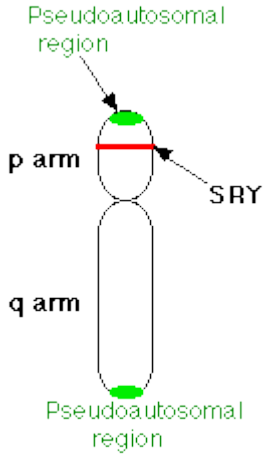
HUMAN Y CHROMOSOME

GENERAL FEATURE

- Cytogenetically, the human Y is an acrocentric chromosome.
- Composed of two pseudoautosomal regions (PARs), a short arm (Yp) and the long arm (Yq) that are separated by a centromere.
- The PARs and the short arm are euchromatic
- The long arm is mostly heterochromatic with the exception of the proximal portion juxtaposed to the centromere is euchromatic in nature.
- PAR1 and PAR2 cover approximately 2600 and 320 kb of DNA, respectively.
- Compared with all other nuclear chromosomes, the Y harbours the smallest number of genes at 568 and is considerably shorter than the X chromosome in length.
- The PARs contain at least 29 genes, with diverse roles in cell signaling, transcription regulation and mitochondrial function.



Y chromosome

GENE OF INTEREST ON Y - Sex determining region on Y [SRY]

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).

- In the year 1959 two scientific reports on the Klinefelter syndrome and on the Turner syndrome, described for the very first time that the human Y chromosome contained at least one sex-determining gene that was responsible for the maleness of the embryo.
- In 1990, the gene responsible for testicular determination, SRY (Sex-determining Region on the Y chromosome), was identified and was found to be located on the short arm of the Y chromosome close to the pseudoautosomal boundary.

- The human SRY is a single exon that encodes a protein of 204 amino acids which contains a conserved DNA-binding domain (the HMG-box: High Mobility Group), suggesting this protein regulates gene expression.
- 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 80^0 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.
- This gene has been shown to be essential for initiating testis development and the differentiation of the indifferent, bipotential, gonad into the testicular pathway.

FUNCTIONAL CASCADE OF *SRY* (towards male development)

SRY has been proposed to be the master gene regulating the cascade of testis determination.

Many genes and loci have been proposed to interact with *SRY* protein, such as *WT-1* (Wilm's tumour gene), *SF-1* (Steroidogenic Factor 1) and *SOX-9* (sex-determining region-box 9).

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 following functions-

1. It activates SOX9 gene. It is an autosomal gene on Chromosome no. 17 (17q→24). SOX9 is also positively regulated by FGF9 and the product of PGD_2 (Prostaglandin D synthase).
2. By the end of the sixth week after conception the Sertoli cells of the fetal testis have begun to differentiate and secrete anti-Müllerian hormone (AMH) which in turn regress the mullerian duct.
3. Within the next two weeks, the Leydig cells appear and begin to secrete testosterone.

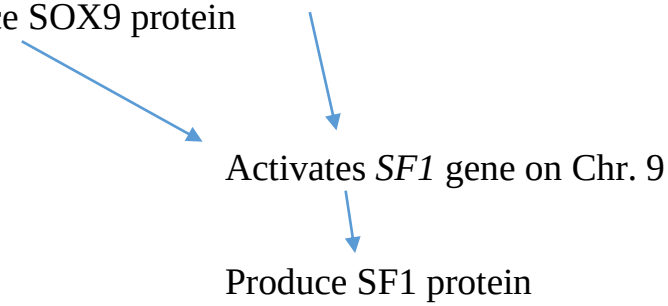
NOTE

However, later scientists argued that SRY protein indirectly induces mesonephric cells to migrate into the genital ridge. SRY protein causes cells in the genital ridge to secrete a chemotactic factor that causes cells from the adjacent mesonephros to migrate in to the genital ridge. The mesonephric cells, rather than SRY protein directly, induce the genital epithelial cells to become Sertoli cells.

Steps:-

- 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.

- Y Chromosome ----→SRY protein ----→Activates *SOX9* gene (chr. No. 17) ----→ Produce SOX9 protein



Activates *SF1* gene on Chr. 9

Produce SF1 protein

- SOX9 protein + SF1 protein----→ Sertoli cells------- --→ Activates *AMH* gene

Cause differentiation of Laydig cells

- Sartoli cells ---→ activates *AMH* gene---→AMH ---→degenerate mullerian duct

Laydig cells----→ produce testosterone

THE OTHER IMPORTANT FUNCTION OF SRY PROTEIN –

It influence the expression of WNT4 and DAX1 gene.

