Non-mosaic chromosome disorders

• Only trisomy 21, trisomy 18, trisomy 13 well defined and compatible with postnatal survival

• Each is associated with
  – Growth retardation
  – Mental retardation
  – Multiple congenital anomalies

• Specific genes on the extra chromosome → direct and indirect modulation of developmental pathways → specific aspects of the abnormal phenotype
The most common and best known
- ~1/800 is born with Down syndrome
- Higher incidence rate among liveborn for mothers ≥ 35
Phenotype

- A distinctive phenotype with variable dysmorphic features
  - **Hypotonia**, the first abnormality noticed in the newborn.
  - **Dysmorphic facial features**
    - Nose → Flat nasal bridge
    - Ears → low-set + folded appearance
    - Eyes → brushfield spots around margin of the iris
    - Short stature
    - Mouth → open
    - Tongue → often furrowed, protruding.
**Phenotype**

- Brachycephaly with a flat occiput
- Short neck with loose skin on the nape
- Characteristic epicanthal folds and upslanting palpebral fissures
- Short and broad hands, often with a single transverse palmar crease and incurved fifth digits, or clinodactyly.
- Highly characteristic dermatoglyphics
- The feet show a wide gap between the first and second toes
The major cause for concern in Down syndrome is mental retardation.

- Delay in development is usually obvious by the end of the first year
- (IQ) is usually 30 to 60 when the child is old enough to be tested.
- Many children with Down syndrome develop into happy, responsive, and even self-reliant persons in spite of these limitations.
Certain malformations are much more common in Down syndrome than in other disorders

- Congenital heart disease in at least 1/3 of all liveborn Down syndrome infants - somewhat higher proportion in abortuses.
- Duodenal atresia and tracheoesophageal fistula.
Prenatal and Postnatal Survival

- 20%-25% of trisomy 21 conceptuses survive to birth
  - ≈¼ die before 1 year (Congenital heart disease)
- 15-fold increase in the risk of leukemia among those who survive the neonatal period
- Premature dementia, associated with neuropathological characteristics of Alzheimer disease
  - nearly all Down syndrome patients
  - age at onset - several decades earlier than the general population
In about **95%** of all patients

Resulting from **meiotic nondisjunction** of the chromosome 21 pair

- About 90% of cases → during **maternal** meiosis, predominantly in **meiosis I**
- About 10% of cases → in **paternal** meiosis, usually in **meiosis II**
In about 4% of Down syndrome patients

Usually 46,XX or XY,rob(14;21)(q10;q10),+21

Also designated der(14;21)

A parent, especially the mother, is a carrier of the translocation
The Chromosomes in Down Syndrome

Robertsonian Translocation

- Has no relation to maternal age
- Carrier mother → relatively high recurrence risk in family
  - Karyotyping of the parents and possibly other relatives is essential before accurate genetic counseling can be provided.
Theoretically, the three types of gametes are produced in equal numbers,

- The theoretical risk of a child should be $\frac{1}{3}$.

- However, unbalanced chromosome complements appear in $\sim 10\%$ to $15\%$ of the progeny of carrier mothers.
In a few % of Down syndrome patients

- Postzygotically in many such cases $\rightarrow$ mosaic

It is important to evaluate if a parent is a carrier (or a mosaic)

- In a carrier parent either:
  - All gametes are $21q21q \rightarrow$ Down syndrome
  - Or all gametes have one chr. 21 $\rightarrow$ monosomy 21 (rarely viable).

- Mosaic carriers $\rightarrow$ risk of Down syndrome recurrence

- The recurrence risk is low

- Prenatal diagnosis should be considered
The Chromosomes in Down Syndrome
Mosaic Down Syndrome

- About 2% of Down syndrome patients are mosaic
  - Usually for cell populations with either a normal or a trisomy 21 karyotype.
  - The phenotype may be milder than that of typical trisomy 21,
  - There is wide variability in phenotypes among mosaic patients
    - possibly reflecting the variable proportion of trisomy 21 cells in the embryo during early development
The Chromosomes in Down Syndrome
Partial Trisomy 21

- Very rarely, a part of the long arm of chromosome 21 is present in triplicate
- Even more rarely patients with no cytogenetically visible chromosome abnormality are identified
  - These can tell what region of chromosome 21 is likely to be responsible for specific components of the Down syndrome phenotype?
In high % of trisomy 21 the abnormal gamete originated during maternal meiosis I
Increased risk of Down syndrome to older mothers
The "older egg" model:
- the older the oocyte, the greater the chance of chromosome nondisjunction.
- 35 to 40 years before the birth of a Down syndrome infant → prophase I of the mother’s primary oocyte → recombination machinery → susceptibility to nondisjunction → Older eggs may be less able to overcome
The risk depends chiefly on the mother's age but also on both parents' karyotypes.

