Dr.: Zahraa Haleem Alqiam & M.Sc Mazin Eidan Hadi
zahraahaleem@uomus.edu.iq & mazin.eidan@uomus.edu.iq

The genetics of sex

A branch of developmental genetics is dealing with the sex determination and sex differentiation, and with all the genetic process by which the male and female gender-specific phenotype develops.

Genomic Structure of the Human X and Y Chromosomes

The human X and Y chromosomes have evolved from a pair of ancestral chromosomes during the past 300 million years . While the X chromosome retained many properties of an autosome, the Y chromosome lost most fits genes and became greatly reduced in size. Its genetic function is now limited to inducing male development during embryonic development and to maintaining spermatogenesis in adult males. The two chromosomes undergo pairing and recombination at the distal ends of their short arms in the pseudo autosomal region (PAR1),whereas all other regions are exempted from recombination.

A. Genomic structure of the human X chromosome

Functional genes are distributed along the X chromosome as shown by the blue squares (each representing one gene). The approximate locations of nine selected landmark genes and their directions of transcription (arrows) are shown. Most of the short arm (Xp) consists of a region that resulted from the translocation of an ancestral autosome into Xp about 105 MYA (million years ago) (X-added region, XAR). The long arm (Xq) is composed of a region that has been conserved during evolution in mammals (XCR, X-conserved region). Five regions of evolutionary conservation, called evolutionary strata S1-S5, have been identified along the X chromosomes. The human X chromosome contains 1098 genes. The X chromosome has 7.1 genes per million base pairs, one of the lowest gene densities in the human genome (average 10–13).

Dr.: Zahraa Haleem Alqiam & M.Sc Mazin Eidan Hadi
zahraahaleem@uomus.edu.iq & mazin.eidan@uomus.edu.iq

B- Genomic structure of the human Y chromosome

The human Y chromosome has a distinct genomic structure comprising five different regions in the euchromatic part:

(i) Two pseudo utosomal regions at the distal ends of the short (PAR1) and long arms (PAR2),

(ii) The Y-specific male determinant (MSY) region of about 35 kb,

(iii) About 8.6 Mb (38% of the euchromatic portion) called X-degenerate, derived from the ancestral autosome,

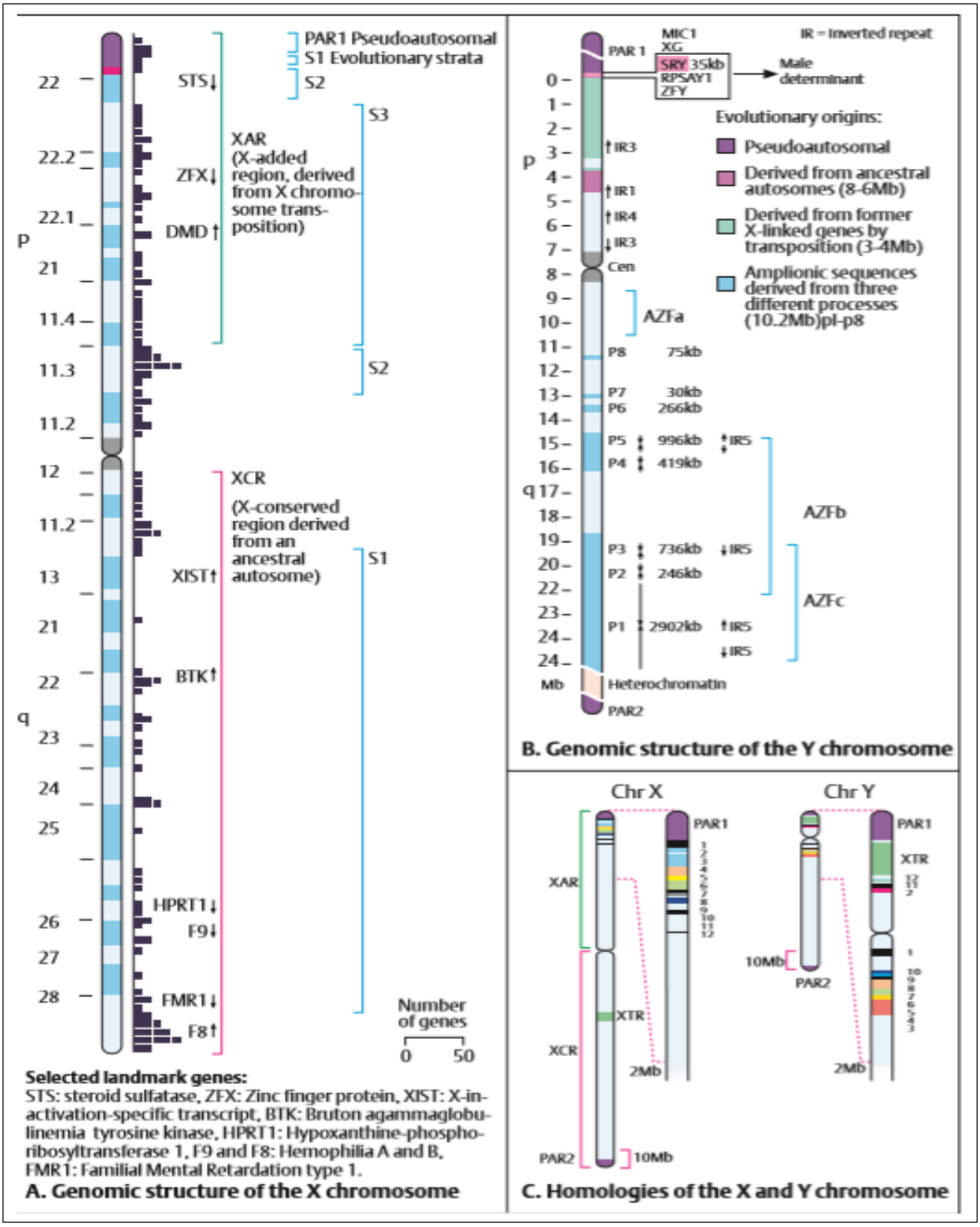
(iv) 3.4 Mb derived from former X-linked genes by transposition (Xtransposed), which occurred about 3–4 MYA, and (v) 10.2 Mb amplified (amplionic) Y specific sequences, designated as P1-P8, derived from three different processes.

