Classical Mendelian Genetics

Objectives

1. Describe the characteristics of the model organisms for genetic studies.
2. Describe Mendel's experimental crosses, their results, and the conclusions he derived from them.
3. Define gene, allele, homozygous, heterozygous, dominant, recessive, genotype and phenotype.
4. State the principles of segregation and independent assortment.
5. Perform a monohybrid and dihybrid cross and determine the genotypic and phenotypic ratios.
6. Contrast autosomal dominant and autosomal recessive traits.
7. Use pedigree charts to determine the genotypes of individuals.

Outline

A. Model Organisms
    1. Characteristics
    2. Common Model Organisms
B. Single Gene Inheritance
    1. Experimental Design
        a. Parental (P_1) Generation
        b. First Filial (F_1) Generation
        c. Second Filial (F_2) Generation
        d. Third Filial (F_3) Generation
    2. Model for Genetic Inheritance
        a. Definitions
        b. Principle of Dominance
        c. Principle of Segregation
        d. Punnett Square
        e. Test Crosses
    3. Single Gene Traits in Humans
C. Multiple Gene Inheritance
    1. Experimental Design
        a. Parental (P_1) Generation
        b. First Filial (F_1) Generation
        c. Second Filial (F_2) Generation
        d. Third Filial (F_3) Generation
    2. Law of Independent Assortment
    3. Probability Calculations
D. Pedigrees

A. Model Organisms

1. Characteristics

- Small
- Fast growing
- Short generation time
- Easy to control mating
- Produce lots of progeny
- Inexpensive
- Small genomes

2. Common Model Organisms

- *Escherichia coli*
    - Single chromosome
    - Used to clone DNA from other species
- Yeast (*Saccharomyces cerevisiae*)
    - Haploid and diploid generations

- Fruit flies (*Drosophila*)

- Roundworm (*Caenorhabditis elegans*)
    - Transparent
    - Development well documented
        - Fate of every cell characterized

- Mouse (*Mus musculus*)
    - Animal model closest to humans
    - Used to characterize some human DNA

- Zebrafish (*Danio rerio*)
    - Develop outside mother
    - Transparent

- *Arabidopsis*
    - Easiest plant model

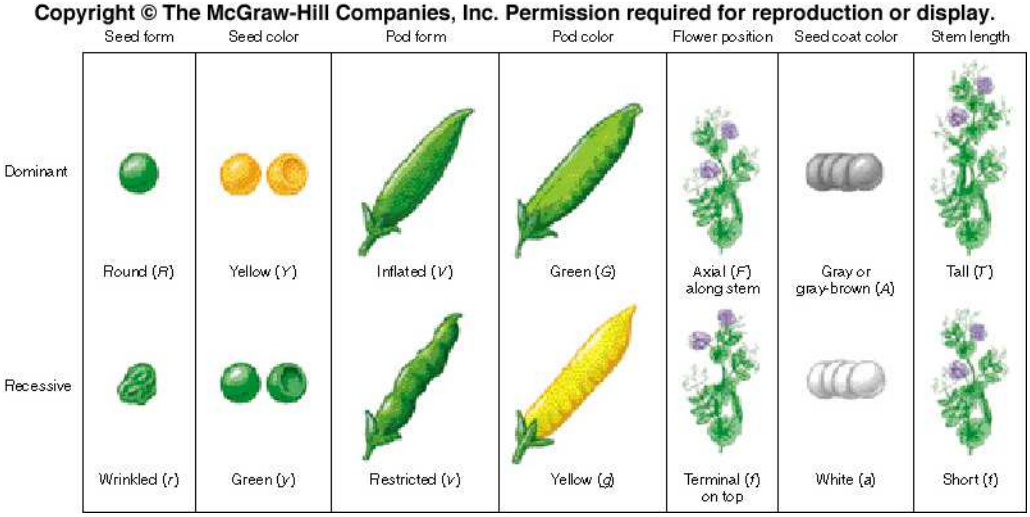
- Corn/Maize (*Zea mays*)