The risk begins to rise sharply, from 1/800 in general, to 1/25 births in the oldest mothers.

The birth rate of younger mothers is much higher.

Thus more than half of the mothers of all Down syndrome babies are younger than 35 years.

The risk of Down syndrome due to translocation or partial trisomy is unrelated to maternal age.

The paternal age appears to have no influence on the risk.
The recurrence risk of trisomy 21 after one affected birth is about 1% overall.

A history of trisomy 21 elsewhere in the family does not appear to significantly increase the risk.

The recurrence risk for Down syndrome due to a translocation is much higher, as described previously.
Trisomy 18, Trisomy 13

- Self study
Autosomal Deletion Syndromes

- Cytogenetically detectable deletions
  - Most seen in only a few patients and are NOT associated with recognized syndromes.
  - Some patients the same or similar deletion, resulting in a clearly recognizable syndrome.
- Overall, cytogenetically visible autosomal deletions occur with an estimated incidence of 1/7000 live births.
Cri du Chat Syndrome

- Terminal or interstitial deletion of part of 5p arm.
  - About 1% of all institutionalized mentally retarded patients.
- The facial appearance, is distinctive
  - microcephaly,
  - hypertelorism,
  - epicanthal folds,
  - low-set ears
  - micrognathia.
- Other features include moderate to severe mental retardation and heart defects.
Cri du Chat Syndrome

- Most cases are sporadic
- 10% to 15% are offspring of translocation carriers.
- Different breakpoints and extent of deleted segment in different patients
- The critical region, missing in all patients is band 5p15.
  - Particularly haploinsufficiency for a gene or genes within band 5p15.2,
- The degree of mental retardation correlates with the size of the deletion
Genomic Disorders: Microdeletion and Duplication Syndromes

- Small but sometimes cytogenetically visible deletions \( \rightarrow \) a form of genetic imbalance (segmental aneusomy)
  - detected by high-resolution karyotyping, FISH, or array CGH.
- Lead to clinically recognizable syndromes
- Many are called contiguous gene syndrome
  - The phenotype is attributable to haploinsufficiency for multiple, contiguous genes within the deleted region.
- For other such disorders, the phenotype is apparently due to deletion of only a single gene,
Genomic Disorders: Microdeletion and Duplication Syndromes

- Fine mapping in a number of these disorders has shown that:
  - The breakpoints localize to low-copy repeated sequences.
  - Aberrant recombination between nearby copies of the repeats causes the deletions.
  - The deletions span several 100s to several 1000s kb.
Model of rearrangements underlying genomic disorders

- **Unequal crossing over** between misaligned sister chromatids or homologous chromosomes containing highly homologous copies of a long repeated DNA.
Unequal recombination between large blocks of flanking repeated sequences that are nearly 99% identical in sequence.

Examples:

Chromosome 17 (p11.2p11.2)

- **Smith-Magenis syndrome**
  - SMS deletion
  - del(17)(p11.2p11.2)
  - Approximately 4 Mb segment deleted de novo in about 70% to 80% of patients
  - Multiple congenital anomalies and mental retardation

- **dup(17)(p11.2p11.2)**
  - A milder, neurobehavioral phenotype
Examples: Chromosome 17 (p11.2-p12)

Duplication or deletion of a 1400-kb region in chromosome 17p11.2-p12, mediated by recombination between a different set of nearly identical repeated sequences:

- **Charcot-Marie-Tooth disease**
- **Hereditary neuropathy with liability to pressure palsies (HNLPP)**

- Different dosages of the gene for peripheral myelin protein
  - two distinct peripheral neuropathies
Mediated by homologous recombination between low-copy repeated sequences

- spanning about 3 Mb
  - Particularly common that is frequently evaluated in clinical cytogenetics laboratories (1/2000 to 4000 live births)
  - Associated with diagnoses of DiGeorge syndrome, velocardiofacial syndrome, or conotruncal anomaly face syndrome.

