Sexual Differentiation

Venus // Mars
Sequential process of sexual differentiation

1. Establishment of genetic sex
2. Translation of genetic sex into gonadal sex
3. Translation of gonadal sex into phenotypic sex

Male phenotype    Female phenotype

<table>
<thead>
<tr>
<th>XY</th>
<th>XX</th>
</tr>
</thead>
<tbody>
<tr>
<td>XYY</td>
<td>XXX</td>
</tr>
<tr>
<td>XXXXY</td>
<td>XXXX</td>
</tr>
<tr>
<td>XYYY</td>
<td>XXXXX</td>
</tr>
<tr>
<td>XYY</td>
<td>XO (Turner’s)</td>
</tr>
<tr>
<td>(OY)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Presence of Y = MALE
Turner’s Syndrome (XO)

- occurs in 1/2500 live births
- caused by a partial or complete absence of the X chromosomes
- during the newborn period is puffy hands and puffy feet
- Broad chest
- short stature
- webbing of skin on the sides of the neck
- shortened 4th metacarpal
- Adolescent girls with Turner syndrome often have failure of puberty

Klinefelter’s syndrome (XXY)

- one in every 500 to 700 male births.
- testicles that haven’t dropped into the scrotum
- small penis
- Learning and behavioral problems
- As adults, infertility
- Decreased sex drive
- Problems getting or keeping an erection
Normally, chromosomes pair, and cross-over, all along their length.

**Pairing region**

**Non-pairing region**

**sry gene** (sex determining region of Y chromosome)

Undifferentiated state

*Default pathway – largely hormone independent*

**Male determining switches**

Hormone dependent

FEMALE

MALE
Mechanism of Action for steroid Endocrine hormones

1. Lipid-soluble hormone diffuses into cell
2. Activated receptor-hormone complex alters gene expression
3. Newly formed mRNA directs synthesis of specific proteins on ribosomes
4. New proteins alter cell’s activity

CRITICAL PERIODS OF DEVELOPMENT (RED DENOTES HIGHLY SENSITIVE PERIODS)

- periods of dividing, organogenesis
- critical period (in weeks)
- full term

<table>
<thead>
<tr>
<th>Period</th>
<th>C.N.S.</th>
<th>Eye</th>
<th>Heart</th>
<th>Ear</th>
<th>Palate</th>
<th>External Genitalia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>heart</td>
<td>eye</td>
<td>heart</td>
<td>ear</td>
<td>palate</td>
<td>external genitalia</td>
</tr>
<tr>
<td>5-8</td>
<td>heart</td>
<td>eye</td>
<td>heart</td>
<td>ear</td>
<td>palate</td>
<td>external genitalia</td>
</tr>
</tbody>
</table>

embryonic period (in weeks): 1-4
fetal period (in weeks): 5-8
full term: 9-10

physiological defects & major morphological abnormalities

- heart
- eyes
- teeth
- palate
- external genitalia
- ear

physical defects & minor morphological abnormalities

- period of dividing, organogenesis
Development of Genitalia and related structures

Classification of sexual differences

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chromosomal</strong></td>
<td>XY</td>
<td>XX</td>
</tr>
<tr>
<td><strong>Gonadal</strong></td>
<td>Testis</td>
<td>Ovary</td>
</tr>
<tr>
<td><strong>Internal ducts</strong></td>
<td>Wolffian (epididymis, vas deferens)</td>
<td>Mullerian (uterus, Fallopian tube)</td>
</tr>
<tr>
<td><strong>External genitalia</strong></td>
<td>Penis, scrotum</td>
<td>Clitoris, vulva</td>
</tr>
<tr>
<td><strong>Phenotypic</strong></td>
<td>“Male”</td>
<td>“Female”</td>
</tr>
<tr>
<td><strong>Behavioural</strong></td>
<td>“Male”</td>
<td>“Female”</td>
</tr>
</tbody>
</table>
## Development of Genital and related structures

### Urogenital Sinus

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Gland</td>
<td>Urethral/paraurethral gland</td>
</tr>
<tr>
<td>Bulbourethral glands</td>
<td>Greater Vestibular Glands</td>
</tr>
</tbody>
</table>

### Phallus

- **Glans penis**
- **Corpora cavernosa**
- **Corpus spongiosum**
- **Ventral aspect of penis**
- **Scrotum**

