Medical Genetics

Dr. Ayesh

Islamic University of Gaza
Faculty of Medicine
Spring, 2012-2013
Textbook:

- Nussbaum et al: Thompson & Thompson Genetics in Medicine 7E
## Course Syllabus

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Introduction: Genetics And Genomics In Medicine</td>
</tr>
<tr>
<td>5</td>
<td>Principles of Clinical Cytogenetics</td>
</tr>
<tr>
<td>6</td>
<td>Clinical Cytogenetics: Disorders of the Autosomes and the Sex Chromosomes</td>
</tr>
<tr>
<td></td>
<td>Midterm exam</td>
</tr>
<tr>
<td>7</td>
<td>Patterns of Single-Gene Inheritance</td>
</tr>
<tr>
<td>8</td>
<td>Genetics of Common Disorders with Complex Inheritance</td>
</tr>
<tr>
<td>9</td>
<td>Genetic Variation in Individuals and Populations: Mutation and Polymorphism</td>
</tr>
<tr>
<td>16</td>
<td>Cancer Genetics and Genomics</td>
</tr>
<tr>
<td></td>
<td>Clinical Case Studies Illustrating Genetic Principles</td>
</tr>
<tr>
<td></td>
<td>Final exam</td>
</tr>
</tbody>
</table>

---

3 Medical Genetics (2012-2013)
Evaluation:

- 2 Exams:
  - Midterm: 30 degrees
  - Final: 60 degrees
- Presentation: 10 degrees
Students Presentations:

- Clinical Case studies illustrating genetic principles
- Pages: 231-321

- Will be assigned later during the course
- Topics illustrated by the instructor will be avoided
- A schedule will be determined starting after the midterm exam
Introduction

Chapter 1
Medical genetics involves any application of genetics to medical practice:
- Studies of the inheritance of diseases in families,
- Mapping of disease genes to specific locations on chromosomes,
- Analyses of the molecular mechanisms through which genes cause disease,
- Diagnosis and treatment of genetic disease,
- Gene therapy,
- Genetic counseling (risks, prognoses, and treatments to patients and their families).
Genetics and genomics in medicine

- Genomic medicine seeks to apply a large-scale analysis of the human genome to improve medical care
  - including the control of gene expression
  - human gene variation
  - interactions between genes and the environment
Any disease is the result of the combined action of genes and environment.

- The relative role of the genetic component may be large or small.

Three main types among disorders with genetic factors:

- Chromosome disorders
- Single-gene disorders
- Multifactorial disorders
Chromosome disorders

- Caused by an excess or a deficiency of the genes contained in whole chromosomes or chromosome segments.
  - E.g. an extra copy of chromosome 21 → Down syndrome
- Common as a group
  - Affecting about 7 per 1000 liveborn infants
  - Accounting for about half of all spontaneous first-trimester abortions
Single-gene defects

- Caused by individual mutant genes
  - One or both of a pair of chromosomes may be affected
  - In a few cases, affects the mitochondrial genome
  - E.g. cystic fibrosis, sickle cell anemia, and Marfan syndrome
- Individually, most are rare,
  - 1 in 500 to 1000 individuals but is usually much less
- As a group are responsible for a significant proportion of disease and death
Multifactorial inheritance

- A result of one, two, or more different genes together can predispose to a serious defect often in concert with environmental factors.
- All have a genetic contribution increased risk for recurrence in relatives of affected individuals increased frequency in identical twins yet show inheritance patterns in families that do not fit the characteristic patterns seen in single-gene defects.
- The majority of diseases 5% in the pediatric population more than 60% in the entire population
Some diseases (e.g., cystic fibrosis) are strongly determined by genes, whereas others (e.g., infectious diseases) are strongly determined by environment.
Eukaryotic Chromosomes

- Eukaryotes have multiple linear chromosomes in a number characteristic of the species
  - Most have two versions of each chromosome, and so are diploid \((2N)\).
  - Diploid cells are produced by haploid \((N)\) gametes that fuse to form a zygote.
  - The zygote then undergoes development, forming a new individual.
Eukaryotic Chromosomes

- Chromosome pairs in diploid organisms are homologous chromosomes
  - One member of each pair (homolog) is inherited from each parent.
- Chromosomes that have different genes and do not pair are nonhomologous chromosomes
Eukaryotic Chromosomes

- Animals and some plants have male and female cells with distinct chromosome sets
  - One sex has a matched pair (e.g., human females with XX) and the other has an unmatched pair (human male with XY)
- **Autosomes** are chromosomes other than sex chromosomes.
Please read chapter 2 of the Textbook,
  - From Cell cycle (page:13) to the end of chapter (page 23)
  - Ask me for any inquiry

The first exam will include questions from topics of the chapter
Principles of Clinical Cytogenetics

