Chapter 24

Genetics and Genetic Diseases
Human Karyotype

1  2  3  4  5  6  7  8
9 10 11 12 13 14 15 16
17 18 19 20 21 22 XX (or XY)

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Sex Determination

Sex chromosome combinations possible in new individual

Female germ cell

Male germ cell

eggs

sperm

XX

XY

XX

XY

sex chromosome combinations possible in new individual
Objectives

• Explain how genes can cause disease
• Distinguish between dominant and recessive genetic traits
• Describe sex-linked inheritance
• List some important inherited diseases
• Describe how nondisjunction can result in trisomy or monosomy and list some disorders that result from it
Objectives

• List some tools used in genetic counseling and how they are used to help clients

• Describe how genetic disorders can be treated
Genetics and Human Disease

• Genetics, begun by Mendel more than 140 years ago, is the scientific study of inheritance
• Inherited traits can produce disease
Punnett Square of a Monohybrid Cross

Female gametes

Dominant phenotype can arise 3 ways, recessive only 1

Male gametes

- A
- a

- AA
- Aa
- Aa
- aa
Chromosomes and Genes

• Mechanisms of gene function
  – Gene—indepeendent genetic units (DNA segments) that carry the genetic code
  – Genes dictate the production of enzymes and other molecules, which in turn dictate the structure and function of a cell
  – Genes are active in the chromatin (strand) form and inactive when DNA is in the chromosome (compact) form
Chromosomes and Genes

• The human genome
  – Genome—entire set of human chromosomes (46 in nucleus of each cell, 1 mitochondrial chromosome)
    • Rough draft of entire human genome (nearly all nucleotides in sequence) published in 2001
    • Contains about 30,000 genes and large amounts of non-coding DNA, termed pseudogenes
Chromosomes and Genes

- Genomics—analysis of the sequence contained in the genome
- Proteomics—analysis of the entire group of proteins encoded by the genome; a group called the human proteome
Chromosomes and Genes

– Genomic information can be expressed in various ways
  
  • Ideogram—cartoon of a chromosome showing the centromere as a constriction and the short segment (p-arm) and long segment (q-arm)
  
  • Genes are often represented as their actual sequence of nucleotide bases expressed by the letters a, c, g, and t
Chromosomes and Genes

• Distribution of chromosomes to offspring
  – Meiotic cell division produces gametes with 23 chromosomes each
  – At conception, two gametes join and produce a zygote with 46 chromosomes— the complete human genome
Meiosis

Diploid parent cell
(Chromatin beginning to condense)

(Chromosomes aligned along center of cell)

Meiosis I

Meiosis II

Haploid gametes

Other possible alignments

Meiosis I

Meiosis I

Meiosis I

Meiosis II

Meiosis II

Meiosis II
Chromosomes and Genes

– Twenty-two pairs of chromosomes are called *autosomes*; each member of a pair resembles its partner

– The remaining pair of chromosomes (pair 23) are called *sex chromosomes*
Chromosomes and Genes

– Genetic variation among offspring is increased by:
  - Independent assortment of chromosomes during gamete formation
  - Crossing-over of genes or linked groups of genes between chromosome partners during meiosis
Gene Expression

• Hereditary traits
  – Dominant genes have effects that appear in the offspring (dominant forms of a gene are often represented by uppercase letters)
  • A genetic carrier is a person who carries a recessive gene but does not show its effects because of masking effect of a dominant gene
  • Codominant genes are two or more genes that are all dominant and when they appear together produce a combined effect in offspring
Gene Expression

- Recessive genes have effects that do not appear in the offspring when they are masked by a dominant gene (recessive forms of a gene are represented by lowercase letters)
Gene Expression

• Sex-linked traits
  – The large X chromosome (“female chromosome”) contains genes for female sexual characteristics and many other traits
  – The small Y chromosome (“male chromosome”) contains only genes for male sexual characteristics
  – Normal males have XY as pair 23; normal females have XX as pair 23
  – Nonsexual traits carried on sex chromosomes are sex-linked traits; most are X-linked traits
The diagram illustrates the genetic inheritance process for gender and color blindness. It shows the following:

- **Mother (carrier)**: XX
- **Ovum**: X or X (carries an X or abnormal X chromosome)
- **Father**: XY
- **Sperm**: X (for XX) or Y (for XY)

The diagram indicates how genes are passed from parents to offspring, with arrows showing the flow of genetic material. The color blindness and gender are determined by the presence of X and Y chromosomes.