B. Single Gene Inheritance

1. Experimental Design

a. Parental (P_1) Generation

- Seven discrete true-breeding traits
    - No intermediate variant
    - Easy to distinguish
        - e.g., seed form, seed color, height

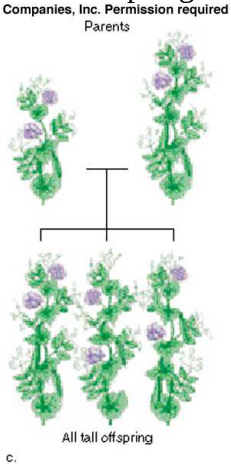


- Cross-pollinated opposite true-breeders
    - Monohybrid cross
    - "X" designates cross
        - e.g., TALL X SHORT

b. First Filial (F_1) Generation

- Offspring from P_1 cross

- All F_1 displayed only one of two traits
  - e.g., ALL offspring were TALL



  - Expressed trait – dominant

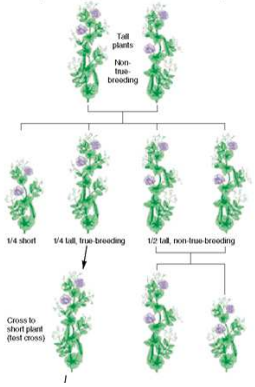
  - Trait not expressed – recessive

- F_1 generation self-pollinates

c. Second Filial (F_2) Generation

- Offspring from F_1 selfing

- Ratio – ¾ dominant, ¼ recessive
  - e.g., 787 TALL, 277 SHORT



- Repeated experiment with other traits
  - Always 3 dominant: 1 recessive

- While recessive trait not seen in F_1, recessive variant still present

d. Third Filial (F_3) Generation

- Offspring from F_2 selfing
  - Test of model from F_2
- Recessive phenotype
  - All true-breeders

- Dominant phenotypes
  - One-third are true breeders

  - Two-thirds are not
    - Phenotypic ratio of these offspring
    - ¾ dominant, ¼ recessive

2. Model for Genetic Inheritance

- How can a trait disappear in one generation, then reappear in ¼ of next?

a. Definitions

- Multiple forms of a gene

  - Allele

  - Locus (pl. loci)

