Chapter 6

Cytogenetics: Karyotypes and Chromosome Aberrations
Chromosome Number

- The number and appearance of chromosomes is an important characteristic in genetic analyses.

**Table 6.1** Chromosome Number in Selected Organisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>Diploid Number (2n)</th>
<th>Haploid Number (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human (Homo sapiens)</td>
<td>46</td>
<td>23</td>
</tr>
<tr>
<td>Chimpanzee (Pan troglodytes)</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>Gorilla (Gorilla gorilla)</td>
<td>48</td>
<td>24</td>
</tr>
<tr>
<td>Dog (Canis familiaris)</td>
<td>78</td>
<td>39</td>
</tr>
<tr>
<td>Housefly (Musca domestica)</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Corn (Zea mays)</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Mouse (Mus musculus)</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Fruit fly (Drosophila melanogaster)</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Nematode (Caenorhabditis elegans)</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

*Table 6-1, p. 121*
Chromosome Shape

- As chromosomes condense and become visible during cell division, certain structural features can be recognized.

- **Centromere**
  - A region of a chromosome to which microtubule fibers attach during cell division.
  - The location of a centromere gives a chromosome its characteristic shape.
• Replicated chromosomes at metaphase consist of sister chromatids joined by a single centromere

Fig. 6-1, p. 122
Centromere Location

- **Metacentric**
  - A chromosome that has a centrally placed centromere

- **Submetacentric**
  - A chromosome whose centromere is placed closer to one end than the other

- **Acrocentric**
  - A chromosome whose centromere is placed very close to, but not at, one end
Chromosomes are identified by size, centromere location, and banding pattern.
A Set of Human Chromosomes

- Human chromosomes are analyzed by construction of karyotypes

- **Karyotype**
  - A complete set of chromosomes from a cell that has been photographed during cell division and arranged in a standard sequence
A Human Karyotype

Fig. 6-3, p. 122
System of Naming Chromosome Bands

- Allows any region to be identified by a descriptive address (chromosome number, arm, region, and band)
Add a few drops of blood. Add phytohemagglutinin to stimulate mitosis.

Draw 10 to 20 ml of blood. Incubate at 37°C for 2 to 3 days.

Transfer to tube containing fixative. Transfer cells to tube. Add Colcemid to culture for 1 to 2 hours to stop mitosis in metaphase.

Centrifuge to concentrate cells. Add low-salt solution to eliminate red blood cells and swell lymphocytes.

Drop cells onto microscope slide. Examine with microscope.

Digitized chromosome images processed to make karyotype.

Stain slide with Giemsa.
Metaphase Chromosomes (a) Arranged Into a Karyotype (b)

Fig. 6-7, p. 125
6.3 Constructing and Analyzing Karyotypes

- Different stains and dyes produce banding patterns specific to each chromosome

- Karyotypes reveal variations in chromosomal structure and number
  - 1959: Discovery that Down syndrome is caused by an extra copy of chromosome 21

- Chromosome banding and other techniques can identify small changes in chromosomal structure
Information Obtained from a Karyotype

- Number of chromosomes
- Sex chromosome content
- Presence or absence of individual chromosomes
- Nature and extent of large structural abnormalities
Four Common Chromosome Staining Procedures

<table>
<thead>
<tr>
<th>Banding technique</th>
<th>Appearance of chromosomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G-banding</strong> — Treat metaphase spreads with trypsin, an enzyme that digests part of chromosomal protein. Stain with Giemsa stain. Observe banding pattern with light microscope.</td>
<td><img src="image" alt="Darkly stained G bands." /></td>
</tr>
<tr>
<td><strong>Q-banding</strong> — Treat metaphase spreads with the chemical quinacrine mustard. Observe fluorescent banding pattern with a special ultraviolet light microscope.</td>
<td><img src="image" alt="Bright fluorescent bands upon exposure to ultraviolet light; same as darkly stained G bands." /></td>
</tr>
<tr>
<td><strong>R-banding</strong> — Heat metaphase spreads at high temperatures to achieve partial denaturation of DNA. Stain with Giemsa stain. Observe with light microscope.</td>
<td><img src="image" alt="Darkly stained R bands correspond to light bands in G-banded chromosomes. Pattern is the reverse of G-banding." /></td>
</tr>
<tr>
<td><strong>C-banding</strong> — Chemically treat metaphase spreads to extract DNA from the arms but not the centromeric regions of chromosomes. Stain with Giemsa stain and observe with light microscope.</td>
<td><img src="image" alt="Darkly stained C band centromeric region of the chromosome corresponds to region of constitutive heterochromatin." /></td>
</tr>
</tbody>
</table>