Legend:
- **X**: Normal X chromosome
- **XX**: Female carrier
- **XY**: Color-blind male
- **YY**: Normal male
- **X**: Abnormal X chromosome
- **XY**: Normal female

The diagram also uses colored arrows to indicate the inheritance pattern, with orange and purple arrows representing different pathways.
Gene Expression

• Genetic mutations
  – Can result in abnormalities in the genetic code that cause disease
  – Most believed to be caused by mutagens
Genetic Diseases

• Mechanisms of genetic disease
  – Single-gene diseases result from individual mutant genes (or groups of genes) that are passed from generation to generation
  – Chromosomal diseases result from chromosome breakage or from nondisjunction (failure of a chromosome pair to separate during gamete formation)
Genetic Diseases

– Chromosomal diseases
  • Trisomy—a chromosome triplet (instead of the usual pair)
  • Monosomy—a single chromosome (instead of a pair)
Down Syndrome
An extra Chromosome 21
A karyotype, performing a genetic analysis
Down Syndrome

- Trisomy of chromosome 21
- Mental impairment and a variety of additional defects
- Can be detected before birth
- Risk of Down syndrome increases dramatically in mothers over age 35
A female with Down Syndrome
Genes

• Units of information about heritable traits
• In eukaryotes, distributed among chromosomes
• Each has a particular locus
  – Location on a chromosome
Karyotype Preparation - Stopping the Cycle

- Cultured cells are arrested at metaphase by adding colchicine
- This is when cells are most condensed and easiest to identify
Karyotype Preparation

- Arrested cells are broken open
- Metaphase chromosomes are fixed and stained
- Chromosomes are photographed through microscope
- Photograph of chromosomes is cut up and arranged to form karyotype diagram
Human Genetic Analysis

• Geneticists often gather information from several generations to increase the numbers for analysis

• If a trait follows a simple Mendelian inheritance pattern they can be confident about predicting the probability of its showing up again
Pedigree

- Chart that shows genetic connections among individuals
- Standardized symbols
- Knowledge of probability and Mendelian patterns used to suggest basis of a trait
- Conclusions most accurate when drawn from large number of pedigrees
Pedigree for Polydactyly

- Male
- Female
- Marriage/mating
- Offspring in order of birth, from left to right
- Individual showing trait being studied
- Sex not specified
- Generation

Gene not expressed in this carrier.

* Gene not expressed in this carrier.
Genetic Disorder

• A rare, uncommon version of a trait

• Polydactyly
  – Unusual number of toes or fingers
  – Does not cause any health problems
  – View of trait as disfiguring is subjective
Genetic Disorder

- Inherited conditions that cause mild to severe medical problems
- Why don’t they disappear?
  - Mutation introduces new rare alleles
  - In heterozygotes, harmful allele is masked, so it can still be passed on to offspring
Autosomal Dominant Inheritance

- Trait typically appears in every generation
Achondroplasia

- Autosomal dominant allele
- In homozygous form usually leads to stillbirth
- Heterozygotes display a type of dwarfism
- Have short arms and legs relative to other body parts
Huntington Disorder

- Autosomal dominant allele
- Causes involuntary movements, nervous system deterioration, death
- Symptoms don’t usually show up until person is past age 30
- People often pass allele on before they know they have it
Autosomal Recessive Inheritance Patterns

• If parents are both heterozygous, child will have a 25% chance of being affected
Galactosemia

- Caused by autosomal recessive allele
- Gene specifies a mutant enzyme in the pathway that breaks down lactose
X-Linked Recessive Inheritance

- Males show disorder more than females
- Son cannot inherit disorder from his father
Examples of X-Linked Traits

• Color blindness
  – Inability to distinguish among some of all colors

• Hemophilia
  – Blood-clotting disorder
  – 1/7,000 males has allele for hemophilia A
  – Was common in European royal families
Duplication

• Gene sequence that is repeated several to hundreds of times
• Duplications occur in normal chromosomes
• May have adaptive advantage
  – Useful mutations may occur in copy
Duplication

- `[A B C D E F G]` normal chromosome
- `[A B C D D D D E F G]` one segment repeated
- `[A B C D D D D D D D E E E F F G]` three repeats
Inversion

A linear stretch of DNA is reversed within the chromosome

segments G, H, I become inverted
Deletion

- Loss of some segment of a chromosome
- Most are lethal or cause serious disorder

Segment C deleted
Translocation

- A piece of one chromosome becomes attached to another nonhomologous chromosome
- Most are reciprocal
- Philadelphia chromosome arose from a reciprocal translocation between chromosomes 9 and 22
Translocation

chromosome
nonhomologous chromosome

reciprocal translocation

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Philadelphia Chromosome

• First abnormal chromosome to be associated with a cancer

• Associated with a chronic leukemia
  – Overproduction of white blood cells
A Reciprocal Translocation

Chromosome 9 and chromosome 22 exchanged pieces
An Altered Gene

- When the reciprocal translocation occurred, a gene at the end of chromosome 9 fused with a gene from chromosome 22.

- This hybrid gene encodes an abnormal protein that stimulates uncontrolled division of white blood cells.
Does Chromosome Structure Evolve?