- Offspring has two genes for each trait

  - Receives one from each parent

    - Homozygous

    - Heterozygous

- Genotype

- Phenotype

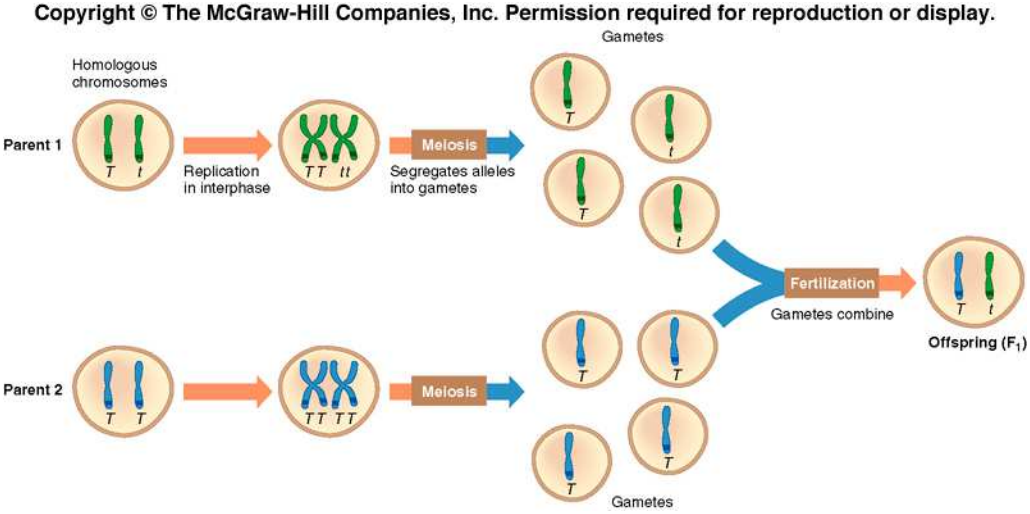
b. Mendel's Principle of Dominance

- Dominant

- Recessive

c. Principle of Segregation

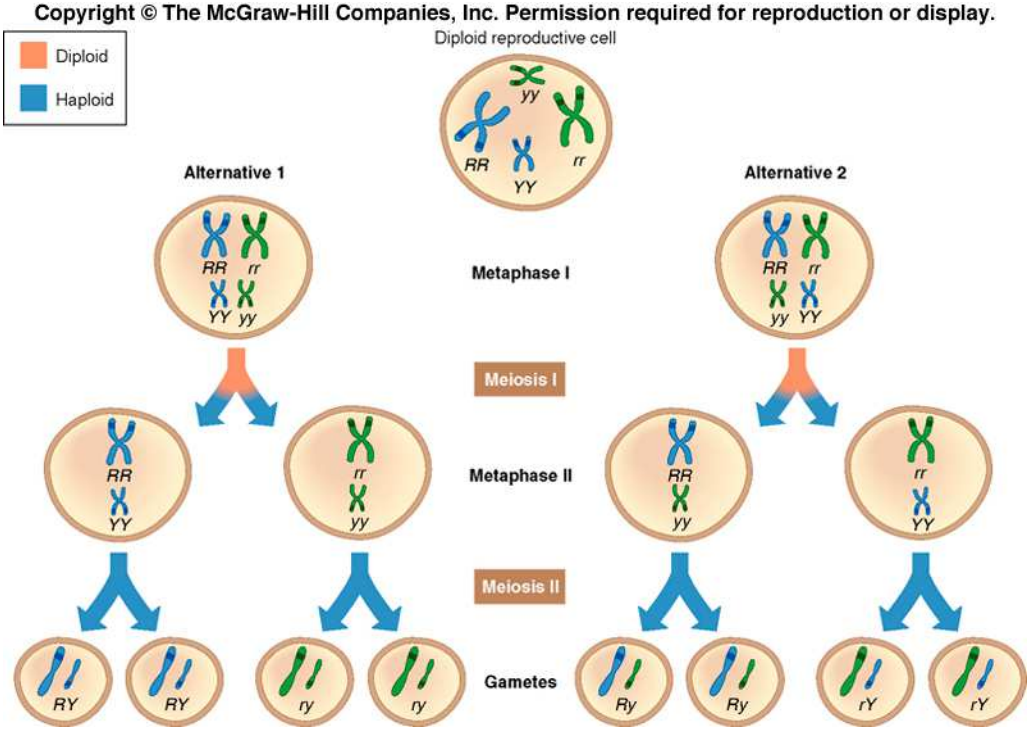
- Gametes carry only one allele for trait



- Fertilization restores two copies

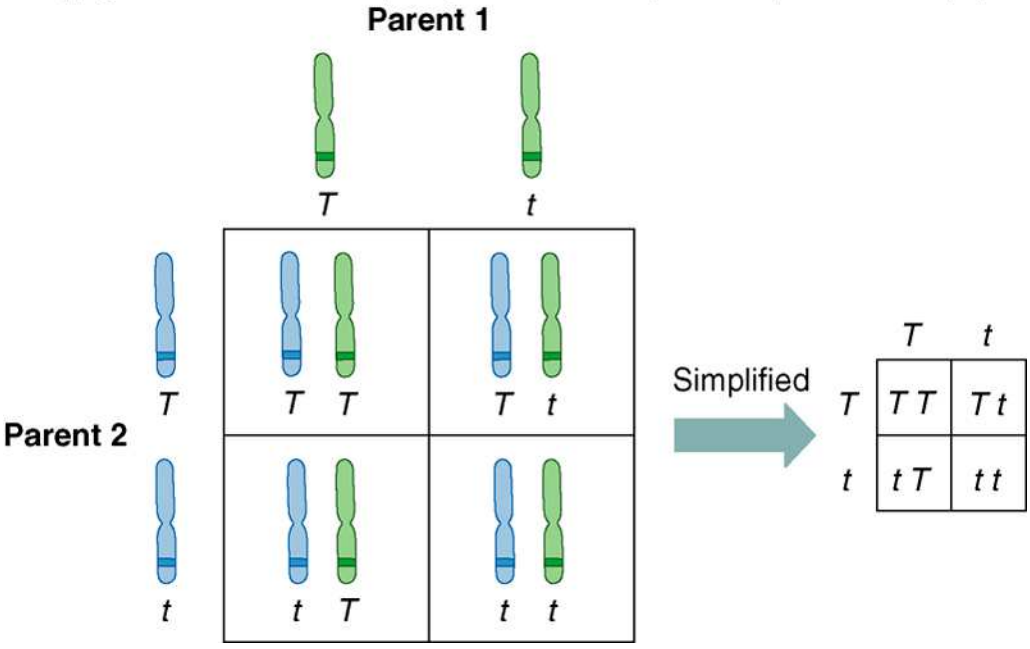
- Correlates with chromosome behavior during meiosis