This is extra info that will not be on the exam.**
Chromosome Painting

- New techniques using fluorescent dyes generate unique patterns for each chromosome

Fig. 6-9a, p. 127
## Table 6.2  Chromosomal Aberrations

<table>
<thead>
<tr>
<th>Chromosomal Abnormality</th>
<th>Syndrome Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,del(5p)</td>
<td>Cri du chat syndrome</td>
</tr>
<tr>
<td></td>
<td>Small head; round face; low-set ears; weak, catlike cry; low, broad nasal ridge; mental retardation</td>
</tr>
<tr>
<td>46,t(9;22) (q34a11)</td>
<td>CML (chronic myelogenous leukemia)</td>
</tr>
<tr>
<td></td>
<td>Enlargement of liver and spleen; anemia; excessive, unrestrained growth of white cells (granulocytes) in the bone marrow</td>
</tr>
<tr>
<td>46,dup(17p12)</td>
<td>Charcot-Marie-Tooth syndrome</td>
</tr>
<tr>
<td></td>
<td>Loss of sensation and muscle atrophy in the feet and legs that spreads to the arms and hands as the disease progresses</td>
</tr>
</tbody>
</table>
Obtaining Cells for Chromosome Studies

- Any nucleus can be used to make karyotype
  - Lymphocytes, skin cells, cells from biopsies, tumor cells

- Sampling cells before birth
  - Amniocentesis
  - Chorionic villus sampling (CVS)
Amniocentesis

- A method of sampling the fluid surrounding the developing fetus by inserting a hollow needle and withdrawing suspended fetal cells and fluid
  - Used in diagnosing fetal genetic and developmental disorders
  - Usually performed in the sixteenth week of pregnancy
Removal of about 20 ml of amniotic fluid containing suspended cells that were sloughed off from the fetus.

A few biochemical analyses with some of the amniotic fluid.

Quick determination of fetal sex and analysis of purified DNA.

Biochemical analysis for the presence of alleles that cause many different metabolic disorders.

Growth for several days in culture medium.

Karyotype analysis.
Chorionic Villus Sampling (CVS)

- A method of sampling fetal chorionic cells by inserting a catheter through the vagina or abdominal wall into the uterus
  - Used in diagnosing biochemical and cytogenetic defects in the embryo
  - Usually performed in the eighth or ninth week of pregnancy
Chorionic villi
Developing placenta
Ultrasound to monitor procedure
Developing fetus
Uterus
Chorion
Amniotic cavity
Rectum
Bladder
Catheter

Fig. 6-11a, p. 128
Methods are being investigated to isolate fetal cells that can pass into the mother’s bloodstream (placental cells, white blood cells, immature red blood cells) for genetic testing.
6.4 Variations in Chromosome Number

- Changes in chromosome number or chromosome structure can cause genetic disorders

- Two major types of chromosomal changes can be detected in a karyotype
  - A change in chromosomal number
  - A change in chromosomal arrangement
Changes in Chromosome Number

- **Polyploidy**
  - Duplication of an entire set of chromosomes
  - $3N = \text{triploid}$
  - $4N = \text{tetraploid}$

- **Aneuploidy**
  - Refers to a single chromosome
  - Trisomy = one extra chromosome (three copies)
  - Monosomy = missing one chromosome of a pair
A Triploid Infant
Causes of Aneuploidy

- **Nondisjunction**
  - The failure of homologous chromosomes to separate properly during meiosis
  - About half of all conceptions are aneuploid.
Nondisjunction

Extra chromosome (n + 1)

Missing chromosome (n - 1)

Normal (n)

Meiosis I

Meiosis II

Gametes

(b)
Nondisjunction

Meiosis I

Meiosis II

Gametes

Extra chromosome \((n + 1)\)

Extra chromosome \((n + 1)\)

Missing chromosome \((n - 1)\)

Missing chromosome \((n - 1)\)
Effects of Monosomy and Trisomy

- Autosomal monosomy is a lethal condition
  - Eliminated early in development (spontaneous abortion)

- Some autosomal trisomies are relatively common
  - Most result in spontaneous abortion
  - Three types can result in live births (13, 18, 21)
Trisomies in Spontaneous Abortions

Survey of 4,088 spontaneous abortions

Percentage of trisomies

Chromosome number
Trisomy 13: Patau Syndrome (47,+13)

- A lethal condition
- 1 in 10,000 births
Trisomy 18: Edwards Syndrome (47,+18)

- A lethal condition
- 1 in 11,000 births
- 80% are females

Fig. 6-17b, p. 133
Trisomy 21: Down Syndrome (47, +21)

- Trisomy 21 is the only autosomal trisomy that allows survival into adulthood
6.5 What Are the Risks for Autosomal Trisomy?