• Alterations in the structure of chromosomes generally are not good and tend to be selected against
• Over evolutionary time, however, many alterations with neutral effects became built into the DNA of all species
Aneuploidy

• Individuals have one extra or less chromosome
• \((2n + 1 \text{ or } 2n - 1)\)
• Major cause of human reproductive failure
• Most human miscarriages are aneuploids
Polyploidy

• Individuals have three or more of each type of chromosome ($3n$, $4n$)
• Common in flowering plants
• Lethal for humans
  – 99% die before birth
  – Newborns die soon after birth
Nondisjunction

- Chromosome alignments at anaphase I
- Nondisjunction at anaphase
- Alignments at metaphase II
- Anaphase II
- Chromosome number
Genetic Screening

- Large-scale screening programs detect affected persons.
- Newborns in the United States are routinely tested for PKU.
  - Early detection allows dietary intervention and prevents brain impairment.
Genetic Diseases

• Examples of single-gene diseases
  – Cystic fibrosis—recessive autosomal condition characterized by excessive secretion of mucus and sweat, often causing obstruction of the gastrointestinal or respiratory tracts
  – Phenylketonuria (PKU)—recessive autosomal condition characterized by excess phenylketone in urine, caused by accumulation of phenylalanine in tissues; may cause brain injury and death
Phenotypic Treatments

• Symptoms of many genetic disorders can be minimized or suppressed by
  – Dietary controls
  – Adjustments to environmental conditions
  – Surgery or hormonal treatments
Prenatal Diagnosis

- Amniocentesis
- Chorionic villus sampling
- Fetoscopy
- All methods have some risks
Genetic Counseling

- Parents-to-be can seek genetic counseling to compare risks of diagnostic procedures against the risk that their child will be affected by a severe genetic disorder.
Preimplantation Diagnosis

- Used with in-vitro fertilization
- Mitotic divisions produce ball of 8 cells
- All cells have same genes
- One of the cells is removed and its genes analyzed
- If cell has no defects, the embryo is implanted in uterus
Genetic Diseases

• Single gene diseases
  – Tay-Sachs disease (TSD) is a recessive condition involving failure to make a subunit of an essential lipid-processing enzyme
Genetic Diseases

• Examples of chromosomal diseases
  – Down syndrome—usually caused by trisomy of chromosome 21; characterized by mental retardation and multiple structural defects
  – Klinefelter syndrome—caused by the presence of two or more X chromosomes in a male (usually trisomy XXY); characterized by long legs, enlarged breasts, low intelligence, small testes, sterility, chronic pulmonary disease
Turner Syndrome

- Inheritance of only one X (XO)
- 98% spontaneously aborted
- Survivors are short, infertile females
  - No functional ovaries
  - Secondary sexual traits reduced
  - May be treated with hormones, surgery
Klinefelter Syndrome

- XXY condition
- Results mainly from nondisjunction in mother (67%)
- Phenotype is tall males
  - Sterile or nearly so
  - Feminized traits (sparse facial hair, somewhat enlarged breasts)
  - Treated with testosterone injections
XYY Condition

• Taller than average males
• Most otherwise phenotypically normal
• Some mentally impaired
• Once thought to be predisposed to criminal behavior, but studies now discredit
Kleinfelter Syndrome
Genetic Diseases

• Chromosomal diseases
  – Turner syndrome—caused by monosomy of the X chromosome (XO); characterized by immaturity of sex organs (resulting in sterility), short stature, webbed neck, cardiovascular defects, and learning disorders
Turner Syndrome
Prevention and Treatment of Genetic Diseases

• Genetic counseling—professional consultations with families regarding genetic diseases
  – Pedigree—chart illustrating genetic relationships over several generations
  – Punnett square—grid used to determine the probability of inheriting genetic traits
Prevention and Treatment of Genetic Diseases

• Karyotype—arrangement of chromosome photographs used to detect abnormalities
Prevention and Treatment of Genetic Diseases

- Karyotype—arrangement of chromosome photographs used to detect abnormalities
  - Amniocentesis—involves collection of fetal cells floating in the amniotic fluid (via a syringe needle through the uterine wall)
  - Chorionic villus sampling—involves collection of embryonic cells from outside of chorionic tissue (via tube through cervical opening)
Prevention and Treatment of Genetic Diseases

- Treating genetic diseases
  - Most current treatments for genetic diseases are based on relieving or avoiding symptoms rather than attempting a cure
  - Gene therapy—manipulates genes to cure genetic problems
    - Most forms of gene therapy have not yet been proven effective in humans
– Gene therapy (cont’d)

• Gene replacement therapy—abnormal genes in existing body cells are replaced by therapeutic genes

• Gene augmentation therapy—cells carrying normal genes are introduced into the body to augment production of a needed protein