- All three clinical syndromes are autosomal dominant conditions with variable expressivity
Examples: Microdeletion within chromosome 22q11.2

- Velo-cardio-facial syndrome
  - certain heart defects
  - effects on facial appearance
  - lack of or underdeveloped thymus and parathyroid glands.

- DiGeorge syndrome
  - the same clinical features as Velo-cardio-facial syndrome
  - + immune system deficiencies associated with lack of a thymus gland
Examples

The reciprocal duplication of 22q11.2

- Much rarer → the 22q11.2 duplication syndrome.
  - a series of dysmorphic malformations and birth defects
- Some patients have a (4n) of this segment of chromosome 22 and are said to have cat-eye syndrome
  - ocular coloboma
  - congenital heart defects
  - craniofacial anomalies
  - moderate mental retardation.
DGS = DiGeorge syndrome
VCFS = Velocardiofacial syndrome
Varying dosage of genes in chromosome 22 reflects two major principles in clinical cytogenetics.

1. with few exceptions, altered gene dosage for any extensive chromosomal or genomic region is likely to result in a clinical abnormality
   - the phenotype will, in principle, depend on haploinsufficiency for or overexpression of one or more genes encoded within the region

2. even patients carrying what appears to be the same chromosomal deletion or duplication can present with a range of variable phenotypes.
   - This could be due to non-genetic causes or to differences in the genome sequence among unrelated individuals.
Abnormalities in sex chromosomes → genetic syndromes. E.g.

- **Klinefelter syndrome**: karyotype 47,XXY
- **Turner syndrome** females have only 45,X

The sex chromosomes play a determining role in specifying primary (gonadal) sex

- **Y** chromosome plays a crucial role in normal male development

Genes of **autosomes** + **sex chromosomes** → sex determination and subsequent sexual differentiation
The Y Chromosome

- In male meiosis
  - X and Y chromosomes normally pair by segments
  - They undergo recombination at the pseudoautosomal region of the X and Y chromosomes.

- Y chromosome is relatively gene poor
  - Contains only ~ 50 genes.
  - The functions of a high proportion of these genes are related to gonadal and genital development.
Embryology of the Reproductive System

- 6th week in both sexes → primordial germ cells in gonadal ridges → a pair of primitive bipotential gonads (indifferent).
- The ovarian pathway is default
- SRY gene/testis-determining factor (TDF), acts as a switch, diverting development into the male pathway.
X and Y chromosomes normally exchange in meiosis I within the Xp/Yp pseudoautosomal region.

Rarely, genetic recombination occurs outside the pseudoautosomal region.
Genetic recombination outside the pseudoautosomal region ➔ Two rare abnormalities: XX males and XY females.

- Incidence for each is ~1/20,000 births
The Testis-Determining Gene

- **XX** males:
  - Phenotypic males
  - 46,XX karyotype
  - usually possess some **Y** chromosomal sequences translocated to the short arm of the **X**.

- **XY** females:
  - Phenotypic females
  - 46,XY karyotype
  - A proportion have lost the testis-determining region of the **Y** chromosome
SRY gene (sex-determining region on the Y)

- Near the Y-chr pseudoautosomal boundary
- Strongly implicated in male sex determination
  - present in many 46,XX males
  - deleted or mutated in a proportion of 46,XY female
- Expressed only briefly early in development in cells of the germinal ridge just before differentiation of the testis.
- Encodes a DNA-binding protein that is a transcription factor,
  - The specific genes that it regulates are unknown.
SRY and SOX9 = transcription factor
Fgf9 = fibroblast growth factor 9
+++ = upregulation

Many more factors

Sertoli cell differentiation
Primordial testis formation
SRY gene (sex-determining region on the Y)

- **SRY** presence or absence does not explain all cases of abnormal sex determination.
  - **not present** in about 10% of unambiguous XX males and in most cases of XX true hermaphrodites or XX males with ambiguous genitalia.
- Mutations in the **SRY** gene account for only ~15% of 46,XY females.
- Other genes are implicated in the sex-determination pathway.
Y-Linked Genes in Spermatogenesis

- Yq Interstitial deletions associated with
  - at least 10% of nonobstructive azoospermia
  - ~6% severe oligospermia.

