Sex determination in human

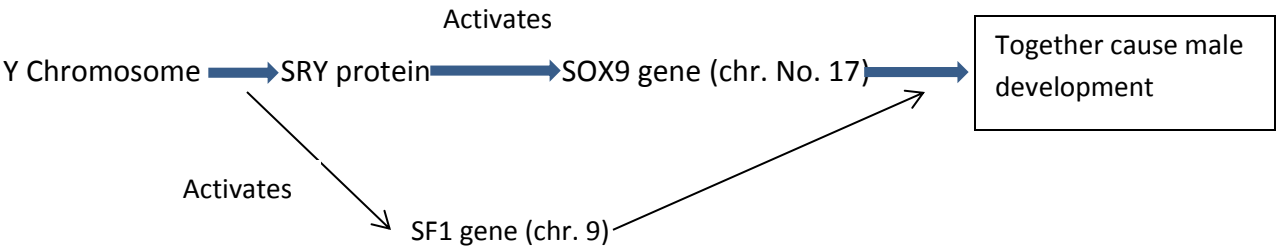
Mammalian sex is determined by the presence or absence of 'Y' chromosome. Initial gene in sex determination cascade is 'SRY'.

SRY gene: Present on 'Y' chromosome, Y (P→11.3) a 35000 bp region of Y near the tip of 'p' arm. (Sex determining region of Y gene).

SRY gene encodes a DNA binding protein with an HMG domain. HMG domain is a 79 amino acid DNA binding motif that is composed of three α- helices. HMG domain binds in the minor groove of dna and cause about 80^{o} bend in the DNA. As a result the DNA becomes unwound and displacement of histones also occurs, which in turn makes the DNA for undergoing transcription.

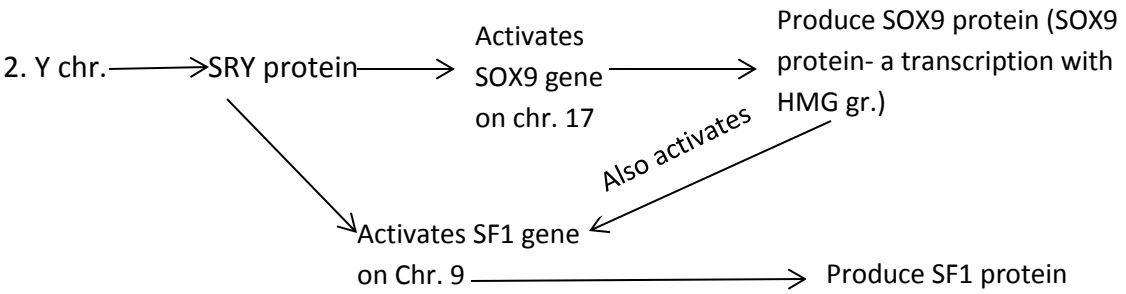
SRY protein activates testis forming pathway at about weak 7 of development. Within undifferentiated gonadal cells if SRY gene is present the protein product of SRY gene (SRY protein) performs 2 functions-

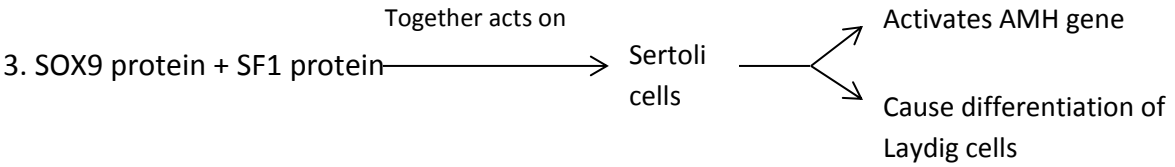
1. It activates SOX9 gene. It is an autosomal gene ; Chromosome no. 17 (17q→24) SOX9 protein is involved in activation of gene that encodes testis determining factor AMH then regress the mullerian duct.
   AMH in combination with TDF forc the interminate gonad to accept the male fate.
2. The 2nd function of SRY protein is to influence the expression of WNT4 and DAX1 gene.
   SRY blocks the expression of WNT4 gene.
   WNT4 protein actually activates the expression of genes that encode ovary determining factor.
   DAX1 protein blocks the expression of proteins that activate expression of TDF. So, SRY protein also blocks the activation of DAX1 gene.

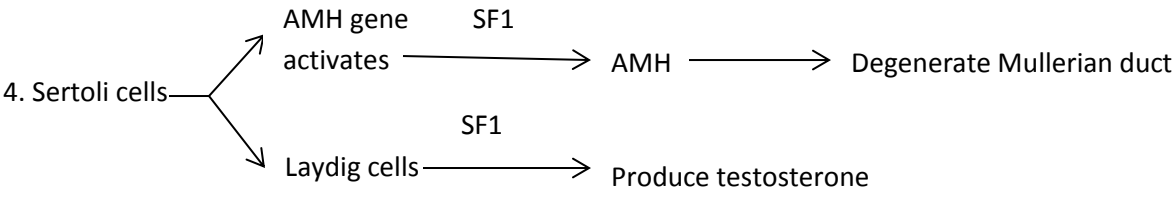


Steps:-

1. Y Chr. → SRY protein(initial) → Acts on genital ridge cells → Help them to release chemotactic factors from these cells. → This chemotactic factor induces mesonephric cells to migrate into XY gonad & induces gonadal epithelium to form sertoli cells.







Shortly after induction by SRY protein, the sertoli cells performs many tasks-

- They induce differentiation of primordial germ cells in Spermatogonia.
- They produce AMH which regress mullerian duct.
- They cause differentiation of Laydig's cells.

DAX1 which encodes an unusual member of the nuclear hormone receptor superfamily, is a gene that may be responsible for a sex reversal syndrome in humans, referred to as dosage sensitive sex reversal, in which XY individuals carrying duplications of XP 21, part of small arm of X-chr. Develops as females (nature article).

Two active DAX1 genes on one X chromosome can abrogate testis formation in human.

DAX1 ⟶ Dosage sensitive sex reversal, adrenal hypoplasia critical region chromosome X, gene 1.

DAX1 gene product can affect the transcription of SF1 gene, and also acts antagonistically to SRY gene.

In humans XY sex reversal is relatively frequent (about 1 in 3000 newborns) and is genetically heterogeneous with loss of function of SRY gene accounting about 15% XX sex reversal is rare (1 in 20,000 newborns) and usually caused by the translocation of SRY onto other chromosome.

The mammalian gonads are derived from the intermediate mesoderm and arise as paired thickenings of the coelomic epithelium on the ventro-medial surface of the mesonephros.

WNT4⟶ gene present on chromosome 1(p) in human. It promotes female sex development. WNT4-wingless type MMTV integration site family member 4. WNT4 is initially required in both sexes for formation of Mullerian duct,

Female sex determination is not a default pathway. It requires ongoing maintenance throughout adulthood. Some genes especially WNT4 is required for female development. Besides β Catenin, RSpo1 and Fox12 genes are also essential as they promote the female pathway by repressing SOX9.

The bi-potential gonads at the earlier stage produce SOX9 under the influence SF1 in both sexes.

In XX supporting cell precursors β catenin levels could accumulate sufficiently to repressing SOX9 activity.

If SRY activity is weak low late it fails to boast SOX9 expression before β catenin levels accumulates sufficiently to shut it down. At later stages FOXL2 increases, which might help, perhaps in concert with ERs to maintain granulosa (follicle) cell differentiation by repressing SOX9 expression.