- The causes of autosomal trisomy are unknown.

- Factors that have been proposed include:
  - Genetic predisposition
  - Exposure to radiation
  - Viral infection
  - Abnormal hormone levels

- Maternal age is the leading risk factor for trisomy
  - 94% of nondisjunctions occur in the mother
  - Meiosis is not completed until ovulation
  - Embryo-uterine interactions that normally abort abnormal embryos become less effective
Maternal Age and Trisomy 21

- Risk for Down syndrome: The graph on the left shows the increasing risk of Trisomy 21 with maternal age, peaking significantly after age 44.

- Percentage of clinically recognized pregnancies: The graph on the right illustrates the increasing percentage of trisomic conceptions with maternal age, also showing a significant increase after age 44.
6.6 Aneuploidy of the Sex Chromosomes

- More common than autosomal aneuploidy
- Can involve both X and Y chromosomes

- A balance is needed for normal development
  - At least one copy of the X chromosome is required for development
  - Increasing numbers of X or Y chromosomes causes progressively greater disturbances in phenotype and behavior
Turner Syndrome (45,X)

- Monosomy of the X chromosome that results in female sterility. Other phenotypic characteristics but otherwise normal.

Fig. 6-20, p. 136
Klinefelter Syndrome (47, XXY)

- Individuals (males) have some fertility problems but few additional symptoms

Fig. 6-22, p. 137
XYY Syndrome (47,XYY)

- Affected individuals are usually taller than normal and some, but not all, have personality disorders
Changes in the structure of chromosomes

- Deletion—loss of DNA
- Duplication—extra DNA
- Translocation—DNA that changes location
- Inversion—order of DNA changes
Structural Changes in Chromosomes

(a) Deletion

(b) Duplication

(c) Reciprocal translocation

(d) Inversion

Fig. 6-24, p. 139
6.9 Other Forms of Chromosome Changes

- **Uniparental disomy**
  - A condition in which both copies of a chromosome are inherited from a single parent

- **Copy number variation**
  - A situation in which a particular gene or chromosomal region is present in multiple copies

- **Fragile sites**
  - Appear as gaps or breaks in chromosome-specific locations
Human Diseases Associated with Copy Number Variants

**Table 6.5** Human Diseases Associated with Copy Number Variants

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td><em>APP</em></td>
<td>Buildup of amyloid protein precursor, death of certain brain cells</td>
</tr>
<tr>
<td>Autosomal dominant adrenolukodystrophy</td>
<td><em>LMNB1</em></td>
<td>Abnormalities of white matter in brain, breakdown of myelin sheath surrounding nerves</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth Type 1A</td>
<td><em>PMP22</em></td>
<td>Numbness in arms, legs, breakdown of myelin sheath surrounding nerves</td>
</tr>
<tr>
<td>Drug metabolism</td>
<td><em>CYP2D6</em></td>
<td>Increase or decrease in rate of drug metabolism, causing side effects and variation in effectiveness of drug</td>
</tr>
<tr>
<td>HIV infection/AIDS</td>
<td><em>CCL3L1</em></td>
<td>Increased susceptibility to HIV infection and AIDS</td>
</tr>
<tr>
<td>Lupus</td>
<td><em>FCGR3B</em></td>
<td>Increased susceptibility to kidney failure</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td><em>SNCA</em></td>
<td>Death of certain brain cells, tremors, increasing rigidity of body</td>
</tr>
<tr>
<td>Smith-Magenis syndrome</td>
<td><em>RAI1</em></td>
<td>Mental retardation</td>
</tr>
<tr>
<td>X-linked hypopituitarism</td>
<td><em>SOX3</em></td>
<td>Short stature, mild mental retardation; affects mostly males</td>
</tr>
</tbody>
</table>
Fragile Sites

- Appear as gaps or breaks in chromosomes

- One fragile site on the X chromosome is associated with a common form of mental retardation in males known as **Fragile X Syndrome**

- Females can also have this, but the phenotypes are much more mild
Fragile Sites on the X Chromosome

(a) Diagram showing Fragile Sites on the X Chromosome labeled FRAX A, B, C, D, and E.

(b) Image of a chromosome with visible fragile sites.