- One or more genes, termed azoospermia factors (AZF), are located on the Y chromosome
  - 3 nonoverlapping regions (AZFa, AZFb, and AZFc) have been defined
  - Contain a series of genes that may be important in spermatogenesis.
Y-Linked Genes in Spermatogenesis

- E.g., DAZ genes (deleted in azoospermia), among several other families, in the AZFc deletion region
  - Encodes RNA-binding proteins
  - Expressed only in the premeiotic germ cells of the testis.

- De novo deletions of AZFc
  - Arise in about 1/4000 males
  - Are mediated by recombination between long repeated sequences.

- AZFa and AZFb deletions, although less common, also involve recombination
Approximately 2% of otherwise healthy males are infertile
- de novo deletions or mutations → severe defects in sperm production
- Karyotyping, Y chromosome molecular testing and genetic counseling before the initiation of assisted reproduction. Are indicated

Not all cases of male infertility are due to chromosomal deletions
- For example, a de novo point mutation has been described in USP9Y (Y-linked gene)
Y-Linked Genes in Spermatogenesis

- USP9Y
  - May function as a ubiquitin-protein or polyubiquitin hydrolase
  - May play an important regulatory role at the level of protein turnover → preventing degradation of proteins
  - Must be required for normal spermatogenesis.
The X Chromosome
Random Chromosome Inactivation

*X inactivation center in Xq13.2*

Different from imprinting (expressed from only one allele but determined by parental origin, not randomly)
Chromosomal Features of X Inactivation

- Random choice of one of two X chromosomes in female cells
  - Inactivation of most X-linked genes on the inactive X
- Inactive X:
  - Heterochromatic (Barr body)
  - Late-replicating in S phase
  - Expresses XIST RNA
  - Associated with macroH2A histone modifications in chromatin
Mechanism of inactivation involves:

- Promoter CpG methylation of many genes on the inactive X chromosome → inactive chromatin state
  - by the enzyme DNA methyltransferase.
- macroH2A histone variant is highly enriched in inactive X chromatin (Histone code)
  - distinguishes the two X's in female cells
- In patients with extra X chromosomes, any X chromosome in excess of one is inactivated
<table>
<thead>
<tr>
<th>Sexual Phenotype</th>
<th>Karyotype</th>
<th>No. of Active X's</th>
<th>No. of Inactive X's</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>46,XY; 47,XXYY</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>47,XXY; 48,XXYY</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>48,XXXY; 49,XXXXY</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>49,XXXXY</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>45,X</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>46,XX</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>47,XXX</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>48,XXXX</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>49,XXXXX</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

*Detection of the histone variant macroH2A in interphase nuclei from females*
Not all genes on the X chromosome are subject to inactivation

- At least 15% of the genes escape inactivation
- Another 10% show variable inactivation in different females
- These genes are not distributed randomly along the X
  - as many as 50% escape inactivation on distal Xp and a few percent on Xq
- Important implications in partial X-aneuploidy
  - Imbalanced Xp genes may have greater clinical significance than imbalanced Xq.
Not all genes on the X chromosome are subject to inactivation
The X inactivation center (XIC) has been mapped to proximal Xq, in band Xq13.
- Contains XIST gene (inactive X (Xi)-specific transcripts)
  - a key master regulatory locus for X inactivation.
  - X inactivation cannot occur in its absence.
  - expressed only from the allele on the inactive X
  - Its product is a noncoding RNA that stays in the nucleus in close association with the inactive X chromosome and the Barr body.
An exception to the normally random inactivation when the karyotype involves a structurally abnormal X

E.g., in almost all patients with unbalanced structural abnormalities of an X (deletions, duplications, and isochromosomes)

- the structurally abnormal chromosome is always the inactive X
- such X chromosome anomalies have less impact on phenotype than similar autosomal abnormalities
Nonrandom X Chromosome Inactivation

46,XX

Abnormal X

Mosaic Random X inactivation

Nonrandom inactivation of abnormal X
Nonrandom X Chromosome Inactivation

- In a **balanced** translocation
  - The **normal X** chromosome is preferentially inactivated,

- In the unbalanced offspring of a balanced carrier
  - **Only** the translocation product carrying the XIC is present, and this chromosome is invariably inactivated
  - **the normal X** is always active.
These nonrandom patterns of inactivation

- Probably reflecting secondary selection against genetically unbalanced cells that could lead to significant clinical abnormalities
- Have the general effect of minimizing, but not always eliminating, the clinical consequences of the particular chromosomal defect.

