Is sex differentiation just a matter of X and Y chromosomes?

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"Sex determination just a matter of X and Y chromosomes" this statement holds little justification in today's era of molecular genetics. Time and again we have come across phenotype female despite 46, XY karyotype and male with 46, XX karyotype. The gender identity of a person depends on various determinants like genetic sex, gonadal sex, internal genitalia, external genitalia and also the secondary sexual characters. Sex determination and differentiation in the prenatal period occurs in a series of complex sequential process that involves many genes, including some that are autosomal.

Nongenomic sexual differentiation has evolved in many species of fishes and reptiles. In these species factors like temperature during embryogenesis influences the sex ratio (Carole et al. 2008). In some species sex determination is delayed until after birth, while some develop sexual phenotypes as a result of the fish's social rank in the group (Baroiller et al. 1999). Whereas in mammals the sex determination is more directly under the control of a single internal event: fertilisation.

Sex differentiation is the developmental process that results in formation of ovary or testis from an indifferent gonad. The decision to form testis or ovaries is the primary sex determining step. Various experiments on mouse have proved that female route of sexual differentiation is the default pathway of sexual development. Classic experiment by Alfred Jost has proved that in the absence of testis or ovary in a mouse, the fetus develops as female (Jost. 1947). Under the presence of the Y-encoded gene, Testis Determining Factor (TDF), male development occurs and in its absence female development is established (Sinclair et al. 1990). The TDF is present on the short arm of the Y chromosome (Jacobs and Ross. 1966). The loss of the TDF gene causes gonadal dysgenesis and transfer of TDF gene to the X chromosome results in XX male.

Since the identification of the importance of Y chromosome in male differentiation over 4 decades ago, two proteins, the H-Y histocompatibility and ZFY (a zinc protein finger) were suggested as the TDF (Page et al. 1987). But experiments done on XX male mice showed inconsistencies of expression of both these proteins and these were also absent in undisputable males with testis (McLaren et al. 1984) (Palmer et al. 1989).

With the help of DNA probes, the Y chromosome was studied thoroughly and the SRY gene (Sex determining Region Y) was found present on phenotype males and absent in all females (Koopman et al. 1991). SRY is a single exon gene located in the short arm of Y chromosome at Yp11. It is the primary factor which differentiates the indifferent gonads into testis and hence establishes male development. SRY gene is active in the somatic cells of the genital ridge of the male embryos and induces Sertoli cell differentiation. In adulthood it is active in both germ cells and sertoli cells (Sinclair et al. 1990).

Females with gonadal dysgenesis show a variety of chromosomal variations including XY. Studies have

revealed 46,XY females with absent, mutated or non-functional SRY gene (Brian et al. 2002). This confirms that SRY is certainly the true sex determining region, the only gene that is required on the Y chromosome for sex determination and is capable of sex reversal too (Kenneth. 2001).

The SRY gene is a transcription factor and the master gene for testes development. It triggers a series of sequence specific regulations on target cells which leads to the male development. SRY expression immediately activates another gene SOX9 (SRY-like box), which is not present on the Y arm but at 17q24. SOX9 is a transcriptional regulator that regulates testes differentiation (Fig 1) (Yoshiakira et al. 2005). It binds to the promoter region of the gene 19p13, to produce Anti Mullerian Hormone (AMH) and probably regulates this gene's expression (Sadler. 2010)

SRY directly or through SOX9 upregulates the production of Steroidegenesis Factor 1 (SF1) present at 9q33. SF1 works with SOX9 to increase the concentration of AMH which leads to the regression of mullerian ducts (Fig 1) (Sadler. 2010). A mutation in SF1 gene encoding can also cause XY sex reversal, with normal female external genitalia, streak gonads, sparse tubules and failure of adrenal development.

