CHAPTER 13: PATTERNS OF INHERITANCE

CHAPTER SYNOPSIS

Early geneticists believed that genetic material from each parent blended in the offspring and that variability was not introduced from outside the species. Blending and lack of variability, though, should result in individuals that greatly resemble rather than differ from one another. This paradox was partly solved by early plant breeders who found that hybrids differed greatly from their parents and often from one another. They reported that certain physical traits disappeared for a generation and reappeared in the next. Gregor Mendel cross-bred seven well-documented varieties of pea. Most importantly, he quantified his experiments, meticulously counted seeds of hundreds of crosses and grouped them by apparent physical traits. Mendelian genetics is derived from the mathematical ratios that describe the segregation and assortment of hereditary material.

Mendel's model states that each parent transmits a set of information about its traits in its gametes. Therefore each individual possesses two factors (genes) for each trait. Each factor exhibits many possible forms (alleles) that do not influence one another; each remains discrete within the cell. An individual may be homozygous and possess two identical alleles, or heterozygous and have two different alleles. The presence of a factor does not ensure its expression; dominant traits are expressed while recessive traits are generally not expressed. The existence of the recessive allele in a heterozygote causes that factor to be masked for a generation. Additionally, there is a difference between an individual's phenotype, or overall appearance, and its genotype, its precise genetic blueprint. Mendel's First Law of Heredity explains how alleles randomly segregate in the gametes, each gamete has an equal chance of receiving either allele. His second law explains that different alleles assort into gametes independently of one another, the presence of an allele of one trait does not preclude the presence or absence of any other allele of any other trait.

It was fortunate that Mendel chose straight forward traits located on separate chromosomes. There are more complex genetic patterns associated with continuous variation, pleiotropic genes, lack of complete dominance, environmental modifications of genes, and epistasis. Many human genetics disorders follow Mendelian principles. Most are recessive like Tay-Sachs disease. Hunington's disease is an example of a dominant allele that remains in populations because its effect is not expressed until after children are born. Human blood groups are an example of traits stemming from multiple alleles. In the ABO system, four phenotypes arise from the combination of three alleles coding for red cell surface antigens. The transmission of a genetic disorder can often be tracked through pedigree analysis, shown in example by Royal hemophilia in the lineages of the British monarchy. Disorders like sickle-cell anemia, are a result of nucleotide changes that alter the linear and three-dimensional structure of critical proteins. Current genetic research uses molecular techniques to try to cure disorders like cystic fibrosis by inserting new genes into disabled cells.

Modern geneticists have modified Mendel's laws to be consistent with discovery of meiosis and crossing over, identification of chromosomes as hereditary material, and the structure of genes and DNA. Genetic recombination is used to construct gene maps, identifying the location of alleles on chromosomes and specific positions within chromosomes. The Human Genome Project has produced vast amounts of data elucidating the genetic sequence of our own genome. A normal human cell possesses twenty-two pairs of autosomal and one pair of sex chromosomes for a total of forty-six chromosomes. Any variance from that number is detrimental and often lethal. Down syndrome, one of the few non-lethal trisomies, results from primary nondisjunction during meiosis. Abnormal separation of the sex chromosomes can result in individuals with extra or absent X or Y chromosomes. The minimal amount of sex chromatin needed for survival is a single X chromosome. A YO zygote fails to develop as the Y lacks the necessary information present on the X. Genetic counseling attempts to prevent the production of children with genetic disorders by identifying parents at risk. Prenatal diagnosis is valuable and uses amniocentesis, ultrasound, and/or chorionic villi sampling.

CHAPTER OBJECTIVES

- Understand the historical background for Mendel's pea experiments.
- Know the key details in Mendel's experiments that enabled him to postulate his laws of inheritance where others had failed.
- State Mendel's model of heredity and Sutton's theory of chromosomal inheritance.
- Understand how gene segregation and independent assortment are different but yet related.
- Calculate expected phenotypic and genotypic ratios from various crosses using the Punnett square method.
- Explain the experimental rationale behind the classical testcross.
- Explain how Mendelian inheritance changes with respect to continuous variation, pleiotropic genes, lack of complete dominance, environmental modifications of genes, and epistasis.
- Differentiate between the cell surface antigens of each blood type in the ABO system and indicate all possible phenotypes and genotypes.
- Understand the importance of crossing over in terms of gene assortment and construction of genetic maps.
- Describe the many genetic disorders discussed in the text, their symptoms, relative frequency in specialized populations, and their genetic basis.
- Understand the consequences of nondisjunction at various stages of gametogenesis and its affect on the sex chromosomes.
- Understand the value and purpose of genetic counseling and describe two techniques of prenatal genetic screening.