  - Independent Assortment of Chromosomes



d. Punnett Square

- Does hypothesis fit data?
  - e.g., TALL X SHORT
    - P_1 – Tall (TT) X short (tt)
    - F_1 – All Tall (Tt)
    - F_2 – ¾ Tall : ¼ short
      - Phenotypic Ratio
    - ¼ TT : ½ Tt : ¼ tt
      - Genotypic Ratio



e. Test Crosses

- Determines genotype of dominant plant
- Test individual crossed with recessive
  - Recessive must be homozygous (tt)
- Possibilities
- All offspring dominant
  - Test individual homozygous dominant (TT)
- ½ offspring dominant, ½ recessive
  - Test individual heterozygous (Tt)

3. Single Gene Traits in Humans

- Mendelian or Unifactorial Traits

Table 4.2

Some Mendelian Disorders in Humans

Disorder	Symptoms
Autosomal Recessive	
Ataxia telangiectasis	Facial rash, poor muscular coordination, involuntary eye movements, high risk for cancer, sinus and lung infections
Cystic fibrosis	Lung infections and congestion, poor fat digestion, male infertility, poor weight gain, salty sweat
Familial hypertrophic cardiomyopathy	Overgrowth of heart muscle, causing sudden death in young adults
Gaucher disease	Swollen liver and spleen, anemia, internal bleeding, poor balance
Hemochromatosis	Body retains iron; high risk of infection, liver damage, excess skin pigmentation, heart and pancreas damage
Maple syrup urine disease	Lethargy, vomiting, irritability, mental retardation, coma, and death in infancy
Phenylketonuria	Mental retardation, fair skin
Sickle cell disease	Joint pain, spleen damage, high risk of infection
Tay-Sachs disease	Nervous system degeneration
Autosomal Dominant	
Achondroplasia	Dwarfism with short limbs, normal size head and trunk
Familial hypercholesterolemia	Very high serum cholesterol, heart disease
Huntington disease	Progressive uncontrollable movements and personality changes, beginning in middle age
Lactose intolerance	Inability to digest lactose, causing cramps after ingestion
Marfan syndrome	Long limbs, sunken chest, lens dislocation, spindly fingers, weakened aorta
Myotonic dystrophy	Progressive muscle wasting
Neurofibromatosis (I)	Brown skin marks, benign tumors beneath skin
Polycystic kidney disease	Cysts in kidneys, bloody urine, high blood pressure, abdominal pain
Polydactyly	Extra fingers and/or toes
Porphyria variegata	Red urine, fever, abdominal pain, headache, coma, death

- Autosomal Dominant
    - Needs to be present in only one parent
    - Generally “gain of function” mutation
    - Usually expressed after reproductive stage
- Autosomal Recessive
    - Must be present in both parents
        - Carriers
    - Generally “loss of function” mutation
        - Usually expressed earlier in life
        - Usually more severe

