Chromosomes, Karyotyping, and Abnormalities (Outline)

- Components and parts of a metaphase chromosome.
- Definitions of karyotype, autosomal and sex chromosomes.
- The field of cytogenetics and its uses for prenatal and postnatal diagnoses
- Sources of cells used for karyotyping
- Compare and contrast the three prenatal diagnosis techniques.
- Mechanisms leading to chromosomal abnormalities of numbers.
- Terms used: polyploidy, aneuploidy: trisomy and monosomy, and mosaicism and their causing mechanisms.

- Abnormalities of chromosomal structure: deletions, duplications, translocations, and inversions.
- Basic shorthand used to describe normal and abnormal karyotypes.
- Common autosomal and sex chromosome aneuploidies.
Portrait of a Chromosome

Figure 13.1
Portrait of a Chromosome

A chromosome consists primarily of DNA and protein

Chromosomes differ in size, shape, banding pattern, and the genes they carry

Essential parts shared by all chromosomes are:
- Telomeres
- Origins of replication sites
- Centromere
Portrait of a Chromosome

**Heterochromatin** is darkly staining
- Consists mostly of repetitive DNA

**Euchromatin** is lighter-staining
- Contains most protein-encoding genes

**Telomeres** are chromosome tips composed of many repeats of TTAGGG
- Shorten with each cell division
Centromeres

- The largest constriction of the chromosome-attachment sites of spindle fibers
- DNA present at the centromere are specific repeated sequence

Subtelomeres

- The region of chromosomes near telomere
- Made of repeats sequences similar to the telomere sequence
Subtelomeres
Viewing Chromosomes

1882
Drawing by German biologist Walther Flemming

Now
Micrograph of actual stained human chromosomes
Cytogenetics

Variations in chromosomal structure occur as cells go through the cell cycle from chromatin to condensed chromosomes

Cytogenetics is a technical field of genetics for visualization of chromosomal variations of metaphase chromosomes

Excess genetic material has milder effects on health than a deficit

Most large-scale chromosomal abnormalities disrupt or halt prenatal development
Karyotype

A visual display of metaphase chromosomes arranged by size and structure

The chromosome pairs 1 through 22 are autosomes. These are sex chromosomes.
Karyotype

A visual display of chromosomes arranged by size and structure

- Autosomes are numbered 1-22 by size
- Sex chromosomes are X and Y

Humans have 24 different chromosome types
Sex chromosomes
Courtesy National Human Genome Research Institute
Centromere Positions

Position of centromeres varies between chromosomes

- At tip – **Telocentric**
- Close to end – **Acrocentric**
- Off-center – **Submetacentric**
- At midpoint – **Metacentric**
Karyotype are used to ....

1) Confirm clinical diagnoses of medical geneticists

2) Reveal effects of some environmental toxins

3) Clarify evolutionary relationships between species
Current sources used for Karyotyping

Tissue is obtained from person

- Fetal tissue: Amniocentesis
  Chorionic villi sampling
  Fetal cell sorting
  *Chromosome microarray analysis*

- Adult tissue: White blood cells
  Skin-like cells from cheek swab

Karyotypes and currently prepared using a combination of dyes and **DNA probes** to stain chromosomes
Prenatal Diagnosis: Amniocentesis

Detects about 1,000 of the more than 5,000 known chromosomal and biochemical problems

Ultrasound is used to follow needle’s movement

Performed between 15-16 weeks (the 2nd trimester) of pregnancy

Figure 13.5a

Fetal cells suspended in the fluid around the fetus are sampled.