Chapter 5
Clinical Cytogenetics

- The study of chromosomes
  - Their structure
  - Their inheritance
  - Applied to the practice of medical genetics
- **Chromosome disorders:**
  - Abnormalities as a result of microscopically visible changes in chromosome number or structure
  - A number of clinical conditions (genetic disease)
    - Reproductive wastage
    - Congenital malformation
    - Mental retardation
    - Pathogenesis of cancer
Chromosome abnormalities

- Responsible for hundreds of identifiable syndromes
- Collectively more common than single-gene disorders
  - In nearly 1% of all live births
  - In about 2% of pregnancies in women older than 35 who undergo prenatal diagnosis
  - In fully half of all spontaneous first-trimester abortions
Examination of chromosomes
- General morphology and organization
- Molecular and genomic composition

Used for routine clinical purpose:
- May be performed on WBCs, skin biopsy, fibroblasts, tumor biopsies
- WBC obtained from peripheral blood are cultured

- WBCs are stimulated to divide and then arrested in metaphase with chemicals

- Hypotonic solutions are used to release chromosomes

- Chromosomes are analyzed

- Chromosomes are fixed and stained by one of several techniques
Clinical indications for chromosome analysis

- **Problems of early growth and development:**
  - Failure to thrive, developmental delay, dysmorphic faces, multiple malformations, short stature, ambiguous genitalia and mental retardation.
  - Most frequent in, but not restricted to children with no definite non-chromosomal diagnosis

- **Stillbirth and neonatal death**
  - About 10% of stillbirth and neonatal death

- **Fertility problems:**
  - Women presenting with amenorrhea
  - History of infertility or recurrent miscarriage
Clinical indications for chromosome analysis

- **Family history:**
  - a known or suspected chromosomal abnormality in a first degree relative

- **Neoplasia**
  - all cancers are associated with one or more chromosomal abnormality

- **Pregnancy in a woman of advanced age (＞35 yrs)**
Chromosome identification

- By a number of specific staining procedures
  - **G-banding** (giemsa stain): most common
  - **Q-banding** (quinacrine stain)
  - **R-banding** (special treatment before staining)
A uniform system of chromosome classification is internationally accepted for identification.
The pattern of bands on each chromosome is numbered on each arm.

For clarity only the G-positive bands are numbered.

Regions and subregions are numbered from the centromere outward (1 is closest).
G-banding

- Allow to precisely described:
  - The location of any band
  - DNA sequences and genes within it
  - Its involvement in a chromosomal abnormality

- Example:
  - **BRCA1** (breast cancer susceptibility) gene
    - 17q21 → long arm of chromosome 17 in region 21
  - Human cystic fibrosis gene
    - 7q31.2-q31.3 → spanning both subregions 2 and 3 on the long arm of chromosome 7
Human chromosomes are often classified by position of centromere

- **Metacentric**
  - Central centromere and equal arms length

- **Submetacentric:**
  - Off-center centromeres and clearly different arms length

- **Acrocentric:**
  - Near the ends centromeres
  - Have small distinctive chromatin masses (satellites) attached to short arms by narrow stalks (secondary constrictions).
  - Stalks contain hundreds of copies of genes encoding rRNA as well as a variety of repetitive sequences.

Medical Genetics (2012-2013)
Special cytological procedure

- **C-banding:**
  - Staining the centromere and other regions containing constitutive heterochromatin (sections of 1q, 9q and 16q adjacent to centromere and distal part of Yq)

- **High resolution banding** (prometaphase banding):
  - G- or R-banding of relatively uncondensed chromosomes at early stage of mitosis (prophase or prometaphase)
  - Reveals 550 to 850 bands compared to 450 bands in standard metaphase preparations
DNA probes specific for individual chromosome, chromosomal region, or genes are used to
- Identify particular chromosomal Rearrangements
- Rapidly diagnose the existence of an abnormal chromosome number
FISH probes can be used with both metaphase and interphase

A repetitive α-satellite DNA probe specific for the centromere of chromosome 17

A whole-chromosome “paint” probe specific for the X chromosome

Probe for factor VIII gene on the X chromosome
FISH
Spectral karyotyping

- 2, 3 and even 4-color applications are routinely used to diagnose specific deletions, duplications, rearrangements in metaphase and interphase preparations.
With highly specialized imaging procedure, 24 different colors can be detected (SKY)
Chromosome and Genome Analysis by Use of Microarrays

- Chromosome analysis at a genomic level by a variety of array-based methods that use comparative genomic hybridization (CGH).
- Assess the relative copy number of genomic DNA sequences in a comprehensive genome wide manner
- Complements and confirms conventional karyotyping
- Can potentially provide very sensitive, high resolution assessment of the genome
Types of chromosomal abnormality

- **Germ cell (Constitutional) abnormality:**
  - present in all cells of the body
  - must have been present very early in development,

- **Somatic or acquired abnormality:**
  - present in only certain cells or tissues.
  - mosaic with two different chromosome constitutions, with both cell types deriving from the same zygote.

