Genetic mechanisms in genital system development and disorders

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Determination Of Sex

- Establishment of chromosomal sex (XX veya XY)
- Sex-specific differentiation of gonads (genes)
- Sex-specific differentiation of internal and external sexual organs
- Phenotypic sex

Establishment of chromosomal sex

Over → Female

Testis → Male

The Y Chromosome and the *SRY* Gene

- 46,XX individuals (phenotypic males)
- 46,XY individuals (phenotypic females)
- *Sry* gene is expressed (in mice) → male gonadal ridge
- Transgenic XX mice (*Sry* +) → testes (+) ♂

Y-Linked Genes in Spermatogenesis

- Y chromosome deletions and microdeletions
- ~ 1 in 2000 to 3000 males
- Yq microdeletions are not syndromic
- *AZF* (*azoospermia factors*); three regions → AZFa, AZFb, AZFc
- AZFc;four copies of the *DAZ genes* (*deleted in azoospermia*)
- De novo deletions of AZFc → ~ 1 in 4000 males

Epigenetic and Chromosomal Features of X Chromosome Inactivation in Somatic Cells

Thompson and Thompson Genetics in Medicine

Feature	Active X	Inactive X
Gene expression	Yes; similar to male X	Most genes silenced; ≈15% expressed to some degree
Chromatin state	Euchromatin	Facultative heterochromatin; Barr body
Noncoding RNA	*XIST* gene silenced	*XIST* RNA expressed from Xi only; associates with Barr body
DNA replication timing	Synchronous with autosomes	Late-replicating in S phase
Histone variants	Similar to autosomes and male X	Enriched for macroH2A
Histone modifications	Similar to autosomes and male X	Enriched for heterochromatin marks; deficient in euchromatin

Genetic causes of sexual development disorders

- Chromosomal
- Single gene defects (autosomal, gonosomal)
- Multifactorial causes

Classification of Disorders of sex development (DSDs)

- Sex chromosomal DSDs
- 46,XY DSDs
- 46,XX DSDs

Sex chromosomal DSDs

- Klinefelter syndrome and its variants
- Turner syndrome and its variants
- 45, X / 46, XY (Mixed gonadal dysgenesis)
- 46, XX / 46, XY

Causes of 46,XY DSDs

- Disorders of gonadal (testicular) development
  - Complete or partial gonadal dysgenesis
  - Ovotesticular DSD
  - Testis regression
- Disorders in androgen synthesis or action
  - Disorders of androgen synthesis
  - Disorders of androgen action
- Other
  - Syndromic
  - Environmental influences

46,XY DSDs

- 15% of patients → deletions or mutations in the *SRY gene*
- *DAX1* gene (Xp21.3) duplication
- *SOX9* gene (17q24) mutations (camptomelic dysplasia)
- *NR5A1* gene (9q33) mutations (10% of patients)
- *WNT4* gene (1p35) duplication
- *AR gene* (Xq12) mutations
- *SRD5A2* gene (2p23.1) mutations

46,XY female

- 15% of cases of complete gonadal dysgenesis→ deletions or mutations in the *SRY* gene
- Infertility
- Tall
- Turner syndrome signs (if the deletion is extensive)
- Streak gonad → no spontaneous puberty!
- Secondary sexual characteristics do not develop spontaneously

Androgen Insensitivity Syndrome

- The androgen receptor (*AR*) gene mutations
- Resistance to the action of androgens
- Androgen production by the testes is normal
- The receptor is non-functional
- Complete (CAIS) or partial (PAIS)
- X-linked
- CAIS; female external genitalia, develop breasts at puberty, but the uterus and fallopian tubes are absent.
- The risk of malignancy!

SRD5A2 gene mutations

- 5α-reductase-2 enzyme defect
- Phenotype: Female genital structure (sometimes cliteromegaly at birth), puberty at expected time (variable virilization), normal male breast structure
- Urogenital: Testis, epididymis, vas deferens, seminal vesicle +, vagina with a blind end.
- Autosomal recessive

Causes of 46,XX DSDs

- Disorders of gonadal (ovarian) development
  - Gonadal dysgenesis
  - Ovotesticular DSD
  - Testicular DSD
- Androgen excess
  - Fetal (*different forms of congenital adrenal hyperplasia*)
  - Fetoplacental
  - Maternal
- Other; e.g. syndromic

46,XX DSDs

- *SRY* (+)
- *SOX3* duplication
- *SOX9* duplication
- *CYP21A2* (6p21.3) mutations

46,XX male

- 80% to 90% of cases → *SRY*$^{+}$ XX male
- Wolffian structures (testes) are present and Müllerian structures absent
- Infertility
- Similar to Klinefelter syndrome; hypogonadism, azoospermia, hyalinization of seminiferous tubules, gynecomastia
- Spontaneous puberty is observed

Congenital Adrenal Hyperplasia

- Several enzymatic steps may be defective
- The most common defect is deficiency of 21-hydroxylase
- Deficiency of 21-hydroxylase → blocks the normal biosynthetic pathway of glucocorticoids and mineralocorticoids
- Incidence; 1 in 12,500 births
- Corticotropin increase → adrenal cortex hyperplasia → cortisol precursors and androgen increase
- Androgen levels ↑(both XX and XY embryos)
- 46,XX infants → born with ambiguous genitalia
- 46,XY infants → born with normal external genitalia

Ambiguous genitalia

- Incidence; 1 in 4,500 births
- Genetic sex? → karyotype analysis
- Phenotype?
- Gonad structure?

Diagnostic Process

- Phenotypic findings
- Functional and anatomical evaluations
- Evaluation of endocrine functions
- Genetic investigation
  - Conventional karyotype
  - Molecular genetics
  - Molecular cytogenetics

Further reading

- Thompson&Thompson, Genetics in Medicine, eighth ed. 2016.
- Emery's Elements of Medical Genetics, 15th ed. 2017.