KEY TERMS

ABO blood groups
allele
autosome
Barr body
centimorgan
character
chorionic villi sampling
chromosomal theory of inheritance
codominant
continuous variation
cross-fertilization
cross-pollination
crossing over
cystic fibrosis
dihybrid
diploid
dominant
Down syndrome
epistasis
first filial (F_1) generation
gene
genetic counseling
genetic disorder
genetic map
genetic recombination
genotype
haploid
hemophilia
heterozygous
high-risk pregnancy
homozygous
human genome project
Huntington's disease
hybridization
Law of Independent Assortment
Law of Segregation
linked genes
locus
Mendelian ratio
Mendel's First Law of Heredity
Mendel's Second Law of Heredity
modified ratio
monosomic
mutant
phenotype
pleiotropic
polygenes
primary nondisjunction
Punnett square
recessive allele
restriction fragment-length polymorphisms (RFLPs)
Rh blood group
second filial (F_2) generation
segregation
self-fertilization
sex chromosome
sex-linked
sickle-cell anemia
syntenic gene
testcross
three-point cross
trait
trisomic
wild type
X chromosome
Y chromosome

CHAPTER OUTLINE

13.0 Introduction

I. ENIGMA OF HEREDITY

A. People in Different Parts of the World Vary in Appearance — fig 13.1

B. Members of a Family Tend to Look Alike

13.1 Mendel solved the mystery of heredity

I. EARLY IDEAS ABOUT HEREDITY: THE ROAD TO MENDEL

A. Variation in Appearance
   1. Similarities within families — fig 13.2
   2. Certain characteristics are more common among families — fig 13.3

B. Classical Assumptions 1: Constancy of Species
   1. Heredity occurs within species
      a. Cannot create bizarre creatures by cross breeding
      b. Common animals are not combinations of breeding
   2. Variation occurs within boundaries of a species

C. Classical Assumption 2: Direct Transmission of Traits
   1. Traits are transmitted directly
      a. Once thought body parts transmitted in sex cells
      b. Darwin proposed gemmules transmitted characteristics to offspring
   2. Thought male and female traits blended in offspring

D. Koelreuter Demonstrates Hybridization Between Species
   1. Assumption 1 and assumption 2 together lead to paradox
      a. If no variation enters from outside species
      b. If variation blended with each generation
      c. In time, would result in little species variation
   2. Koelreuter hybridized tobacco plants
      a. Offspring appeared different from either parent
      b. Crosses of hybrids resulted in further variation
      c. Offspring resembled parents or grandparents

E. The Classical Assumptions Fail
   1. Koelreuter's experiments signal beginning of modern genetics
   2. Traits masked for a generation, reappeared in next
   3. Alternative forms segregating among offspring
      a. Heritable features called characteristics
      b. Alternative forms segregate among progeny
      c. Alternative forms called traits

F. Knight Studies Heredity in Peas
   1. Crossed true-breeding peas, purple and white flowers — fig 13.4
      a. All offspring of first cross had purple flowers
      b. Offspring of next cross had both color flowers
      c. Purple flowers predominated over white flowers
   2. Failure to quantify results prolonged discovery of important concepts

II. MENDEL AND THE GARDEN PEA

A. Carried Out First Quantitative Studies
1. Austrian monk educated in a monastery fig 13.5
2. Studies science and math at University of Vienna
3. Initiated experiments on plant hybridization fig 13.6

B. Why Mendel Chose the Garden Pea
1. Expected segregation among offspring, via early studies
2. Many true-breeding traits, studied only seven
3. Small plants, easy to grow, short generation time
4. Male and female parts within flower fig 13.7
   a. Self-fertilized male and female from same flower
   b. Cross-pollinated female with other flower's pollen, cross-fertilization resulted

C. Mendel's Experimental Design
1. Reasons for Mendel's success
   a. Focused on only a few traits
   b. Selected comparable traits
2. Conducted experiments in three stages
3. Allowed several generations of self-fertilization
   a. Progeny produced only a single form of a trait
   b. Assured that forms of traits were transmitted regularly
4. Conducted crosses between alternate forms of a trait fig 13.8
   a. Removed male parts from a flower with white flowers
   b. Fertilized with pollen from plant with purple flowers
   c. Performed reciprocal crosses white flower pollen on purple flower plant
5. Allowed self-pollination of hybrids
   a. Allowed segregation of alternate forms of traits
   b. Counted number of offspring of each type per generation
   c. Quantification of results most important to studies

III. WHAT MENDEL FOUND

A. Mendel's Seven Traits Produced Recognizable and Scorable Results fig 13.9

B. The F_1 Generation
1. First filial (F_1) progeny resembled one of parents
2. Trait expressed in F_1 called dominant
3. Trait masked in F_1 called recessive
4. All seven traits had dominant and recessive forms

C. The F_2 Generation
1. Planted F_1 seeds to produce F_2 (second filial) generation examining flower color
2. Counted F_2 generation, determined proportion of dominant to recessive fig 13.10
   a. Three fourths of plants exhibited dominant form fig 13.9
   b. One fourth of plants exhibited masked, recessive form
   c. Dominant:recessive ratio was close to 3:1 for all seven traits
3. Obtained same results comparing round and wrinkled seed shape fig 13.11

D. A Disguised 1:2:1 Ratio
1. Recessive individuals always bred true
2. One third of dominant individuals bred true
3. Two thirds of dominant individuals produced 3:1 progeny

4. 3:1 ratio really 1:2:1 ratio fig 13.12
   a. 1/4 dominant, pure breeding
   b. 1/2 dominant, not pure breeding:recessive
   c. 1/4 pure breeding, recessive