- **Numerical or Structural**
- May affect autosomes, sex chromosomes or both
Abnormalities of Chromosome Number

- **Heteroploid**: A chromosome complement with any chromosome number other than 46

1. **Euploid**: Exact multiple of haploid chromosome number (n)
   - **diploid** (2n) is normal for human somatic cells
   - **haploid** (n) is normal for germ cells

- **Triploidy and Tetraploidy**
  - Occasionally observed in clinical material
  - Infants can be liveborn
Abnormalities of Chromosome Number

- **Heteroploid**: A chromosome complement with any chromosome number other than 46

1. **Euploid**: Exact multiple of haploid chromosome number (n)
   - **Diploid** (2n) is normal for human somatic cells
   - **Haploid** (n) is normal for germ cells

- **Triploidy and Tetraploidy**
  - Occasionally observed in clinical material
  - Infants can be liveborn
Abnormalities of Chromosome Number

- **Heteroploid**: A chromosome complement with any chromosome number other than 46

2. **Aneuploid**: Any chromosome number other than euploid
   - Most common and clinically significant type of human chromosome disorder
   - Occurs in at least 5% of all clinically recognized pregnancies
   - **Trisomy** ➔ three copies of a particular chromosome.
   - **Monosomy** (less often) ➔ one representative of a particular chromosome.
Observed in 1% to 3% of recognized conceptions
Most result from fertilization by two sperms (dispermy).
A proportion of the cases results from failure of one of the two meiotic divisions (diploid egg or sperm)
Phenotype of triploid karyotype depends on source of extra chromosome set:
- Extra-paternal set: abnormal placenta (partial hydatidiform moles)
- Extra-maternal set: spontaneously aborted earlier in pregnancy
Tetraploidy (4n) 92,XXXX 92,XXYY

- Much rarer than triploidy
- Absence of XXXY or XYYY suggests failure of completion of an early cleavage division of zygote
Most common type of trisomy in liveborns is trisomy 21 (47,XX or XY, +21)

The chromosome constitution seen in 95% of Down syndrome.
Other trisomies observed in liveborns include trisomy18 and trisomy13.

It is notable that 13, 18, and 21 are with lowest number of genes located on them.

- Trisomy for autosomes with greater number of genes is lethal.

Monosomy for entire chromosome is almost always lethal.

- An important exception is monosomy for X chromosome (Turner syndrome).
Most commonly caused by meiotic nondisjunction

Consequences of nondisjunction during meiosis I and II are different.
Causes of Aneuploidy

- Nondisjunction has been associated with aberrations in frequency or placement, or both, of recombination events in meiosis-I.
  - Too few (or even no) recombinations, or too close to centromere or telomere favor non-disjunction.
- Another mechanism involves premature separation of sister chromatids in meiosis I instead of II.
  - The separated chromatids may by chance segregate to oocyte or to polar body (unbalanced gamete)
More complicated forms of multiple aneuploidy

- A **gamete** has an extra representative of **more than one** chromosome
  - Nondisjunction can take place at **two successive meiotic divisions**
  - Nondisjunction can by chance take place in both **male and female** gametes simultaneously
- The resulting zygotes with unusual chromosome numbers are **extremely rare** except for sex chromosomes.
More complicated forms of multiple aneuploidy

- Nondisjunction can occur in mitotic division after zygote formation.
  - at early cleavage ➔ clinically significant mosaicism
  - In some malignant cell lines and some cell cultures ➔ highly abnormal karyotypes
Interphase multicolor FISH is an important diagnostic tool

- Three-color fluorescence in situ hybridization analysis of human sperm

18, X, Y
Interphase multicolor FISH is an important diagnostic tool

- **Prenatal** evaluation of aneuploidy of chromosomes 13, 18, 21, X and Y.

No need to culture cells

- chr 18, *aqua*
- chr X, *green*
- chr Y, *red*
- chr 18, *aqua*
- chr X, *green*
- chr 13, *green*
- chr 21, *red*
Structural Abnormalities

- Structural rearrangements as a result of breakage followed by reconstitution in an abnormal combination
- Less common than aneuploidy
  - Present in about 1 in 375 newborns.
- Chromosome rearrangements can occur spontaneously at a low frequency and may be induced by (clastogens)
  - e.g., ionizing radiation, some viral infections, and many chemicals.
- Like numerical abnormalities, structural rearrangements may be present in all cells or in a mosaic.
Structural Abnormalities

- May be defined as
  - **Balanced** - no net gain or loss of chromosomal material
  - **Unbalanced** – gain or loss of chromosomal material
  - **Stable**: capable of passing through meiotic and mitotic cell divisions unaltered
    - To be stable, a rearranged chromosome must have a functional centromere and two telomeres
  - **Unstable**
Unbalanced Rearrangements