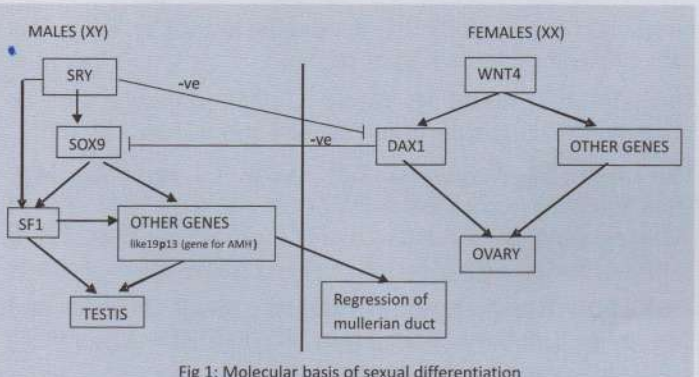

Fig 1: Molecular basis of sexual differentiation

Genes other than SRY also play an important role in sexual differentiation. WNT4 (1p35) is an ovary determining gene. WNT4 knockout female mice have no mullerian ducts and have decreased level of oocytes development (Uusitalo. et al. 1999). WNT4 also upregulates gene DAX1 (in X arm, at Xp21) (Fig 1). It has been recently shown that duplication in WNT4 has caused upregulation of DAX1 expression and has caused sex reversal in a 46, XY individual (Ottolenghi et al. 2007). A XX mice, with WNT4 knockout has found to have testosterone synthesis in fetal ovary and masculinisation of Wolffian duct. Apart from DAX1, some other genes responsible for ovarian differentiation are also regulated by WNT4, but these have not been identified yet.

DAX1 is involved in both sex determination and steroidogenesis. In early stage of development two genes the SOX9 and DAX1 play an important role. In females, in the absence of SRY, DAX1 maintains protein expression in the gonads and inhibits SOX9 (Fig 1), whereas in the males SRY presence increases SOX9 expression and switches off DAX1. Gonadal dysgenesis with resulting female differentiation has occurred to an 46, XY person with intact SRY but duplication of DAX1 leading to its double dosage with SOX9 inhibition (Jordan et al. 2001). It has been suggested that overdosage of DAX 1 leads to an anti-testis effect (Sodder. 2005).

There are many other genes that plays important role in development of a normal male or female phenotype. WT1 gene, Wilms' tumor, is named so because it is not found in its chromosome location 11p13, in patients suffering from this disease. WT1 is necessary for normal renal and gonadal development but not for early mullerian duct development. Phenotype girls with an XY genotype and renal disease may have WT1 deficiency (van Lingen. 1998).

Hormones also play an important role in early sexual differentiation. SF1 stimulates the differentiation of Sertoli cells and Leydig cells. It also upregulates the synthesis of enzymes to produce testosterone in Leydig cells, increase of testosterone develops the Wolffian ducts while lack of secretions gives way to the development of Mullerian duct.

Another gene, SRD5A2 present at 2p23, if mutated or absent can result into 5-alpha reductase type 2 deficiency which inhibits the production of dihydrotestosterone (DHT). This results in few people born with external genitalia that appear female or ambiguous and they are often raised as females. Hence they are 46, XY females inspite of the presence of SRY genes and testis (Jill. 2010).

Androgen Insufficiency syndrome (AIS) is another condition where loss or mutation occurs in the androgen receptor (AR) gene. This AR gene has been localized to the long arm of the X chromosome (Xq11-13). Absence or mutation of this gene results in complete or incomplete loss of androgen receptors. Complete loss of receptors results in XY individual, with SRY gene, testes and production of DHT, but the body cannot use these androgens at all. People with this type of condition have external female genitalia, and are raised as females (Christian. 2010).

So, apart from Y and X chromosome linked genes, there are other autosomal genes which also play an

important role in male and female sex determination. We have seen that be it SRY gene on the Y chromosome or DAX1 gene of the X chromosome, they trigger, inhibit or work sequentially with other genes located on autosomal chromosomes or sex chromosomes to get the end result.

Hence, it can be concluded by stating that perhaps X and Y chromosome is not the only sex determining factors. SRY gene on the Y chromosome is the sex determining switch, its presence makes way for testis development and its absence leads to proliferation of the ovary. But one point of view is that gender of an individual is first established at birth by looking at the external genitalia and not by karyotyping or molecular analysis.

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