Figure 13.6

© GE Medical Systems
Prenatal Diagnosis: Chorionic Villi Sampling

- Performed during 10-12th week (1st trimester) of pregnancy
- Provides earlier results than amniocentesis
- Limited detection of some metabolic problems
- Has greater risk of spontaneous abortion

Figure 13.5b

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Prenatal Diagnosis: Fetal Cell Sorting

Fetal cells are distinguished from maternal cells by a fluorescence-activated cell sorter - Identifies cell-surface markers

A new technique detects fetal mRNA in the bloodstream of the mother

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Figure 13.5c

Fetal cells in maternal bloodstream are sampled.
FISH

Fluorescence in situ hybridization

DNA probes labeled with fluorescing dye bind complementary DNA

Fluorescent dots correspond to three copies of chromosome 21
Chromosome Abnormalities

A karyotype may be abnormal in two ways:

1) In chromosome number
2) In chromosome structure

Abnormal chromosomes account for at least 50% of spontaneous abortions

Due to improved technology, more people are being diagnosed with chromosomal abnormalities
## Table 13.7  Causes of Chromosomal Aberrations

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Numerical Abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Polyplody</td>
<td>Error in cell division (meiosis or mitosis) in which not all chromatid pairs separate in anaphase</td>
</tr>
<tr>
<td></td>
<td>Multiple fertilization</td>
</tr>
<tr>
<td>Aneuploidy</td>
<td>Nondisjunction (in meiosis or mitosis) leading to lost or extra chromosomes</td>
</tr>
<tr>
<td><strong>Structural Abnormalities</strong></td>
<td></td>
</tr>
<tr>
<td>Deletions and duplications</td>
<td>Translocation</td>
</tr>
<tr>
<td></td>
<td>Crossover between a chromosome that has a pericentric inversion and its noninverted homolog</td>
</tr>
<tr>
<td>Translocation</td>
<td>Exchange between nonhomologous chromosomes</td>
</tr>
<tr>
<td>Inversion</td>
<td>Breakage and reunion of fragment in same chromosome, but with wrong orientation</td>
</tr>
<tr>
<td>Dicentric and acentric</td>
<td>Crossover between a chromosome with a paracentric inversion and its noninverted homolog</td>
</tr>
<tr>
<td>Ring chromosome</td>
<td>A chromosome loses telomeres and the ends fuse, forming a circle</td>
</tr>
</tbody>
</table>
# Table 13.2  
**Chromosome Abnormalities**

<table>
<thead>
<tr>
<th>Type of Abnormality</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyploidy</td>
<td>Extra chromosome sets</td>
</tr>
<tr>
<td>Aneuploidy</td>
<td>An extra or missing chromosome</td>
</tr>
<tr>
<td>Monosomy</td>
<td>One chromosome absent</td>
</tr>
<tr>
<td>Trisomy</td>
<td>One chromosome extra</td>
</tr>
<tr>
<td>Deletion</td>
<td>Part of a chromosome missing</td>
</tr>
<tr>
<td>Duplication</td>
<td>Part of a chromosome present twice</td>
</tr>
<tr>
<td>Translocation</td>
<td>Two chromosomes join long arms or exchange parts</td>
</tr>
<tr>
<td>Inversion</td>
<td>Segment of chromosome reversed</td>
</tr>
<tr>
<td>Isochromosome</td>
<td>A chromosome with identical arms</td>
</tr>
<tr>
<td>Ring chromosome</td>
<td>A chromosome that forms a ring due to deletions in telomeres, which cause ends to adhere</td>
</tr>
</tbody>
</table>
Polyploidy

- Cell with extra set of chromosomes is **polyploid**

- **Triploid** (3N) cells have three sets of chromosomes
  - Produced in one of two main ways:
    - Fertilization of one egg by two sperm
    - Fusion of haploid and diploid gametes

- Triploids account for 17% of all spontaneous abortions and 3% of stillbirths and newborn deaths
Triploidy

Figure 13.11
Aneuploidy

- A normal chromosomal number is **euploid**
- Cells with extra or missing chromosomes are **aneuploid**, i.e. gain or loss of a single chromosome
- Most autosomal aneuploids are spontaneously aborted
- Those that are born are more likely to have an extra chromosome (**trisomy**) rather than a missing one (**monosomy**)
Nondisjunction

- The failure of chromosomes to separate normally during meiosis

- Produces gamete with an extra chromosome and another with one missing chromosome

- Nondisjunction during Meiosis I results in copies of both homologs in one gamete