- The phenotype is likely abnormal.
- Any change that disturbs normal balance of functional genes can result in abnormal development.
  - **Deletions** of part of chromosome ➔ **partial monosomy**
  - **Duplications** of part of chromosome ➔ **partial trisomy**
- Detection:
  - Karyotyping ➔ Large deletions or duplications (a few million bp)
  - FISH or microarray CGH ➔ Smaller deletions or duplications
Detection of Unbalanced Rearrangements

Two-color FISH of a case with DiGeorge syndrome (deletion of 22q11.2).
A. Duplication of chromosome 12p apparently normal routine karyotype and symptoms of Pallister-Killian syndrome

B. Terminal deletion of chromosome 1p by array CGH in a patient with mental retardation

C. 5 Mb de novo deletion of chromosome 7q22 in a patient with a complex abnormal phenotype; originally undetected by routine karyotyping.
Small **submicroscopic** deletions, duplications and translocations have been detected
- changes of a **telomere** region in patients with **idiopathic mental retardation**

**FISH** array CGH of telomeric and subtelomeric regions may be indicated in unexplained mental retardation

*chromosome 3p (red)*  
*chromosome 11q (green).*
Deletions

- Loss of a chromosome segment resulting in chromosome imbalance
  - **Terminal deletion**: involves loss of the chromosome tip
  - **Interstitial deletion**: when two breaks occur and the material between them is lost
Deletions

- Caused by:
  - Chromosome break with a subsequent loss of acentric segment
  - Unequal crossing over between misaligned homologous chromosomes in some cases
  - Abnormal segregation of a balanced translocation or inversion
Clinical consequences depend upon:
- Size of deleted segment
- Number and function of lost genes

Deletion $\rightarrow$ one normal and one deleted homologues
- Monosomic for the lost genetic information

Haploinsufficiency is a clinically reflected consequence
- Inability of a single copy of the genetic material to carry out functions normally carried out by two copies
Duplications

- Can originate by
  - Unequal crossing over
  - Abnormal segregation from meiosis in a carrier of a translocation or inversion.
Duplications

- Appears to be less harmful than deletion
- It may disrupt gene → Often some phenotypic abnormalities
  - duplication of all or a portion of 12p → Pallister-Killian syndrome:
    - characteristic craniofacial features, mental retardation, and other birth defects
  - likely related to trisomy or tetrasomy for specific genes in duplicated region
Marker Chromosomes

- Very small, unidentified, frequently mosaic
- Usually called **Supernumerary chromosomes** or **Extra Structurally Abnormal Chromosomes**
  - Usually in addition to the normal chromosome complement
- Tiny marker chromosomes consist of little more than centromeric heterochromatin
  - Hard to specifically identify by banding
  - Precise identification requires FISH with various paint probes (SKY)
- Larger markers contain some material from one or both arms
  - The present genes are imbalanced
Marker Chromosomes

- Prenatal frequency of de novo supernumerary chromosomes is estimated to be 1 in 2500.
- Risk of fetal abnormality depends on marker origin (from very low to 100%).
  - Relatively high risk, Specific syndromes are associated with bisatellited chromosome 15 derived markers and with centric portion of X.
- A subclass of marker chromosomes represents small fragments of chromosome arms.
  - Somehow acquired centromere activity Neocentromeres.
Ring Chromosomes

- Marker chromosomes that lack telomeric sequences
  - Formed by breaks in the two ends followed by reuniting of the broken ends
- Rare, but have been detected for every chromosome
Ring Chromosomes

- Mitotically stable if they contain a centromere
  - Problems during disjunction at mitosis anaphase
    - Larger and smaller rings may result due to breakage followed by fusion at time of disjunction
Isochromosomes

- One arm is missing & the other is duplicated in a mirror-image
- A person with 46 chromosomes carrying an isochromosome
  - **Partial monosomy**: single copy of one arm
  - and **partial trisomy**: 3 copies of the second arm
- At least two mechanisms:
  1. Misdivision through centromere in meiosis II
  2. more commonly, exchange involving one arm of a chromosome and its homolog (or sister chromatids) → **isodicentric** chromosomes
Figure 3 Possible modes of division of the centromere as depicted by de la Chapelle et al.

(a) Transverse misdivision giving rise to an isochromosome for the long arm and another for the short arm;

(b) breakage distally in the centromeric region producing a dicentric isochromosome and an acentric fragment;

(c) breakage in the proximal part of one arm producing a dicentric chromosome with two chromatid fragments a short distance apart.
The most common isochromosome is \textit{i}(Xq) in some individuals with \textbf{Turner syndrome}.

- \textit{i}(18p) and \textit{i}(12p) have also been seen.