- ***WNT4*** (wingless type MMTV integration site family member 4) gene present on chromosome 1(p) in human. It promotes female sex development. WNT4 is initially required in both sexes for formation of Mullerian duct.
- ***DAX1*** (Dosage sensitive sex reversal, adrenal hypoplasia critical region chromosome X, gene 1.) 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, in which XY individuals carrying duplications of part of small arm of X-chr develops as females. Two active *DAX1* genes on one X chromosome can abrogate testis formation in human.

- 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 *DAX*1 gene.

Female sex determination requires ongoing maintenance throughout adulthood. Some genes especially *WNT4* is required for female development. Besides β Catenin, *RSpo1* and *Fox12* ((Forkhead box L2) genes are also essential as they promote the female pathway by repressing SOX9.

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.

The bi-potential gonads at the earlier stage produce SOX9 under the influence SF1 in both sexes. In XX supporting cell β catenin levels could accumulate sufficiently to repress SOX9 activity. If SRY activity is weak, low or 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 to maintain granulosa (follicle) cell differentiation by repressing SOX9 expression

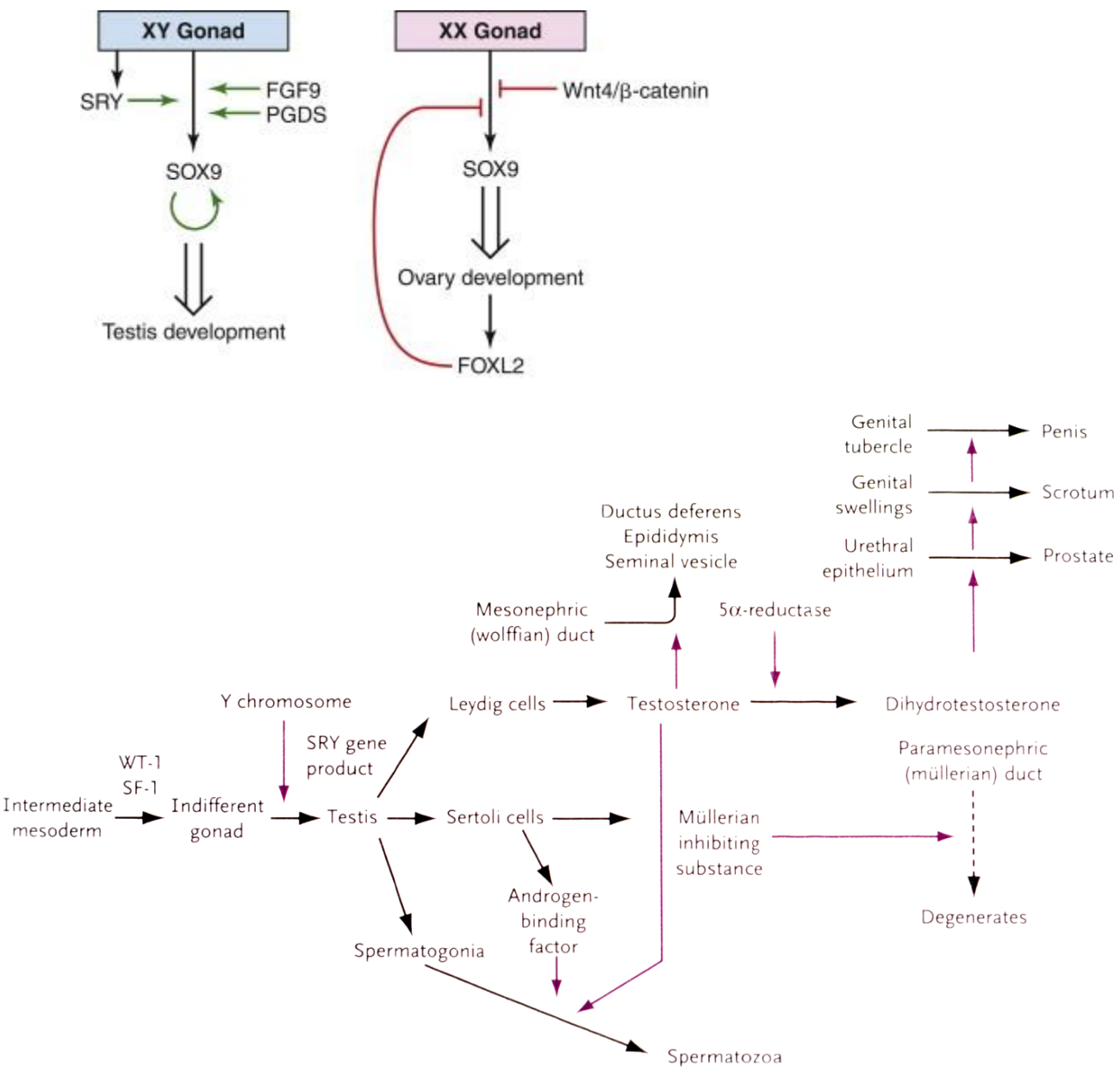


Figure 15-22

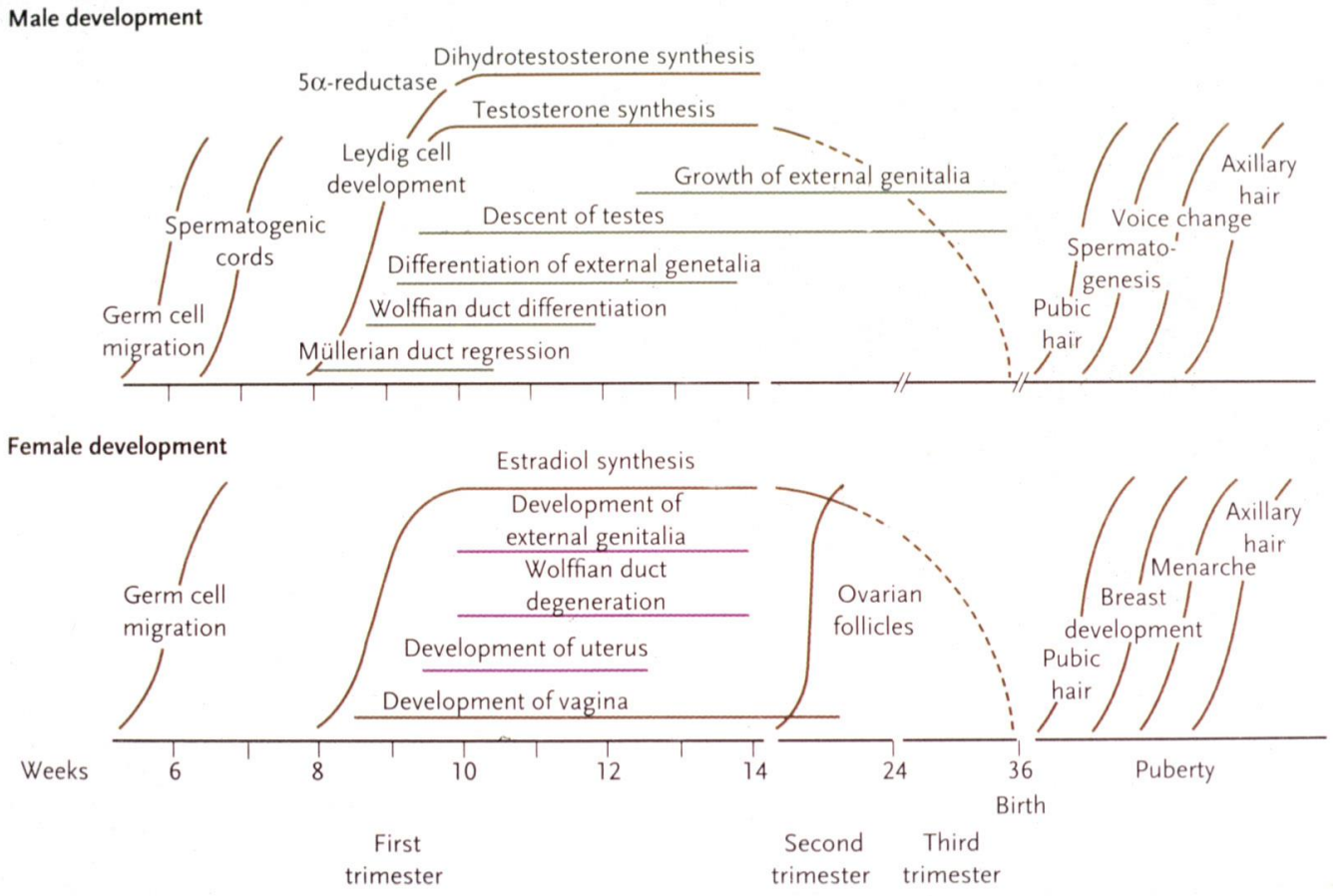

Male development
Dihydrotestosterone synthesis
5α-reductase
Testosterone synthesis
Leydig cell development
Growth of external genitalia
Axillary hair
Spermatogenic cords
Descent of testes
Voice change
Spermato-genesis
Differentiation of external genetalia
Germ cell migration
Wolffian duct differentiation
Pubic hair
Müllerian duct regression
Female development
Estradiol synthesis
Development of external genitalia
Axillary hair
Germ cell migration
Wolffian duct degeneration
Menarche
Breast development
Ovarian follicles
Development of uterus
Pubic hair
Development of vagina
Weeks
6
8
10
12
14
24
36
Birth
Puberty
First trimester
Second trimester
Third trimester

Figure 15-20