Determination of an individual's X inactivation pattern by cytogenetic or molecular analysis is indicated in all cases involving X;autosome translocations.
X-Linked Mental Retardation

- High frequency of mutations, microdeletions, or duplications $\Rightarrow$ X-linked mental retardation.

- $>50$ X-linked genes have been identified in families $\Rightarrow$ X-linked syndrome
  - Mental retardation + several abnormal phenotypic features
  - Mutations in many other genes $\Rightarrow$ isolated or nonsyndromic X-linked mental retardation
- Often of the severe to profound kind.
Cytogenetic Abnormalities of the Sex Chromosomes

- Sex chromosomes disorders tend to occur as isolated events
  - predisposing factors = old maternal age and errors of maternal meiosis I.
- Clinical indications for a sex chromosome abnormality that need cytogenetic or molecular studies include
  - delay in onset of puberty
  - primary or secondary amenorrhea
  - Infertility
  - ambiguous genitalia
Cytogenetic Abnormalities of the Sex Chromosomes

- Sex chromosome abnormalities are among the most common of all human genetic disorders
  - overall incidence of about 1/400 to 500 births
- Their associated phenotypes are, in general, less severe than comparable autosomal disorders
  - X chromosome inactivation, as well as the low gene content of the Y, minimizes the clinical consequences of sex chromosome imbalance.
Cytogenetic Abnormalities of the Sex Chromosomes

○ Trisomies (XXY, XXX, and XYY)
  ○ The most common sex chromosome defects in live-born infants and in fetuses
  ○ Rare in spontaneous abortions.

○ Monosomy for the X (Turner syndrome)
  ○ less frequent in live-born infants
  ○ most common chromosome anomaly reported in spontaneous abortions.
Cytogenetic Abnormalities of the Sex Chromosomes

- **Structural** abnormalities of the sex chromosomes are **less common**
  - most frequently observed defect is *i(Xq)*,
    - complete or mosaic form in at least 15% of females with Turner syndrome.

- **Mosaicism** is **more common** for sex chromosome abnormalities than for autosomal abnormalities,
  - in some patients it is associated with relatively **mild** expression of the associated phenotype.
<table>
<thead>
<tr>
<th>Sex</th>
<th>Disorder</th>
<th>Karyotype</th>
<th>Approximate Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Klinefelter syndrome</td>
<td>47,XXY</td>
<td>1/1000 males</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48,XXXY</td>
<td>1/25,000 males</td>
</tr>
<tr>
<td></td>
<td>Others (48,XXYY; 49,XXXY; mosaics)</td>
<td></td>
<td>1/10,000 males</td>
</tr>
<tr>
<td></td>
<td>47,XYY syndrome</td>
<td>47,XYY</td>
<td>1/1000 males</td>
</tr>
<tr>
<td></td>
<td>Other X or Y chromosome abnormalities</td>
<td></td>
<td>1/1500 males</td>
</tr>
<tr>
<td></td>
<td>XX males</td>
<td>46,XX</td>
<td>1/20,000 males</td>
</tr>
<tr>
<td></td>
<td>Overall incidence: 1/400 males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Turner syndrome</td>
<td>45,X</td>
<td>1/5000 females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46,X,i(Xq)</td>
<td>1/50,000 females</td>
</tr>
<tr>
<td></td>
<td>Others (deletions, mosaics)</td>
<td></td>
<td>1/15,000 females</td>
</tr>
<tr>
<td></td>
<td>Trisomy X</td>
<td>47,XXX</td>
<td>1/1000 females</td>
</tr>
<tr>
<td></td>
<td>Other X chromosome abnormalities</td>
<td></td>
<td>1/3000 females</td>
</tr>
<tr>
<td></td>
<td>XY females</td>
<td>46,XY</td>
<td>1/20,000 females</td>
</tr>
<tr>
<td></td>
<td>Androgen insensitivity syndrome</td>
<td>46,XY</td>
<td>1/20,000 females</td>
</tr>
</tbody>
</table>
The 4 well-defined syndromes associated with sex chromosome aneuploidy are important causes of infertility or abnormal development, or both.