- Isochromosomes are frequently seen in karyotypes of solid and hematological malignancies.
**Dicentric Chromosomes**

- A rare type, in which two chromosome segments each with a centromere, fuse end to end, with loss of acentric fragments.
  - from different chromosomes or from two chromatids of a single chromosome
Dicentric Chromosomes

- May be mitotically stable, if
  - one centromere is inactivated
  - or the 2 centromeres coordinate their movement at anaphase (formerly, pseudodicentric)

- Most commonly, involve
  - the sex chromosome
  - or the acrocentric chromosomes
**Balanced Rearrangements**

- All chromosomal material is present but packaged differently.
  - Do not usually have a phenotypic effect.
- Carriers are likely to produce a high frequency of unbalanced gametes.
  - Increased risk of having abnormal offspring.
  - Risk can range from 1 to 20% depending on rearrangement.
- Chromosome breaks may possibly disrupt genes.
Inversions

- 2 breaks on a single chromosome → inversion of the segment between the breaks → reconstitution at the original site

- **Paracentric inversions** do not involve the centromere
  - Don’t change the arms proportions → identifiable by FISH

- **Pericentric inversions** involve the centromere
  - May change the proportions of the chromosome arms and the banding pattern → more easily identifiable
Inversions

- An inversion does not usually cause an abnormal phenotype in carriers.
- A carrier is at risk to produce unbalanced offspring.
  - A loop is formed when the chromosomes pair at meiosis.
  - When recombination occurs, it can cause unbalanced gametes.
○ In paracentric: the risk that a carrier will have a liveborn child with an abnormal karyotype is very low

○ The unbalanced recombinant chromosomes are acentric or dicentric
  ○ may not lead to viable offspring
Pericentric: can lead to unbalanced gametes with duplicates and deficiencies.

Each pericentric inversion is associated with a particular risk of unbalanced karyotype (about 5% to 10%).

Large pericentric inversions more likely to lead to viable recombinant offspring
  - because unbalanced segments in recombinants are smaller.
Translocations

- Involve exchange of genetic material between two, usually nonhomologous, chromosomes
- Two main types:
  - Reciprocal
  - Robertsonian.
Reciprocal Translocations

- Exchange of broken-off fragments.
  - Usually only 2 chromosomes involved
  - Rare complex translocations involve 3 or more
- Relatively common
  - Found in about 1 in 600 newborns.
  - Commonly found in couples with 2 or more spontaneous abortions and in infertile males
- Usually harmless, although more common in institutionalized mentally retarded individuals.
- Associated with a high risk of unbalanced gametes and abnormal progeny.
Reciprocal Translocations

- When chromosomes of a carrier of balanced reciprocal translocation pair at meiosis → quadrivalent figure is formed (cross shaped)
At anaphase, chromosomes segregate in one of three ways:

- **Alternate**: the usual type of meiotic segregation → both types of gamete balanced.
- **adjacent-1**: homologous centromeres go to separate daughter cells
- **adjacent-2**: homologous centromeres pass to same daughter cell (rare)
Additionally, balanced translocation chromosomes can also segregate 3:1

- leading to gametes with 22 or 24 chromosomes
- Observed in 5-20% of sperm from balanced translocation carrier, depending on specific translocation
Robertsonian Translocations

- Fusion of the long arms of 2 acrocentric chromosomes at the centromeres with loss of both short arms
  - Results in 45 chromosomes only
  - The loss of rRNA genes from the short arm is not deleterious
- Can be monocentric or pseudodicentric depending on breakpoint location
Robertsonian Translocations

- (13q14q) and (14q21q) are relatively common.
  - 13q14q is found in about 1 in 1300
- Rare homozygotes for 13q14q exist
  - Phenotypically normal with 44 chromosomes (no normal 13’s or 14’s).
- Phenotypically normal carriers have risk of unbalanced gamete and thus offspring.
  - Risk varies according to particular translocation and sex of carrier
  - Carrier females have a higher risk of transmitting translocation to an affected child
Insertions

- A non-reciprocal type of translocation.
  - A segment removed from one chromosome and inserted into another in usual or inverted orientation.
- Rare, as they require 3 breaks
- Abnormal segregation in an insertion carrier can produce offspring with deletion or duplication as well as normal and balanced carriers.
- Average risk of producing an abnormal child is up to 50%, and prenatal diagnosis is indicated.
**Mosaicism**

- Two or more different chromosome complements present in an individual.
- May be either **numerical** or less commonly **structural**.
- Typically detected by conventional karyotyping but can be suspected in interphase FISH or array CGH.
- A common cause is **nondisjunction** in an early postzygotic mitotic division.
  - E.g., \(47^{+21}\) zygote lose the additional 21 and become \(46/47^{+21}\) mosaic.
- Effects on development vary with:
  - timing of nondisjunction event
  - nature of chromosomal abnormality
  - proportions of different chromosome complements present
  - tissues affected.
# Incidence of Chromosome Anomalies