**Male**

- **Y chromosome**
  - Primordial gonad
  - **SRY gene**
    - Testis

**Male external genitalia**

**Anti-Mullerian hormone, AMH**

**Testosterone**

**Dihydrotestosterone (DHT)**

**Wolffian duct**

**MALE**
No Y chromosome

Primordial gonad

No SRY gene

Ovary

NO Anti-Mullerian hormone, AMH

No Testosterone

Mullerian duct maintained

Uterus

Fallopian tube

Female external genitalia

NO DHT

Wolffian duct
Y chromosome

Primordial gonad

SRY gene

Testis

Anti-Mullerian hormone, AMH

Testosterone

(Mullerian duct)

-  

Wolffian duct

Dihydrotestosterone (DHT)

Male external genitalia

Sexual differentiation of brain “Gender”
Sexual differentiation of brain

- While chromosomal regulation of sexual differentiation of the brain is well understood, the genes involved and their actions are still under investigation.
- The SRY gene is a major player in the process.
- Gene mutations have revealed that prenatal testosterone masculinizes the brain.
- The complexity of other genes now known to play a role, discovered through the Human Genome Projects, are an area of active research.
- New genes include: DMRT-1, GATA 4, KIMI, LHX9, EMX2, M33, SFI, PODI, Vnn 9, and FGF-9

Hermaphrodite

- An organism having both male and female reproductive organs, such as earthworms

Based upon Greek Mythology

- **Hermaphroditus** was the child of Aphrodite and Hermes. Born a remarkably handsome boy, he was transformed.
- At the age of fifteen he traveled to the cities of Lycia and Caria. In the woods of Caria (modern Turkey) he encountered Salmacis the Naiad in her pool. She was overcome by lust for the boy, and tried to seduce him, but was rejected. When he thought her to be gone, Hermaphroditus undressed and entered the waters of the empty pool. Salmacis sprang out from behind a tree and jumped into the pool. She wrapped herself around the boy, forcibly kissing him and touching his breast. While he struggled, she called out to the gods that they should never part. Her wish was granted, and their bodies blended into one intersex form
What causes ambiguous genitalia?

- **True Intersex (hermaphroditism)** - children who have:
  - both ovarian and testicular tissues.
  - both internal reproductive organs.
  - external genitalia that are partially ambiguous.
  - chromosomes that are either 46, XX, 46, XY, or a mixture (referred to as "mosaic").

- **Gonadal dysgenesis** - children who have:
  - an undeveloped gonad.
  - internal sex organs that are usually female.
  - external genitals that may vary between normal female and normal male, with the majority female.
  - chromosomes that are 45, X, 46, XY, 46, XX, or a mixture (referred to as "mosaic").

What causes ambiguous genitalia?

- **Pure gonadal dysgenesis** - a female child who has a 46, XY karyotype, underdeveloped gonads, internal female reproductive organs and female external genitalia.

- **Pseudo-intersex (hermaphroditism)** - children who have questionable external genitalia, but have only one sex internal reproductive organs. The term male (gonads are testes) or female (gonads are ovaries) pseudohermaphrodite refers to the gonadal sex (the internal reproductive organs).
Causes of Male Pseudohermaphroditism

- **Mutated SRY Gene** - children who have:
  - 46, XY karyotype.
  - normal female external genitalia.

- **Androgen insensitivity syndrome** - children who have:
  - 46, XY karyotype.
  - normal female external genitalia.

- **5-alpha-reductase deficiency** - children who have:
  - 46, XY karyotype.
  - genital ambiguity.
  - Enzyme responsible for converting testosterone into dihydrotestosterone (DHT)

Causes of Female Pseudohermaphroditism

- **Congenital adrenal hyperplasia (CAH):**
  - is caused by a defect in an enzyme (21-hydroxylase) in the steroid hormone synthesis pathway in the adrenal gland.
  - is the most common cause of ambiguous genitalia in newborns.
  - causes females to be masculinized due to a deficiency of the enzyme 21-hydroxylase.
  - is present in about one in 15,000 newborns.
  - is inherited by an autosomal recessive gene.