These are thought to be derived from former X-and Y linked genes and to have acquired autosomal male fertility factors by transposition and retroposition. They are termed amplionic because they consist of amplified palindromic sequences (amplicons) of various sizes with a marked sequence similarity of 99.9% over long stretches of DNA(ten to hundreds of kilobases). They contain both coding and noncoding genes. Most genes in the amplionic segments are expressed exclusively in testes ,presumably being required for spermatogenesis. Since the male-specific sequences on the Y chromosome do not participate in crossing over, they are deprived of one mechanism for replacing mutations or structural rearrangements with normal sequences. Gene conversion between these palindromic sequences (Y-Y conversion) presumably serves as a mechanism for restoring normal sequences that have been rendered nonfunctional in one arm of a palindrome.

C. Homologies between and the X and Y chromosomes

The X and Y chromosomes share regions of homology due to their common evolutionary origin. Medical relevance Three regions, AZFa, AZFb, and AZFc ,in the

long arm of the Y chromosome are associated with male infertility when deleted, due to failure to produce viable sperm cells (azoospermia).



Dr.: Zahraa Haleem Alqiam & M.Sc Mazin Eidan Hadi
zahraahaleem@uomus.edu.iq & mazin.eidan@uomus.edu.iq

Sex-determining region SRY

Sex-determining region SRY Experiments in animals and clinical observations of human males with various sized deletions of the Y chromosome indicate that only a small region of the distal short arm of the Y chromosome is required to induce male development. This region is named SRY(sex-related Y). SRY is a small region on the short arm of the human Y chromosome. Within this region, the gene SRY (sex-determining region Y) was identified. It is located just proximal to the pseudo autosomal region 1 (PAR1). The PAR1 is homologous to the distal segment of the short arm of the X chromosome. Homologous pairing occurs here with crossing over during male meiosis.

SRY gene The SRY gene, located atYp11.32, consists of a single exon. It has a TATAAA motif for binding transcription factor TFIID**.** SRY is a member of the SOX family of transcription factors. It contains conserved high-mobility group (HMG)motif, which binds to DNA and causes reversible bending **(2).** The bending opens the double helix and permits access of transcription factors. HMG proteins are no histone DNA-binding proteins.