As a group, those with sex chromosome aneuploidy show reduced levels of psychological adaptation, educational achievement, occupational performance, economic independence, intelligence (IQ) tests.
# Follow-up observations on patients with sex chromosome aneuploidy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Karyotype</th>
<th>Phenotype</th>
<th>Sexual Development</th>
<th>Intelligence Development</th>
<th>Behavioral Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinefelter syndrome</td>
<td>47,XXY</td>
<td>Tall male</td>
<td>Infertile; hypogonadism</td>
<td>Learning difficulties (some patients)</td>
<td>May have poor psychosocial adjustment</td>
</tr>
<tr>
<td>XYY syndrome</td>
<td>47,XYY</td>
<td>Tall male</td>
<td>Normal</td>
<td>Normal</td>
<td>Frequent</td>
</tr>
<tr>
<td>Trisomy X</td>
<td>47,XXX</td>
<td>Female, usually tall</td>
<td>Usually normal</td>
<td>Learning difficulties (some patients)</td>
<td>Occasional</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>45,X</td>
<td>Short female, distinctive features</td>
<td>Infertile; streak gonads</td>
<td>Slightly reduced</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Klinefelter syndrome
47,XYY Syndrome and XXYY, XXXYY
Trisomy X (47,XXX)
Turner Syndrome (45,X and Variants)

- Self study
Various X-linked and autosomal genes play role in ovarian and testicular development and development of male and female external genitalia. External or internal genitalia abnormalities may result from a cytogenetic abnormality of the sex chromosomes, chromosomal changes elsewhere in the karyotype, single-gene defects, and non-genetic causes.
Karyotyping is an essential part of the investigation of such patients. It can help guide both surgical and psychosocial management. It is important for genetic counseling. It helps determine location and nature of genes involved in sex determination and sex differentiation.
Analysis of some 46,XY females revealed

- SRY gene was not deleted or mutated
- Duplication of DAX1 gene in Xp21.3 → TF

Tightly regulated interaction between DAX1 and SRY.

- An excess of SRY (6th week) → testis formation
- An excess of DAX1 (duplication) → suppress the normal male-determining function of SRY → ovarian development
SOX9 gene is normally expressed early in development in the genital ridge
  - Appears to be required for normal testis formation
  - Has a role in other aspects of development

Mutations in the SOX9 on 17q → Campomelic dysplasia
  - Autosomal dominant disorder with usually lethal skeletal malformations.
  - ~75% of 46,XY patients are sex reversed and are phenotypic females.
Gonadal Dysgenesis
Autosomal genes

- Monosomy of SOX9 gene → testes fail to form → the default ovarian pathway is followed.
- Duplication of SOX9 even in the absence of SRY → can initiate testis formation
  - has been reported to lead to XX sex reversal
The WT1 gene in 11p13
- implicated in Wilms tumor, a childhood kidney neoplasia
- encodes a TF that is involved in interactions between Sertoli and Leydig cells in the developing gonad.
- **Dominant WT1 mutations** → disrupted normal testicular development.

XY patients with **Denys-Drash** syndrome have ambiguous external genitalia

Patients with the more severe **Frasier syndrome** show XY complete gonadal dysgenesis.
### Examples of Genes Involved in Abnormalities of Sex Determination and Differentiation

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cytogenetic Locus</th>
<th>Abnormal Sexual Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRY</td>
<td>Yp11.3</td>
<td>XY female (mutation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>XX male (gene translocated to X)</td>
</tr>
<tr>
<td>SOX9</td>
<td>17q24</td>
<td>XY female (with campomelic dysplasia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>XX male (gene duplication)</td>
</tr>
<tr>
<td>SF1</td>
<td>9q33</td>
<td>XY sex reversal and adrenal insufficiency</td>
</tr>
<tr>
<td>WT1</td>
<td>11p13</td>
<td>XY female (Frasier syndrome) or male pseudohermaphrodite (Denys-Drash syndrome)</td>
</tr>
<tr>
<td>DAX1</td>
<td>Xp21.3</td>
<td>XY female (gene duplication)</td>
</tr>
<tr>
<td>ATRX</td>
<td>Xq13.3</td>
<td>XY sex reversal (variable)</td>
</tr>
<tr>
<td>WNT4</td>
<td>1p35</td>
<td>XY female, cryptorchidism (gene duplication)</td>
</tr>
<tr>
<td>FOXL2</td>
<td>3q28</td>
<td>Premature ovarian failure</td>
</tr>
</tbody>
</table>
# Cytogenetic Abnormalities Associated with Cases of Sex Reversal or Ambiguous Genitalia