E. Mendel's Model of Heredity
   1. Mendel determined four things about the nature of heredity
      a. Plants did not produce blended, intermediate characteristics
      b. For each trait with two alternates, one was not expressed in F_1 generation
      c. Expression of traits segregated among progeny of a cross
      d. Expression of F_2 generation produced 3:1 Mendelian ratio
   2. Mendel's model has five elements
      a. Parents transmit factors that provide information about traits
      b. Each individual contains two factors for each trait
         1) May code for same form or alternative forms
         2) Diploid set of chromosomes in individuals, thus two forms
         3) Haploid chromosomes randomly distributed in gametes
      c. Not all copies of a factor are identical
         1) Alternate forms of factor called alleles
         2) Individual is homozygous when both alleles are the same
         3) Individual is heterozygous when alleles are different
         4) Position of gene on DNA is called its locus
      d. Alleles from each parent do not influence one another
         1) They remain discrete and "uncontaminated"
         2) They do not blend with one another
         3) They further segregate randomly when forming progeny
      e. Presence of a factor does not ensure its expression
         1) Dominant heterozygote expressed, recessive unexpressed
         2) Genotype is the totality of the genes (blueprint)
         3) Phenotype is the expression of the genes (visible outcome)
   3. Mendel's traits exhibited complete dominance of one allele over another
      a. Exhibited in all seven traits studied by Mendel
      b. Exhibited by many human traits tbl 13.1

IV. HOW MENDEL INTERPRETED HIS RESULTS

A. Mendel Tested His Model, Predicted Results
   1. Expressed model in terms of simple symbols
   2. Example: Purple-white flower cross (letter choice is from most common trait)
      a. Dominant purple flowers designated *P*
      b. Recessive white flowers designated *p*
      c. True-breeding recessive thus designated *pp*
      d. True-breeding dominant designated *PP*
      e. Heterozygote designated *Pp* (dominant trait first)
      f. Mendel's original cross designated *pp* × *PP*

B. The F_1 Generation
   1. Each parent can produce gametes of only its kind
      a. Purple gametes contain only *P* allele
      b. White gametes contain only *p* allele
   2. Resulting progeny all *Pp*, since *P* is dominant, all purple heterozygotes
   3. Recessive *p* allele present but not expressed

C. The F_2 Generation
   1. Alleles segregate randomly in gametes, either *P* or *p*
   2. Construct Punnett square to determine progeny of cross — fig 13.13
   3. Square predicts 3:1 phenotypic ratio — fig 13.14

D. The Laws of Probability Can Predict Mendel's Results
   1. Expression of dominant trait is 3/4 (three chances in four)
   2. Expression of recessive trait 1/4 (one chance in four)
   3. Make simple predictions about outcomes of crosses
      a. If F_1 parents are both *Pp,* determine probability of offspring being *pp*
      b. 1/2 chance that male parent donates *p*, 1/2 chance female donates *p*
      c. $1/2 \times 1/2 = 1/4$ chance of progeny being *pp*
      d. Same result as determined by Punnett square — fig 13.13

E. Further Generations
   1. Three kinds of F_2 individuals — fig 13.14
      a. Pure-breeding white flowers (*pp*)
      b. Heterozygous purple flowers (*Pp*)
      c. Pure-breeding purple flowers (*PP*)
   2. Closer examination of 3:1 ratio indicates 1:2:1 genotypic ratio

F. Mendel's First Law of Heredity: Segregation
   1. Alternative forms encoded by discrete alleles
   2. Alternative alleles separate at random along metaphase plate
   3. Explained segregation without cellular knowledge, chromosomes, or meiosis

G. The Testcross
   1. Used to determine genotype of dominant phenotype
   2. Observing phenotype insufficient, *PP* and *Pp* appear same
   3. Cross unknown to organism of known lineage — fig 13.15
      a. Homozygous dominant (*PP*) produces dominant phenotype (*Pp* or *PP*)
      b. Heterozygous (*Pp*) produces all possible genotypes of offspring (*PP*, *Pp*, *pp*)
      c. Homozygous recessive as known parent (*pp*) produces two totally different results
         1) All *Pp* offspring indicates *PP* unknown
         2) Half *Pp*, half *pp* offspring indicates *Pp* unknown
   4. Mendel's testcross helped determine identity of 3:1 F_1 generation — fig 13.14
      a. Experimental cross with homozygous recessive
      b. Predicted resulting 1:1 ratio
      c. Observed 1:1 ratio as predicted
   5. Testcross used to determine genotype when two genes involved
      a. F_2 individual with both dominant traits (*A_B_*)
      b. Could be any one of four genotypes: *AABB*, *AaBB*, *AABb* or *AaBb*
      c. Performed test cross *A_B_* × *aabb*
      d. Determined F_2 genotype based on whether further generations bred true
         1) Was AABB if both bred true
         2) Was AaBB if only B bred true
         3) Was AABb if only A bred true
         4) Was AaBb if neither bred true

H. Mendel's Second Law of Heredity: Independent Assortment
   1. Mendel questioned effect of traits upon one another
   2. Genes located on different chromosomes assort independent of one another
   3. Step 1: Establish pure-breeding lines differing in two traits