- **Overproduction of male hormones before birth:**
  - is often due to adrenal gland abnormality (as described in CAH above)
  - high levels of male hormones may also enter the placenta via the mother, such as when the mother receives progesterone to prevent a miscarriage or has a hormone-producing tumor.
To determine the sex, a physician will consider the following:

- a pelvic ultrasound (to check for the presence of female reproductive organs)
- a genitourethrogram to look at the urethra and vagina if present
- a chromosomal analysis (to help determine genetic sex: 46, XX or 46, XY)
- fertility potential of a female intersex
- size and potential for growth of a penis present in a male intersex
- ability of an internal reproductive organ to produce appropriate sex hormones for the gender “assigned” to the child
- risk of future health conditions (i.e., cancer) that may develop in the original reproductive organs later in life
- the actions of male or female hormones on the fetal brain
- your opinion or preference

Y chromosome
Primordial gonad
Deleted/mutant SRY gene
Ovary

i.e. XY FEMALE!
No Y chromosome
No SRY gene
Ovary
Adrenal
Testosterone
NO Anti-Mullerian hormone, AMH
Mullerian duct maintained
Uterus
Fallopian tube
Masculinization of external genitalia
DHT
Wolffian duct
Clitoromegaly

Clitoromegaly and Posterior Labial Fusion
What can go wrong?

1. “Testicular feminization” (androgen insensitivity syndrome)

- Phenotypic female
- Not menstruating
- Blind-ending vagina
What can go wrong?

1. “Testicular feminization” (androgen insensitivity syndrome)

Mode of Inheritance
AIS is inherited in an X-linked recessive manner.

Prevalence
Standard references quote prevalence of 2-5/100,000 for complete AIS (CAIS) and are based on estimates derived from otherwise healthy phenotypic females found to have histologically normal inguinal or abdominal testes. A recent survey done in the Netherlands over a ten-year period based on reported cases of AIS reported a minimal incidence of 1/99,000 [Boehmer et al 2001].

What can go wrong?

1. “Testicular feminization” (androgen insensitivity syndrome)

Natural History

Complete AIS (CAIS; testicular feminization; Tfm). Individuals with CAIS have normal female external genitalia. They typically present either before puberty with inguinal masses that are subsequently identified as testes or at puberty with primary amenorrhea and sparse to absent pubic or axillary hair. Breasts and female adiposity develop normally. Sexual identity and orientation are unaffected. CAIS almost always runs true in families; that is, affected XY relatives usually have normal female external genitalia and seldom have any sign of external genital masculinization, such as clitoromegaly or posterior labial fusion [Boehmer et al 2001].
What can go wrong?

1. “Testicular feminization”  
(androgen insensitivity syndrome)

Natural History

Partial AIS (PAIS) and predominantly female external genitalia presents in a manner similar to CAIS; however, affected individuals have signs of external genital masculinization including clitoromegaly or posterior labial fusion.

Partial AIS with ambiguous genitalia or predominantly male genitalia (PAIS; Reifenstein syndrome). Determining the sex of rearing may be an issue for children with frank genital ambiguity. In families with PAIS, phenotypic disparity may warrant opposite sexes-of-rearing. Individuals with PAIS and predominantly male genitalia are raised as males. Gynecomastia at puberty and impaired spermatogenesis occur in all individuals with PAIS. Pubic hair is usually moderate; facial, body, and axillary hair are often reduced.

Mild AIS (MAIS; undervirilized male syndrome). The external genitalia of these individuals are unambiguously male. They usually present with gynecomastia at puberty. They may have undermasculinization that includes sparse facial and body hair and small penis. Impotence may be a complaint. Spermatogenesis may or may not be impaired. MAIS almost always runs true in families.
Clitoromegaly and Posterior Labial Fusion.
The 46, XX male syndrome is a rare sex chromosomal disorder in man

- It mostly occurs due to unequal crossing over between X and Y chromosomes during meiosis, possibly due to translocated SRY gene.
- Eleven SRY-positive 46,XX males were compared with age-matched controls: 101 47,XXY Klinefelter patients, 78 healthy men, and 157 healthy women.
- The 46,XX males were significantly smaller than Klinefelter patients or healthy men, resembling female controls in height and weight.
- The incidence of maldescended testes was significantly higher than that in Klinefelter patients and controls.
- All XX males were infertile and most were hypogonadal.

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