- Nondisjunction during Meiosis II results in both sister chromatids in one gamete
Chromosome Abnormalities involving chromosome numbers are caused by non-disjunction during anaphase
- Homologous chromosomes during Meiosis I
- Sister chromatids during Meiosis II
Nondisjunction at Meiosis I
Nondisjunction at Meiosis II
Aneuploidy can also arise during mitosis after the zygote formation, producing groups of somatic cells with the extra or missing chromosomes

- autosomal aneuploidy
- sex chromosome aneuploidy

An individual with two chromosomally-distinct cell populations is called a mosaic

A mitotic non-disjunction event that occurs early in development can have serious effects on the health of the individual
Autosomal Trisomies

Most autosomal aneuploids cease developing as embryos or fetuses

Most frequently seen trisomies in newborns are those of chromosomes 21, 18, and 13
- Carry fewer genes than other autosomes

<table>
<thead>
<tr>
<th>Type of Trisomy</th>
<th>Incidence at Birth</th>
<th>Percent of Conceptions That Survive 1 Year After Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (Patau)</td>
<td>1/12,500–1/21,700</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>18 (Edward)</td>
<td>1/6,000–1/10,000</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>21 (Down)</td>
<td>1/800–1/826</td>
<td>85%</td>
</tr>
<tr>
<td>Situation</td>
<td>Oocyte</td>
<td>Sperm</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>Normal</td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Female nondisjunction</td>
<td>XX</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>XX</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Male nondisjunction (meiosis I)</td>
<td>X</td>
<td>XY</td>
</tr>
<tr>
<td>Male nondisjunction (meiosis II)</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>YY</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Male and female nondisjunction</td>
<td>XX</td>
<td>YY</td>
</tr>
</tbody>
</table>
Sex Chromosome Aneuploidy

Missing one or having one or more additional copies the sex chromosomes

- Turner syndrome
- Triplo-X
- Klinefelter Syndrome
- XXYY Syndrome
- XYY Syndrome
Chromosome Structural Abnormalities

http://glencoe.mcgraw-hill.com/sites/0011042009/student_view0/chapter13/changes_in_chromosome_structure.html

Figure 13.15

- **a.** Normal sequence of genes
- **b.** Deleted sequence of genes
- **c.** Duplicated sequence of genes
- **d.** Inverted sequence of genes
Chromosomal Structural Abnormalities

- **Deletions**
  - missing a segment from a chromosome

- **Duplications**
  - Presence of an extra segment on a chromosome
    (*Deletions and duplications often not inherited, arise de novo*)

- **Translocations**
  - two non-homologous chromosomes exchange segments
    - Balanced and unbalanced translocations

- **Inversions**
  - A chromosomal segment is flipped in orientation
# Chromosomal Shorthand

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>What It Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,XY</td>
<td>Normal male</td>
</tr>
<tr>
<td>46,XX</td>
<td>Normal female</td>
</tr>
<tr>
<td>45,X</td>
<td>Turner syndrome (female)</td>
</tr>
<tr>
<td>47,XXY</td>
<td>Klinefelter syndrome (male)</td>
</tr>
<tr>
<td>47,XYY</td>
<td>Jacobs syndrome (male)</td>
</tr>
<tr>
<td>46,XY, del (7q)</td>
<td>A male missing part of the long arm of chromosome 7</td>
</tr>
<tr>
<td>47,XX, + 21</td>
<td>A female with trisomy 21 Down syndrome</td>
</tr>
<tr>
<td>46,XY, t(7;9)(p21.1; q34.1)</td>
<td>A male with a translocation between the short arm of chromosome 7 at band 21.1 and the long arm of chromosome 9 at band 34.1</td>
</tr>
<tr>
<td>48, XXYY</td>
<td>A male with an extra X and an extra Y</td>
</tr>
</tbody>
</table>
Figure 13.19

a.

Homologous chromosomes

Reciprocal translocation

Homologous chromosomes

b.

Courtesy Lawrence Livermore National Laboratory