4. Step 2: Cross contrasting pairs of traits
   a. Results in F_1 generation of identical dihybrids
   b. Dihybrids are individuals heterozygous for two genes
5. Step 3: Allow dihybrids to self-fertilize
   a. 1/4 chance for a single trait to occur
   b. 1/4 x 1/4 = 1/16 for any pair to occur
   c. Predicts 9:3:3:1 ratio
6. Example: Shape=Round (*R*) or wrinkled (*r*) and color= Yellow (*Y*) or green (*y*)
   a. Four types of gametes possible: *RY*, *Ry*, *rY*, *ry*
   b. Sixteen types of offspring all equally possible fig 13.16
   c. Nine individuals possess *R_Y_* = round, yellow
   d. Three individuals possess *R_yy* = round, green
   e. Three individuals possess *rrY_* = wrinkled, yellow
   f. One individual possesses *rryy* = wrinkled, green
   g. Observation fulfills prediction
7. Genes assort independently when traits on different chromosomes
8. Chromosomes assort independently during meiosis in gamete formation

V. MENDELIAN INHERITANCE IS NOT ALWAYS EASY TO ANALYZE

A. Little Note Given to Mendel's Work in His Lifetime

1. Mendel's work rediscovered after his death
2. Discovered by independent investigators in planning own publications
3. Difficulty in confirming some aspects of his work
   a. Difficult to obtain simple ratios in some crosses
   b. Expression of genotype not straightforward
      1) Phenotype affected by actions of many genes and the environment
      2) Not all alleles express complete dominance

B. Continuous Variation

1. Most traits reflect action of polygenes, genes act sequentially or jointly
2. Trait shows a range of small differences like height and weight
   a. Genes all segregate independently, gradation in degree of difference fig 13.17
   b. Gradation called continuous variation
3. Analyze traits by grouping individuals into categories, not dealing with raw data
   a. Example: Height
   b. Measure height, round fractions to nearest higher value
   c. Each value, phenotypic category, plotted as histogram
   d. Graph approximated bell-shaped curve

C. Pleiotropic Effects

1. Pleiotropic gene has more than one effect on phenotype
2. Example: Cuenot's experiments on yellow fur in mice
   a. Dominant trait, unable to obtain true-breeding strain
   b. Homozygous yellow offspring died
   c. Allele for yellow fur not only produced color, but was lethal
3. One gene affects many traits (in polygeny many genes affect one trait)
4. Difficult to predict since genes perform other unknown functions
5. Characteristic of many inherited disorders
   a. Cystic fibrosis symptoms affect many organs
   b. Are effects of one mutated gene encoding chloride ion transmembrane channel
6. Sickle-cell anemia
   a. Defect in oxygen-carrying hemoglobin molecule
   b. Produces numerous systems and organ damage

D. Lack of Complete Dominance
   1. Alternative alleles not dominant or recessive fig 13.18
   2. Some heterozygous are intermediate between condition of each parent
   3. Example: Japanese four-o'clock flower color, parents red or white
      a. F_1 offspring all pink in color
      b. F_2 offspring ratio 1:2:1 (red:pink:white
      c. Thus all heterozygotes pink, intermediate in color

E. Environmental Effects
   1. Expression of gene modified by environment
   2. Traits usually sensitive to temperature or light
   3. Example: Arctic fox fur pigment made only in warm weather fig 13.19
   4. Example: *ch* allele in Himalayan rabbits and Siamese cats
      a. Allele encodes heat-sensitive version of tyrosinase
      b. Enzyme mediates production of dark pigment melanin
      c. *ch* version of allele inactivates above 33°C
      d. Where body temperature is lower (ears, snout, feet, tip of tail) melanin is produced
      e. Where body temperature is higher (body) melanin not produced (white)

F. Epistasis
   1. Difficulty in obtaining Mendel's simple ratios associated with dihybrid crosses
      a. Four different progeny phenotypes possible from dihybrid cross
         1) Display dominant phenotype for both genes
         2) Display dominant phenotype for one gene, but not other
         3) Display neither dominant phenotype
      b. When classes look alike, it is difficult to identify each
   2. Observed in varieties of corn producing purple anthocyanin pigment
      a. Emerson crossed two true-breeding varieties without any purple pigment
      b. All F_1 plants produced purple seeds
      c. F_2 cross produced 56% plants with pigment, 44% without
      d. Deduced two genes responsible for seed coat color
         1) Second cross was like Mendelian dihybrid cross
         2) Obtained modified ratio of 9:7
   3. Why was Emerson's ratio modified?
      a. Genes may act sequentially in biochemical pathway
         1) Defect early in pathway blocks rest of pathway
         2) Cannot determine if rest of pathway is working properly
      b. Gene interaction where one gene modifies expression of other gene
      c. Pigment producing pathway explained
         1) Molecule (colorless) → intermediate (colorless) → anthocyanin (purple)
         2) Plant needs one functional copy of gene for both enzymes fig 13.20
         3) Of 16 genotypes, 9 code for at least one dominant gene for both enzymes
         4) Remaining 7 (3+3+1) lack dominant alleles at one or both loci