<table>
<thead>
<tr>
<th>Type</th>
<th>Approximate Proportion of Abnormal Karyotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneuploidy</td>
<td></td>
</tr>
<tr>
<td>Autosomal trisomy</td>
<td>0.52</td>
</tr>
<tr>
<td>Autosomal monosomy</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>45,X</td>
<td>0.19</td>
</tr>
<tr>
<td>Triploidy</td>
<td>0.16</td>
</tr>
<tr>
<td>Tetraploidy</td>
<td>0.06</td>
</tr>
<tr>
<td>Other</td>
<td>0.07</td>
</tr>
</tbody>
</table>
# Live Births and Spontaneous Abortions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pregnancies</th>
<th>Spontaneous Abortions (%)</th>
<th>Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>10,000</td>
<td>1500 (15)</td>
<td>8500</td>
</tr>
<tr>
<td><strong>Normal chromosomes</strong></td>
<td>9,200</td>
<td>750 (8)</td>
<td>8450</td>
</tr>
<tr>
<td><strong>Abnormal chromosomes</strong></td>
<td>800</td>
<td>750 (94)</td>
<td>50</td>
</tr>
<tr>
<td>Triploid or tetraploid</td>
<td>170</td>
<td>170 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Turner syndrome (45,X)</td>
<td>140</td>
<td>139 (99)</td>
<td>1</td>
</tr>
<tr>
<td>Trisomy 16</td>
<td>112</td>
<td>112 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>20</td>
<td>19 (95)</td>
<td>1</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>45</td>
<td>35 (78)</td>
<td>10</td>
</tr>
<tr>
<td>Trisomy, other</td>
<td>209</td>
<td>208 (99.5)</td>
<td>1</td>
</tr>
<tr>
<td>Klinefelter syndrome (47,XXY), (47,XXX), (47,XYY)</td>
<td>19</td>
<td>4 (21)</td>
<td>15</td>
</tr>
<tr>
<td>Unbalanced rearrangements</td>
<td>27</td>
<td>23 (85)</td>
<td>4</td>
</tr>
<tr>
<td>Balanced rearrangements</td>
<td>19</td>
<td>3 (16)</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>39</td>
<td>37 (95)</td>
<td>2</td>
</tr>
</tbody>
</table>
Nomenclature of chr. abnormality

- A standard set of abbreviations
- Indicates the nature of abnormality and the technology used for analyses if performed
<table>
<thead>
<tr>
<th>Abbrev.</th>
<th>Meaning</th>
<th>Example</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>cen</td>
<td>Centromere</td>
<td>46,XX</td>
<td>Normal female karyotype</td>
</tr>
<tr>
<td>del</td>
<td>Deletion</td>
<td>46,XY</td>
<td>Normal male karyotype</td>
</tr>
<tr>
<td>der</td>
<td>Derivative chr.</td>
<td>der(1)</td>
<td>Female with cri du chat s.</td>
</tr>
<tr>
<td>dic</td>
<td>Dicentric chr.</td>
<td>dic(X;Y)</td>
<td>Translocation chr. Derived from chr.1 with cen of chr.1</td>
</tr>
<tr>
<td>dup</td>
<td>Duplication</td>
<td></td>
<td>Translocation chr. with centromeres of X and Y</td>
</tr>
<tr>
<td>fra</td>
<td>Fragile site</td>
<td>46,Y,fra(X)(q27.3)</td>
<td>Male with fragile X chr.</td>
</tr>
<tr>
<td>i</td>
<td>Isochromosome</td>
<td>46,X,i(X)(q10)</td>
<td>Female with isochr. Long arm X</td>
</tr>
<tr>
<td>ins</td>
<td>Insertion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inv</td>
<td>inversion</td>
<td>inv(3)(p25q21)</td>
<td>Pericentric inv of chr.3</td>
</tr>
<tr>
<td>Abbrev.</td>
<td>Meaning</td>
<td>Example</td>
<td>Condition</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>mar</td>
<td>Marker chr.</td>
<td>$47,XX,+mar$</td>
<td>Female with an extra unidentified chr.</td>
</tr>
<tr>
<td>mat</td>
<td>Maternal origin</td>
<td>$47,XY,+der(1)mat$</td>
<td>Male with an extra der(1) chr. Inherited from mother</td>
</tr>
<tr>
<td>p</td>
<td>Short arm</td>
<td></td>
<td>Female with ring X chr.</td>
</tr>
<tr>
<td>pat</td>
<td>Paternal origin</td>
<td></td>
<td>Reunion at centromeric region of chr’s 13,21</td>
</tr>
<tr>
<td>q</td>
<td>Long arm</td>
<td>$46,X,r(X)$</td>
<td>Female with balanced translocation, breaks in 2q22 and 8p21</td>
</tr>
<tr>
<td>r</td>
<td>Ring</td>
<td>$Rob(13;21)(q10;q10)$</td>
<td>Deletion distal to q21 (i.e., q21 is present)</td>
</tr>
<tr>
<td>rob</td>
<td>Robertsonian translocation</td>
<td>$46,XX,t(2;8)(q22;p21)$</td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>Translocation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ter</td>
<td>Terminal or telomere</td>
<td>$46,X,del(X)(pter \rightarrow q21)$</td>
<td></td>
</tr>
<tr>
<td>Abbrev.</td>
<td>Meaning</td>
<td>Example</td>
<td>Condition</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>+</td>
<td>Gain of</td>
<td>47,XX,+21</td>
<td>Female with trisomy 21</td>
</tr>
<tr>
<td>-</td>
<td>Loss of</td>
<td>45,XX,-22</td>
<td>Female with monosomy 22</td>
</tr>
<tr>
<td>:</td>
<td>break</td>
<td>5qter → 5p15:</td>
<td>With deletion breakpoint in 5p15</td>
</tr>
<tr>
<td>::</td>
<td>Break &amp; join</td>
<td>2pter→2q22::8p21→8pter</td>
<td>Der(2) portion of t(2;8)</td>
</tr>
<tr>
<td>/</td>
<td>mosaicism</td>
<td>46,XX/47,XX,+8</td>
<td></td>
</tr>
<tr>
<td>ish</td>
<td>In situ hybridization</td>
<td>ish 22q11.2(D22S75 X2)</td>
<td>Probe for locus D22S75 in 22q11.2 (for DiGeorge S.). X2 = 2 signals (normal)</td>
</tr>
<tr>
<td>arr</td>
<td>Array Comparative genomic hybrid.</td>
<td>arr cgh 1-22(#BAC)x2, X(#BAC)x2, Y(#BAC)x0 arr cgh 1-22(#BAC)x2, X(#BAC)x1, Y(#BAC)x1 arr cgh 22q11.2(BAC name)x1 or arr cgh 22q11.2(D22S75)x1</td>
<td>Female normal G-bandning, deletion identified by FISH</td>
</tr>
<tr>
<td>cgh</td>
<td></td>
<td></td>
<td>Normal female array CGH pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal male array CGH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Loss of DiGeorge S. critical region</td>
</tr>
</tbody>
</table>
Monosomies are more deleterious than trisomies
- Complete monosomies are generally not viable except for monosomy X
- Complete trisomies are viable for chr. 13, 18, 21, X, Y.

