 2008; Barrionuevo *et al.*, 2009). Although, it is possible to substitute the function of SOX8 for that of SOX9 in activating *Amh* expression, the activity of the former is at a somewhat reduced level in mice compared to the latter (Schepers *et al.*, 2003). Other SD genes have been described in several fish, but further studies of these will be needed in order to completely describe their involvement in SD (Yano *et al.*, 2011).

## HORMONAL INFLUENCE ON SEX DETERMINATION

Hormones may exert an influence on sex determination that overrides the effect of genes.

Estrogens are produced from conversion of androgens, which is controlled by product of the cytochrome P450 Aromatase gene, controlling female development (Wang *et al.*, 2012). Sex reversal in a genotypic male (female phenotype) has been observed in teleost Medaka, *O. luzonensis*, fish in which investigators inactivated AMH by mutating *AMHRII* (Nakamura *et al.*, 2012). The importance of hormonal influence on SD is further illustrated by the frog, *Rana rugosa* (*R. rugosa*), which has an XX/XY SD system. *R. rugosa* develops as a female with ovaries when P450 aromatase is at high levels in developing follicles (Kato *et al.*, 2004). It is possible to achieve sex reversal from female genotype to male phenotype in birds, reptiles, fish and mammals with the administration of exogenous hormone or diminution of endogenous hormone (Elbrecht and Smith, 1992 ; Hudson *et al.*, 2005; Wibbels and Crews, 1994; Belaid *et al.*, 2001; Piferrer and Bla'zquez, 2005; Cheshenko *et al.*, 2008; Calatayud *et al.*, 2010). Male genotype can be converted to female phenotype as in *Xenopus laevis*, in which overexpression of P450 aromatase leads to production of estrogen, causing ovary development in a gonad otherwise genetically designated to be a testis (Yoshimoto, 2010).

## CONCLUSION

Sex hormone levels, which clearly play a role in sex determination, are directed by gene activity. It appears that in some cases, there are genetic means of determining sex that are not under the control of a "master gene". In Medaka, the master SD gene for masculinization is *Dmy*, however this is superseded by the effects of the novel gene *gsdfy*, a member of the TGF- $\beta$  Superfamily that

includes AMH (Myosho *et al.*, 2012). SF1 and aromatase are expressed in the gonads of the Temperature-Sex Dependent (TSD) red-eared slider turtle through an increase in expression levels of P450 aromatase (Shoemaker and Ramsey 2007; Sakata *et al.*, 2005). It appears that the concept of a "master gene" may not allow for an accurate description of the way that sex is determined. As illuminated by Joan Roughgarden in her book *Evolution's Rainbow, ...*, "Sex (whether the primordial germ cells mature as a sperm or egg) and bodily gender (starting with whether the gonad differentiates as a testis or an ovary) are subject to biochemical negotiation". It is possible that the environmental influences in SD act upon genes that are responsible for hormone levels, and whether the female or male hormones predominate determines sex.

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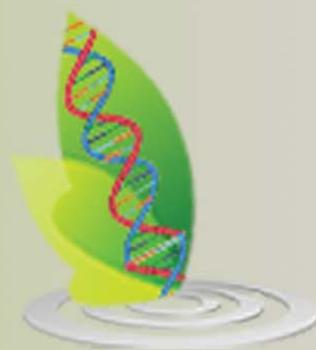
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