G. Other Examples of Epistasis
   1. Epistatic interactions of color genes result in finished coat color in many animals
   2. Example: Coat color in Labrador retrievers fig 13.21
      a. Results from interaction of two genes
         1) *E* gene determines deposition of dark eumelanin pigment in fur
            a) If *ee* no pigment is deposited, coat color is yellow
            b) If *E_* (*EE* or *Ee*) pigment is deposited, coat color is brown or black
         2) *B* gene determines darkness of pigment, the distribution of melanosomes
            a) *E_bb* fur is brown (chocolate lab)
            b) *E_B_* fur is black

3) *B* gene has effects even in yellow labs
   a) Genotype *eebb* have brown pigment on nose, lips, rims of eyes
   b) Genotype *eeB_* have black pigmented areas

b. Genetic test can identify coat colors in puppies

13.2 Human genetics follows Mendelian principles

I. HUMAN GENE DISORDERS

A. Variant Alleles Exist in Populations
1. Mutation involves random changes in genes
2. Variant alleles are rarely produced by mutations

B. Variant Alleles May be Detrimental
1. Offspring may suffer effects of mutant gene
   a. Are usually recessive to other alleles
   b. Are maintained in populations in heterozygous carriers
2. Genetic disorder: Detrimental gene at high frequency in population

II. MOST GENE DISORDERS ARE RARE

A. A Notable Gene Disorder
1. Tay-Sachs disease causes fatal brain deterioration in children fig 13.22
2. Highest occurrence in Jewish populations
   a. 1 in 300,000 of overall population exhibit disease
   b. 1 in 28 in specific population carry defective gene
   c. 1 in 3,500 of same population exhibit disease
3. Carriers do not exhibit disease
4. Allele codes for nonfunctional form of hexosaminidase A
   a. Cannot degrade gangliosides in brain cell lysosomes
   b. Lysosomes fill with gangliosides, swell and burst, killing brain cells

B. Not All Gene Defects Are Recessive
1. Huntington's Disease is hereditary condition caused by dominant allele fig 13.23
2. Causes progressive deterioration of brain cells
3. Maintained in population, 1 in 24,000 affected
   a. Symptoms develop after reproductive activity
   b. Allele often transmitted prior to its expression
4. Heterozygous parent has 50% chance of passing disease to child
   a. With recessive disorder there is a 50% chance of passing allele to offspring
   b. Must then mate with another carrier to produce disease

III. MULTIPLE ALLELES: THE ABO BLOOD GROUPS

A. Most Genes Possess More than Two Possible Alleles
1. Often neither allele is completely dominant over any other
2. Alleles are then considered to be co-dominant

B. ABO Blood Groups Contain Co-Dominant Genes
1. Three alleles encode cell surface antigens
   a. Antigens are sugars that are attached to lipids on blood cell surface
   b. Gene encoding the enzyme that adds the sugar is designated I
   c. Allele B(I^B) codes for galactose
   d. Allele A (I^A) codes for galactosamine

e. Allele O (*i*) codes for neither sugar
2. I^A and I^B are codominant and can be expressed together
3. I^A and I^B are both dominant over *i*
4. Four phenotypes produced from three alleles fig 13.24
   a. Type A: Genotype I^AI^A or Iai adds only galactosamine
   b. Type B: Genotype I^BI^B or Ibi adds only galactose
   c. Type AB: Genotype I^AI^B adds both sugars
   d. Type O: Genotype ii adds neither sugar
5. Four phenotypes called ABO blood groups
6. Blood may agglutinate due to presence of antigens
   a. Type A blood recognizes type B blood and reacts with B antigens
   b. Type A blood recognizes type AB blood reacts with B antigens
   c. Type A blood does not recognize type O blood since no antigens
   d. Type AB blood does not recognize either A or B as foreign

C. The Rh Blood Group
1. Associated with presence of Rh cell surface markers
   a. Rh-positive possess marker, most adult humans
   b. Rh-negative lacks marker, fewer in number
   c. Rh-negative is homozygous recessive condition
2. Blood may agglutinate due to presence of antigens
   a. Rh-negative mother, Rh-positive child (Rh-positive father)
   b. Rh-positive blood crosses placenta into mother's blood
   c. Induces production of anti-Rh antibodies in mother's blood
   d. In later pregnancy, Rh antibodies can cross back
   e. Cause next Rh-positive baby's blood to clump: Erythroblastosis fetalis

IV. PATTERNS OF INHERITANCE CAN BE DEDUCED FROM PEDIGREES

A. Hemophilia Is a Well-Documented Inherited Disease
1. Excessive bleeding results from a loss of activity in blood clotting factors
2. Disorder due to recessive condition
   a. Most clotting proteins located on autosomes
   b. Two (VII and IX) located on X chromosome, are sex-linked
      1) More prominent in males since they possess only one X
      2) If X defective, no proteins made
      3) Y lacks comparable allele

B. A Pedigree of Royal Hemophilia
1. Most common form has defective IX
2. Called Royal hemophilia, prominent in family of Queen Victoria fig 13.25
3. Carried into royal families of Europe fig 13.26