<table>
<thead>
<tr>
<th>Cytogenetic Abnormality</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>dup 1p31-p35</td>
<td>XY female (WNT4 gene duplication)</td>
</tr>
<tr>
<td>del 2q31</td>
<td>XY female, mental retardation</td>
</tr>
<tr>
<td>del 9p24.3</td>
<td>XY female, ambiguous genitalia</td>
</tr>
<tr>
<td>del 10q26-qter</td>
<td>XY female</td>
</tr>
<tr>
<td>del 12q24.3</td>
<td>XY ambiguous genitalia, mental retardation</td>
</tr>
<tr>
<td>dup 22q</td>
<td>XY true hermaphroditism</td>
</tr>
<tr>
<td>dup Xp21.3</td>
<td>XY female (DAX1 gene duplication)</td>
</tr>
</tbody>
</table>
A number of genes have been implicated in normal ovarian maintenance:
- E.g., RSPO1, FOXL2

Two structurally normal Xs are necessary for ovarian maintenance:
- 45,X females:
  - normal initiation of ovarian development in utero
  - germ cell loss
  - oocyte degeneration
  - ovarian dysgenesis.

Xq abnormalities frequently lead to premature ovarian failure.
Pseudohermaphroditism

- Pseudohermaphrodites, unlike true hermaphrodites, have gonadal tissue of only one sex that matches their chromosomal constitution.
- In general, ambiguous development of the genital ducts and external genitalia should always be evaluated cytogenetically:
  - To determine the sex chromosome constitution of the patient
  - To identify potential chromosome abnormalities frequently associated with dysgenetic gonads.
Female Pseudohermaphroditism

- Female pseudohermaphrodites
  - 46,XX karyotypes
  - Normal ovarian tissue
  - Ambiguous or male external genitalia.

- Usually due to congenital adrenal hyperplasia (CAH)
  - Inherited adrenal cortex cortisol biosynthesis enzymes defects →
    - Ovarian development is normal
    - Excessive production of androgens → masculinization of the external genitalia
      - Clitoral enlargement and labial fusion to form a scrotum-like structure.
Female Pseudohermaphroditism

- Any one of several enzymatic steps may be defective in CAH,
  - the most common defect is deficiency of 21-hydroxylase, (1/12,500 births)

- Female infants → ambiguous genitalia
- Male infants → normal external genitalia
25% of patients have the simple virilizing type
75% have a salt-losing type due to mineralocorticoid deficiency
- clinically more severe and may lead to neonatal death.

Screening test in newborns
- preventing the serious consequences of the salt-losing defect in early infancy
- prompt diagnosis, and hormone replacement therapy for affected males and females.

Prompt medical, surgical, and psychosocial management of 46,XX CAH patients
- associated with improved fertility rates and normal female gender identity.
Male Pseudohermaphroditism

- **46,XY**, incompletely masculinized or female external genitalia
  - The gonads are exclusively testes
  - The genital ducts or external genitalia are incompletely masculinized

- Result from genetically and clinically heterogeneous disorders:
  - Disorders of testis formation during embryological development, in 46,XY individuals
  - Abnormalities of gonadotropins
  - Inherited disorders of testosterone biosynthesis and metabolism,
  - Abnormalities of androgen target cells.
Several forms of androgen insensitivity result in male pseudohermaphroditism.

E.g. deficiency of 5α-reductase

- inherited condition
- results in feminization of external genitalia in affected males.
- testicular development is normal
- the penis is small
- there is a blind vaginal pouch.
- Gender assignment can be difficult.
Male Pseudohermaphroditism

- X-linked androgen insensitivity syndrome (formerly known as testicular feminization).
  - 46,XY
  - Apparently normal female external genitalia,
  - A blind vagina and no uterus or uterine tubes.
- Testes are present either within the abdomen or in the inguinal canal.
- The testes secrete androgen normally.
- Absence of androgen receptors in the appropriate target cells → end-organ unresponsiveness to androgens.
Male Pseudohermaphroditism

- The receptor protein
  - specified by the normal allele at the X-linked androgen receptor locus
  - forms a complex with testosterone and dihydrotestosterone.
  - stimulates the transcription of target genes required for differentiation in the male direction.

- The molecular defect has been determined in hundreds of cases
  - a complete deletion of the androgen receptor gene
  - point mutations in the androgen-binding
  - Point mutations in DNA-binding domains of the androgen receptor protein.