There are also sex revertants, when female phenotype is formed because of a mutated SRY. In these cases, the HMG (high mobility group) part, the DNA binding domain of the protein is wrong, and in the absence of DNA binding the differentiation cascade cannot start. Although the SRY alone is sufficient for male sex determination, i.e. to induce the differentiation, however, many other autosomal (e.g. chromosome 17 localized SOX9 [SRY HMG box related genes] a transcription factor encoding gene), and X chromosome localized genes are necessary to switch on SRY and to the whole process of sexual differentiation. For the normal sexual differentiation not only the sufficient quality and quantity of the inductors, but their adequate receptors are necessary, too. Their mutations also cause disturbed sexual development.

Sex Differentiation

Sex differentiation is a series of consecutive developmental processes during early embryogenesis resulting in either the female or the male gender. Initially all anatomical structures involved are undifferentiated. Under the influence of various genes they develop into either sex.

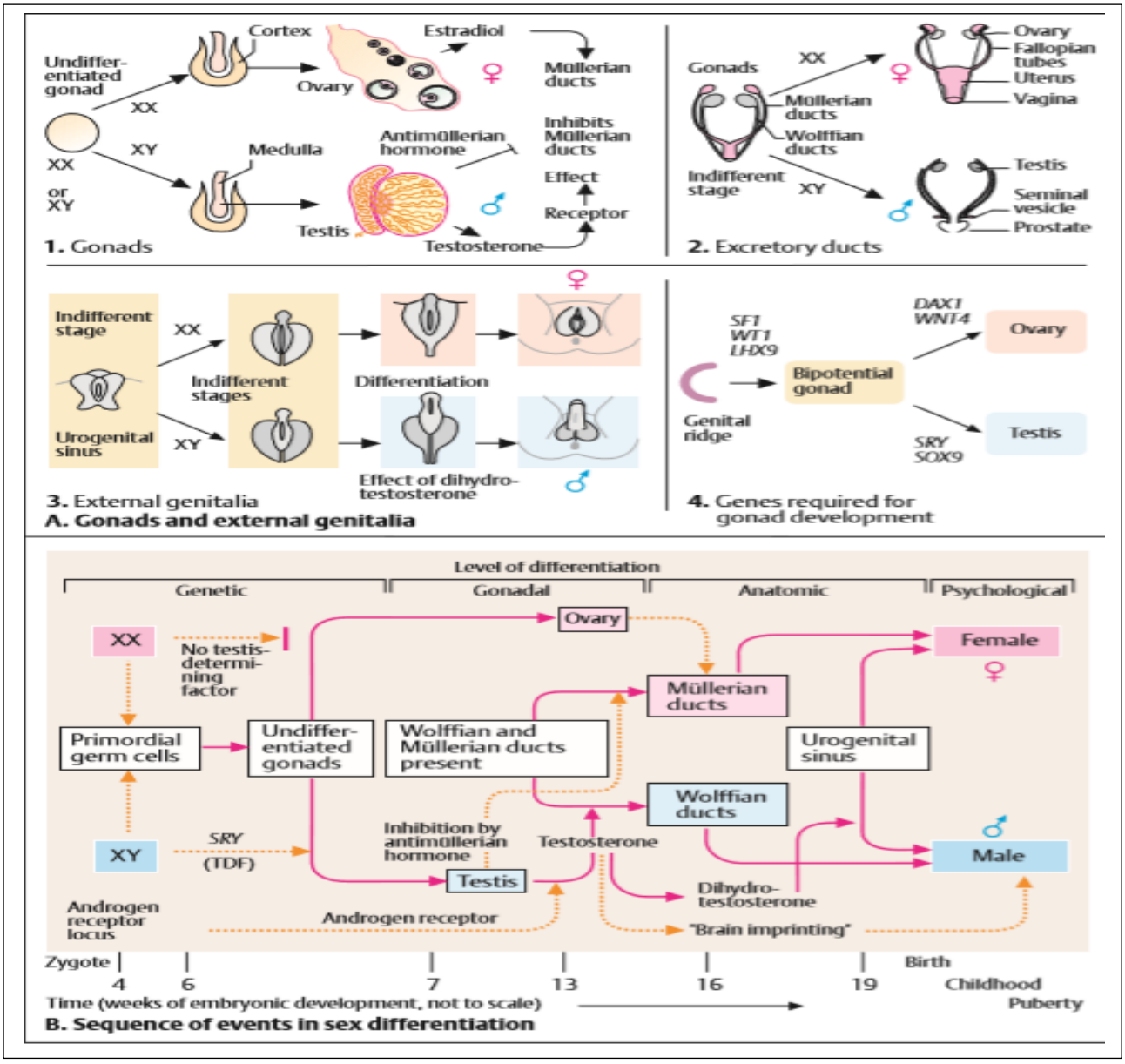
A. Gonads and external genitalia

The gonads **(1),** the efferent (mesonephric and paramesonephric) ducts **(2),** and the external genitalia **(3)** all develop from an indifferent anlage. At about the end of the sixth week of pregnancy in humans, after the primordial germ cells of the embryo have migrated into the initially undifferentiated gonads, an inner portion (medulla) and an outer portion (cortex) of the gonads can be distinguished **(1).**In XY embryos, early embryonic testes develop at about the 10thweek ofpregnancy under the influence of a testis-determining factor(TDF),the SRY gene. If this is not present, ovaries develop. The early embryonic testis produces two hormones, testosterone, with a male differentiating effect, and the Müllerian inhibition factor MIF (anti Müllerian hormone). MIF inhibits the development of female anatomical structures. The excretory ducts differentiate under the influence of the hormones produced by the early gonads **(2).** The Müllerian ducts, precursors of the Fallopian tubes, the uterus, and the upper vagina, develop when a male differentiating influence is absent. The Wolffian ducts, precursors of the male efferent ducts (vas deferens, seminal vesicles, and prostate), develop under the influence of testosterone, a male steroid hormone formed in the fetal testis. If testosterone is absent or ineffective, the Wolffian ducts degenerate. The external genitalia develop after the gonads have differentiated into testes or ovaries. In humans this occurs relatively late, in the 15th to 16th week **(3).