V. GENE DISORDERS CAN BE DUE TO SIMPLE ALTERATIONS OF PROTEINS

A. Gene Defects Often Affect Specific Proteins: Sickle-Cell Anemia
1. Improper transport of oxygen due to defective hemoglobin
   a. Red blood cells become stiff and sickle-shaped fig 13.27
   b. Blood cells clog blood vessels, are unable to enter small vessels
   c. Affected individuals usually have intermittent illness, shortened life span
2. Results from alteration in single amino acid
   a. Valine replaces glutamic acid at a single location on protein's outer edge
   b. Causes "sticky patch" that causes hemoglobin molecules to adhere to each other
   c. Forms long chains of hemoglobin molecules

B. High Frequency of Disease in Areas with Endemic Malaria
   1. Disorder of homozygotes but heterozygotes slightly affected
   2. Most common disorder among those of African descent
   3. Heterozygosity for sickle-cell confers resistance to malaria fig 13.28

VI. SOME DEFECTS MAY SOON BE CURABLE

A. A Common Fatal Gene Disorder: Cystic Fibrosis
   1. Most common gene defects result from single recessive mutations tbl 13.2
   2. Most common genetic disorder in Caucasians
   3. Affected individuals secrete thick mucus
      a. Clogs airways of lungs, ducts of pancreas and liver
      b. No known cure
   4. Defect in single *cf* gene
      a. 1 in 20 carry single copy of defective gene
      b. 1 in 2,500 are homozygous recessive, exhibit disease
   5. Function of gene discovered due to extreme salty characteristic of sweat
      a. Quinton isolated sweat ducts from skin in 1985
      b. Placed section in 3x concentrated salt solution, monitored ion movements
         1) Normally Na^+ and Cl^- driven into duct by diffusion
         2) Only Na^+ entered duct from CF individual, no Cl^-
   6. Defect in transport of chloride ions across membranes
      a. Responsible gene is cystic fibrosis transmembrane regulator (CFTR)
      b. Does not function normally in CF patients fig 4.8

B. Gene Identified and Transferred to Affected Individuals
   1. Gene located on chromosome 7
   2. Working copies of CFTR inserted into adenovirus
      a. Transferred to culture human lung cells, defective cells "cured"
      b. Normal human *cf* gene transferred to rat lung cells
         1) Gene first inserted into cold virus
         2) Rat inhaled virus
         3) Rat lung cells began producing normal human CFTR protein
   3. Trials in human CF patients begun in 1993
      a. Initially unsuccessful
      b. Future hopeful

13.3 Genes are on chromosomes

I. CHROMOSOMES: THE VEHICLES OF MENDELIAN INHERITANCE

A. Many Organelles Segregate in Meiosis, Chromosomes Not Obvious Carriers of Heredity

B. The Chromosomal Theory of Inheritance
   1. Support for Sutton's theory formulated in 1902
      a. Reproduction involves union of egg and sperm
      b. Mendel's theory expected hereditary contributions of two individuals
      c. Since sperm contains virtually only a nucleus, hereditary material resides there
   2. Diploid adults have two copies of each chromosome, gametes have one copy
   3. Chromosomes segregate in meiosis, characteristic consistent with Mendel's theory

C. Problems with the Chromosomal Theory
   1. If Mendelian traits are determined by genes on chromosomes
   2. And if Mendelian independent assortment reflects meiotic assortment
   3. Then why is number of assorting traits far greater than number of chromosome pairs?

D. Morgan's White-Eyed Fly
   1. Helped support chromosomal theory of inheritance
   2. Discovered mutant, white-eyed male fruit fly fig 13.29
      a. Crossed with wild type red-eyed female
      b. All progeny had red eyes, concluded red eye color dominant
   3. Crossed progeny of F_1 generation
      a. 82%: 18% approximated 3:1 ratio red to white eyes
      b. All recessive white eye flies were male
   4. Testcross F_1 females to white-eyed male
      a. 1:1:1:1 ratio
      b. Eye color and sex equally represented, female and male could have white eyes

E. Sex Linkage
   1. Sex determination in fruit flies
      a. Two kinds of sex chromosomes, X and Y
      b. XX = female, XY = male
   2. Morgan's explanation: Eye color gene associated with sex chromosome fig 13.30
      a. Eye color gene located on the X chromosome
      b. Since Y chromosome doesn't have eye color gene, eye color is white
   3. Sex linked trait
   4. White-eye trait is recessive to red-eye trait

F. Morgan's Experiment Presented First Clear Data that Genes Resided on Chromosomes
   1. Segregation of white-eye gene corresponded to segregation of sex chromosomes
   2. Traits segregate because chromosomes do during meiosis

II. GENETIC RECOMBINATION

A. More Independently Assorting Factors than Chromosomes
   1. de Vries suggested that homologous chromosomes exchange elements in meiosis
   2. Janssens discovered chiasmata in chromosomes during meiosis
      a. Of the four chromatids, two crossed, two did not
      b. Proposed exchange of chromosomal arms
      c. Not accepted due to questioning of required precision of exchange

B. Crossing Over
   1. Stern's experiments on fruit flies fig 13.31
      a. Examined two sex-linked traits on chromosomes with abnormal ends
      b. Observed corresponding changes in genetic traits
   2. Crossing over can occur anywhere along length of homologues
      a. Crossing over more likely if genes far apart
      b. Independent assortment still occurs if genes far apart fig 13.32