Phenotype in partial aneusomies depends on:
- Size of unbalanced segment
- Imbalance monosomic or trisomic
- Region of genome and genes involved

In a mosaic karyotype, “all bets are off”

Rings give a phenotype specific to genome region involved, but are commonly mosaic.

Inversions
- Pericentric: risk of birth defects in offspring increases with size of inversion
- Paracentric: very low risk of abnormal phenotype
Most of the autosomal abnormalities can be diagnosed at birth.

Most sex chromosome abnormalities, with the exception of Turner syndrome, are not recognized clinically until puberty.

Balanced rearrangements are rarely identified clinically unless a carrier gives birth to a child with an unbalanced chromosome complement.

Unbalanced rearrangements are likely to come to clinical attention because of abnormal appearance and delayed physical and mental development.
Expression of the disease phenotype of some disorders, depends on parental origin of mutant allele or abnormal chromosome.

- Differences are the result of genomic imprinting.

Imprinting is a normal process caused by alterations in chromatin:
- occur in the germline of one parent, but not the other
- occur at characteristic locations in the genome.
- includes the covalent modification of DNA, such as
  - methylation of cytosine to form 5-methylcytosine
  - modification or substitution in chromatin of specific histone types

*Medical Genetics (2012-2013)*
Parent-of-Origin Effects: Genomic Imprinting

- Affects the expression of a gene but not its primary DNA sequence
  - It is a reversible form of gene inactivation but not a mutation, (an epigenetic effect).

- Takes place during gametogenesis, before fertilization

- After conception, the imprint controls gene expression within the imprinted region in some or all of the somatic tissues of the embryo.

- The imprinted state persists postnatally into adulthood
Control over this conversion process appears to be governed by DNA elements called **imprinting centers**
- located within imprinted regions throughout the genome
- their precise mechanism of action is not known
- they initiate the **epigenetic** change in chromatin, which then spreads outward along the chromosome over the imprinted region.
It is likely that as many as a hundred genes in the human genome show imprinting effects. Some regions contain a single imprinted gene; others contain clusters, spanning in some cases well over 1 Mb along a chromosome, of multiple imprinted genes.
Gray: maternally expressed
Blue: paternally expressed
Parental origin of genetic material (15q11-q13) can have a profound effect on the clinical expression of a defect.