** Full development of male external genitalia depends on a derivative of male-inducing testosterone, 5-dihydrotestosterone, a metabolite of testosterone producedbytheenzymaticactionof5α-reductase. The differentiation of the gonadal ridge in to the bipotential gonad, and this into ovary or testis, requires several genes .see figure (Male sex determination)

B-Sequence of events in sex differentiation

Four levels can be schematically defined: **(i)** genetic**,(ii)** gonadal, **(iii) anatomical**, as prenatal stages, and **(iv)** from early childhood on, psychological .A fifth, the legal gender, recorded as “female” or “male” in all legal documents, can be added .Each level is reached in a series of temporally regulated successive steps. First the primordial germ cells differentiate into early embryonic testes under the influence of the testis-determining factors (TDF), mainly the SRY gene (in humans) or the Sry gene in other mammals and other genes. Male differentiation includes suppression of the Müllerian ducts by the Müllerian Inhibitor Factor. In the absence of SRY no testes develop and no subsequent male differentiation stages occur. In the absence of testes, ovaries develop, the Wolffian ducts degenerate, and the Müllerian ducts differentiate in to Fallopian tubes, uterus, and the upper vagina. The male differentiating effect of testosterone depends on the function of an intracellular androgen receptor. Testosterone also has an effect on the central nervous system by influencing the psychosexual orientation

apparent later in life ("brain imprinting"). When testosterone is absent or ineffective due to a receptor defect, gender orientation is female.



The sex differentiation abnormalities can be primarily caused by the following inherited disorders:

a. Mutations of SRY, rarely of RSPO1 or structural abnormalities affecting these gene
b. Disorders of steroid (androgen / estrogen) biosynthesis
c. Mutations of the androgen receptor
d. Defects of the AMH gene

e. X0/XY mosaicism
f. Mutations in genes involved in the differentiation of mesoderm or the nephrogonotome (for example SF1, WT-1).

The X chromosome inactivation

The extra-embryonic membranes (placenta) have imprinted parental origin dependent X chromosome inactivation. The placenta always has the paternal X in inactive form. The inactive X chromosome can be detected in interphase. Adhering to the nuclear membrane, a heavily stained sex chromatin, the so-called Barr body is seen in the epithelial cell nuclei Adrumstick-shaped appendix of the segmented nucleus of neutrophils is a particular manifestation of the inactive X.