C. Using Recombination to Make Genetic Maps
   1. Crossing over more likely if genes are far apart
   2. Frequency of crossing over used to determine relative positions of genes
      a. Distance between genes = frequency of crossing over
      b. One map unit, centimorgan = 1% recombination

3. Modern technology creates more precise gene maps
   a. Map position of restriction sequences
   b. Sequences recognized by DNA-cleaving restriction endonucleases
4. Recombination maps still valuable for widely separated genes
5. Three-point cross
   a. Monitor recombination among three or more genes
      1) Syntenic alleles located on same chromosome
      2) Linked genes do not assort independently
   b. Three-point cross involves three linked genes
   c. First genetic map constructed by Sturtevant on fruit flies fig 13.33
      1) Wild type (+) is most frequent allele of a locus
      2) Other alleles given specific symbols
6. Analyzing a three-point cross
   a. Traits examined were all located on the X chromosome
      1) *y* = yellow body color (normal is grey)
      2) *w* = white eye color (normal is red)
      3) *min* = miniature wing length (normal is 50% longer)
   b. Crossed female with all three mutations to male without any
      1) All progeny were heterozygotes
      2) Any resultant crossing-over produced recombinant chromosomes
      3) Detected changes in progeny
   c. Conducted testcross of female heterozygotes to triply recessive males
      1) Males contribute Y with no genes or X with all three recessives
      2) Tabulation of results of cross tbl 13.3
      3) Consider traits in pairs to determine if a crossover event was involved
      4) Similarly analyze other pairs to determine position of other genes
      5) Greatest distance 33.8 separates outside genes *y* and *min*
      6) Gene *w* is between them, much closer (1.3 vs. 32.6) to *y*

D. The Human Genetic Map
   1. Human genetic maps used to determine genetic disorders fig 13.34
   2. Genetic engineering permits isolation and sequencing of specific genes
      a. Differences in nucleotide sequence may suggest therapies
      b. May allow replacement of non-functional gene with functional one
   3. Human genome project
      a. Collective attempts to map entire set of human chromosomes
      b. Map initially consists of library of thousands of fragments
      c. Screen library to determine which fragment contains gene of interest
      d. Entire genomes of smaller genomes (some yeast, bacteria) already determined
      e. Completion of project within the decade

III. HUMAN CHROMOSOMES

A. Morphology of Human Chromosomes
   1. 46 chromosomes in 23 pairs
   2. Divided into seven groups: A to G fig 13.35

B. Human Sex Chromosomes
   1. 22 pairs of autosomes, 2 sex chromosomes
   2. XX is normal female, XY is normal male
   3. Y has few active genes, counterparts to X alleles
      a. Genes for maleness present on Y
      b. Male possesses at least one Y

C. Sex Chromosomes in Other Organisms
   1. Sex determination may be different among species tbl 13.4
   2. XX is female, XY is male in fruit flies and most vertebrates
   3. In birds, male is ZZ and female ZW
   4. In insects like grasshopper, females are XX and males are XO (no Y chromosome, only X)
      a. XX is normal female in humans and fruit flies
      b. XY is normal male in humans and fruit flies
      c. Y has few active genes, counterparts to X alleles

D. Sex Determination
   1. *SRY* gene on Y chromosome involved in development of male sex characteristics
      a. Expressed early in development
      b. Masculinizes genitalia and secondary sexual organs
      c. Organs would otherwise be female
   2. Females do not undergo same changes since they lack the Y chromosome
   3. In fish and some reptiles, gene expression and sex is altered by environmental changes

E. Barr Bodies
   1. With XX, females do not produce twice as much protein as male
      a. One X inactivated in form of Barr body
      b. Other X active and expressed, activity of X is random in each cell
      c. Barr body stains deeply, attached to nuclear membrane fig 13.36
   2. X-inactivation occurs in other animals
      a. Examples: Color patches on tortoiseshell and calico cats
         1) *O* allele specifies orange fur, *o* specifies black fur
         2) Skin cell X chromosome inactivated early in development
         3) If cell's remaining X has *O* allele, orange fur will be produced
         4) If cell's remaining X has *o* allele, black fur will be produced
      b. Process is random, color patches appear randomly in coat
      c. Normally only females are heterozygous at *O* gene fig 13.37
         1) Most calico cats are female
         2) Male calico's have an XXY genotype
      d. White fur due to allele at the white spotting gene

IV. HUMAN ABNORMALITIES DUE TO ALTERATIONS IN CHROMOSOME NUMBER

A. Primary Nondisjunction
   1. Caused by failure of chromosomes to separate in meiosis
   2. Can result in severe abnormalities