<table>
<thead>
<tr>
<th></th>
<th>Prader-Willi Syndrome</th>
<th>Angelman Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>15q11-q13 deletion</td>
<td>~70% (paternal)</td>
<td>~70% (maternal)</td>
</tr>
</tbody>
</table>
Prader-Willi is a relatively common dysmorphic syndrome:
- Obesity
- Excessive and indiscriminate eating habits
- Small hands short stature
- Hypogonadism
- Mental retardation.
Deletion of 15q11-q13 on one homologue
Angelman Syndrome

- Angelman syndrome is rare unusual:
  - facial appearance
  - short stature, severe mental retardation
  - Spasticity
  - Seizures
Uniparental Disomy

- The presence of two chromosomes, or portions thereof, inherited from only one parent.
  - **Isodisomy**: the identical chromosome is present in duplicate
  - **Heterodisomy**: if both homologues from one parent are present

- About 30% of Prader-Willi syndrome
  - do not have cytogenetically detectable deletions
  - They have two normal chromosome 15's, both inherited from the mother

- About 3%-5% of Angelman syndrome also have uniparental disomy,
  - Contain two intact chromosome 15's of paternal origin
A few patients with Prader-Willi syndrome and Angelman syndrome appear to have a defect in the imprinting center itself.

- The switch from female to male imprinting during spermatogenesis or from male to female imprinting during oogenesis fails to occur.
- Fertilization by a sperm carrying an abnormally persistent female imprint → Prader-Willi syndrome.
- Fertilization of an egg that bears an inappropriately persistent male imprint → Angelman syndrome.
E6-AP ubiquitin-protein ligase gene

- Mutations in the maternal copy of **E6-AP ubiquitin-protein ligase gene** → Angelman syndrome
  - The gene is located in **15q11-q13** and is maternally expressed.
  - It is likely that the large maternal **15q11-q13 deletions** and the **uniparental disomy** of paternal 15 seen in Angelman syndrome cause the disorder
    - they result in loss of the maternal copy of this critically important, imprinted gene.
  - Mutations in a single imprinted gene have not yet been found in Prader-Willi syndrome.
<table>
<thead>
<tr>
<th></th>
<th>Prader-Willi Syndrome</th>
<th>Angelman Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>15q11-q13 deletion</td>
<td>~70% (paternal)</td>
<td>~70% (maternal)</td>
</tr>
<tr>
<td>Uniparental disomy</td>
<td>~30% (maternal)</td>
<td>~5% (paternal)</td>
</tr>
<tr>
<td>Single-gene mutation</td>
<td>None detected</td>
<td>E6-AP ubiquitin-protein ligase (10% of total but seen only in familial cases)</td>
</tr>
<tr>
<td>Imprinting center mutation</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Unidentified</td>
<td>&lt;1%</td>
<td>10%-15%</td>
</tr>
</tbody>
</table>
Other Disorders due to Uniparental Disomy of Imprinted Regions

- E.g. Beckwith-Wiedemann syndrome: Uniparental disomy for a portion of chromosome 11 (11p15)
  - an excess of paternal or a loss of maternal contribution of genes, or both, including the insulin-like growth factor 2 gene.
  - Affected children are very large at birth
  - have an enlarged tongue
  - frequent protrusion of the umbilicus
  - Life-threatening severe hypoglycemia and development of malignant neoplasms of kidney, adrenal, and liver.
Cytogenetics of Hydatidiform Moles and Ovarian Teratomas

- An abnormal pregnancy
  - the placenta is converted into a mass of tissue called a **hydatid** cyst.
  - abnormal growth of the chorionic villi (called a **mole**)
    - the epithelium proliferates
    - the stroma undergoes cystic cavitation
  - A mole may be
    - **complete**, with no fetus or normal placenta present
    - **partial**, with remnants of placenta and perhaps a small atrophic fetus
Most complete moles are diploid, 46,XX.
- The chromosomes are all paternal in origin,
- with rare exceptions, all genetic loci are homozygous.
- a single 23,X sperm fertilizes an ovum that lacks a nucleus, and its chromosomes then double.

Absence of any maternal contribution →
- hyperplasia of the trophoblast
- grossly disorganized or absent fetal tissue

About half of all cases of choriocarcinoma (a malignant neoplasm of fetal, not maternal, tissue) develop from hydatidiform moles.
Ovarian teratomas (benign tumors) arise from 46,XX cells containing only maternal chromosomes.

In conclusion:
- Normal fetal development requires both maternal and paternal genetic contributions.
- Paternal genome is especially important for extraembryonic development.
- Maternal genome is critical for fetal development.
Partial moles are triploid; in about two thirds of cases
- the extra chromosome set is of paternal origin.

Fetal development is severely abnormal in both maternal or paternal origin, but the defects are different.
- An extra paternal set results in abundant trophoblast but poor embryonic development
- An extra maternal set results in severe retardation of embryonic growth with a small, fibrotic placenta.