B. Nondisjunction Involving Autosomes
   1. Monosomics possess one less copy of an autosome, do not survive
   2. Trisomics possess one extra copy of an autosome, most do not survive
      a. Trisomy in one of five smallest chromosomes may survive
      b. Extra 13, 15, 18 causes severe developmental defects
      c. Extra 21 or 22 may survive to adulthood, retarded skeletal and mental development
   3. Down Syndrome
      a. Results from extra chromosome 21 fig 13.38
         1) Usually entire chromosome is present
         2) In 3% only small portion is present, called translocation Down syndrome
      b. Gene causing syndrome may be similar to one that causes Alzheimer's disease
         1) Correlation with cancer-causing genes
         2) Cancer, leukemia more common in Down syndrome

c. Arises from primary nondisjunction during meiosis
   1) More likely to occur in pregnancy of older women fig 13.39
   2) Woman produces all eggs by time she is born
   3) Men produce new sperm continually

C. Nondisjunction Involving the Sex Chromosomes
1. The X chromosome fig 13.40
   a. Produces XX gamete and O gamete
   b. XX plus normal X results in XXX individual
      1) Two Barr bodies, one active X
      2) Sterile, but otherwise normal female
   c. XX plus normal Y results in XXY individual
      1) Kleinfelter syndrome
      2) Sterile male with female characteristics
   d. O plus normal Y results in nonviable OY individual
   e. O plus normal X results in XO individual
      1) Turner syndrome
      2) Sterile female with specific appearance, low-normal mental capabilities
2. The Y Chromosome
   a. Produces YY gametes
   b. YY plus normal X results in XYY individual
      1) Fertile males with normal appearance
      2) Greater numbers of individuals in penal institutions
      3) Controversial theory about antisocial behavior in XYY males
      4) Most XYY males do not develop such behaviors

V. GENETIC COUNSELING

A. In Absence of Cures, Seek to Not Produce Children with Disorders
1. Genetic counseling
   a. Identify parents at risk
   b. In high-risk pregnancy, likelihood that child will inherit disorder
2. High risk of Down syndrome in older women fig 13.39

B. Prenatal Diagnosis of Disorders
1. Amniocentesis fig 13.41
   a. Sample amniotic fluid during fourth month
   b. Observe fetus and position via ultrasound
   c. Fetal cells grown in culture
   d. Cells examined for major chromosomal damage
2. Chorionic villi sampling
   a. Sample placental tissue
   b. Can be performed earlier than amniocentesis at eight weeks
3. Tests for genetic disorders
   a. Enzyme activity tests: PKU, Tay-Sachs
   b. Association with genetic markers
      1) Cut DNA with restriction enzymes
      2) Observe restriction fragment-length polymorphisms, RFLPs fig 13.42

INSTRUCTIONAL STRATEGY

PRESENTATION ASSISTANCE:

Mendelian genetics is one of the classic discussions in introductory biology. Most students are introduced to this in high school, but few really understand what is meant by segregation and independent assortment. Segregation of alleles is hard to visualize without a good understanding of meiosis. One can truly respect Mendel's scientific ability when realizing that neither chromosomes nor meiosis had been discovered yet.

The most frequent mistake a beginner makes in calculating a dihybrid cross is putting the two alleles for the same trait in a single gamete. Make them separate (segregate) those letters! A normal gamete can have only one of each allele.

There is a lot of new terminology associated with genetics. Homozygous and heterozygous are frequently confused as are phenotype and genotype and, for some strange reason, allele and locus. Again, understanding the meanings of prefixes, suffixes, and root words helps enormously. A background in a romance language has enormous benefits.

Many of your students are medical-school bound and relate to the topic of this chapter because they see its direct application to their futures. Examining one's own genetic background is to some extent health-oriented fortune telling. By studying the ailments of one's parents, grandparents, and other relatives, a picture of one's own future begins to develop. Most serious diseases are not under strict genetic control, but research indicates a strong genetic component in many, including cancer and heart disease.

Examination of sex chromosome abnormalities is an excellent chance to review meiosis, in terms of determining at what point of gametogenesis each nondisjunction occurs. One may want to discuss the sex chromosome tests associated with Olympic sports competition.

There are recent developments concerning the identification of a genetic marker associated with Huntington's disease. It may be worth while to discuss the moral and ethical implications of genetic therapy. Would you want to know whether or not you were going to develop the disease? Or perhaps worse, your children? Recent psychiatric studies show that those tested as possessing the gene for Huntington's disease do not become significantly depressed when faced with the news. Rather, they are less depressed than those who have not been tested or whose tests are inconclusive. (Southern blot / probe tests are 95% to 98% accurate in identifying this gene.) Genetics have been implicated in autoimmune diseases like multiple sclerosis and lupus as well.

There's a very interesting article on "genomic imprinting" in the December 1997 issue of *Equus*. The authors present the phenomenon of paternal imprinting as the reason that certain Thoroughbred sires are quality racehorses themselves, sire barely better-than-average progeny, but whose daughters produce again superb quality racehorses. They cite Secretariat as a most evident example.

VISUAL RESOURCES:

Many different kinds of apparatus are available to illustrate Mendelian genetics, including modeling clay and pop-it beads. Several very sophisticated bead kits are sold through biological supply houses; unfortunately, most are too small to be useful in a class larger than twenty-five students.

Much of the visual material is better handled in the lab, after initial exposure to the basics in the lecture. Try to keep the genetics-oriented lab instructors from showing too many of their own short-cuts. Have them stick to the old Punnett square. Students that derive short cuts on their own may gain a better understanding of the material.