C. Multiple Gene Inheritance

1. Experimental Design
a. Parental (P_1) Generation

- Dihybrid cross
  - Cross-pollinated P_1's that bred true for two alternate traits

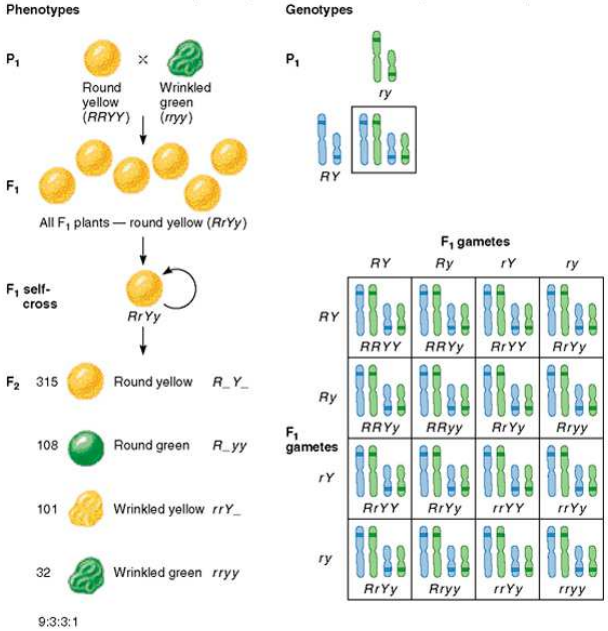
  - Double Dominant X Double Recessive
    - e.g., ROUND YELLOW (RRYY) X WRINKLED GREEN (rryy) seeds

b. First Filial (F_1) Generation

- All display both dominant traits
    - e.g., ALL offspring produced ROUND YELLOW (RrYy) seeds

- F_1 generation self-pollinates

c. Second Filial (F_2) Generation
- F_2 offspring
  - 9/16 Round Yellow
  - 3/16 Round green
  - 3/16 wrinkled Yellow
  - 1/16 wrinkled green



- Test crossed plants with double recessive
  - e.g., WRINKLED GREEN (rryy)

d. Third Filial (F_3) Generation

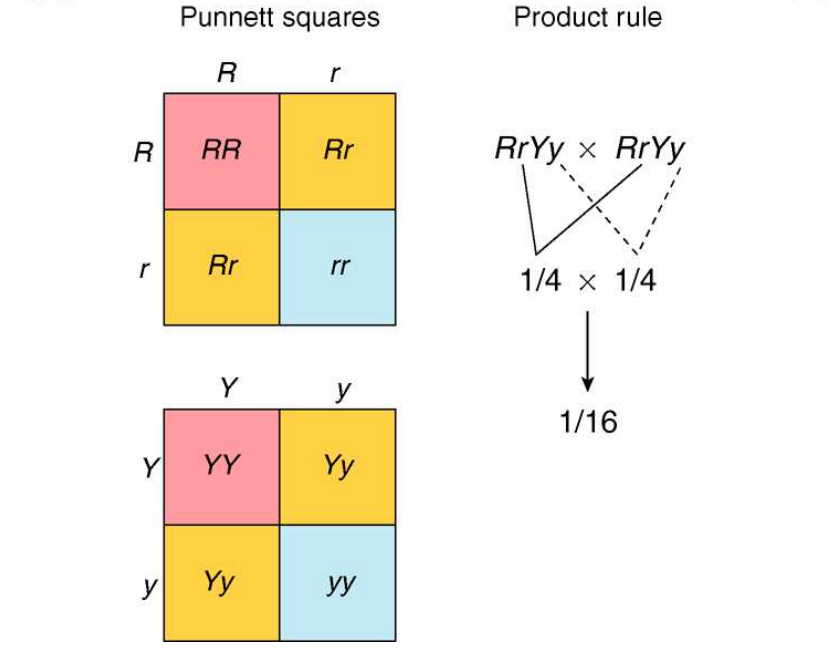
- Offspring from F_2 test cross

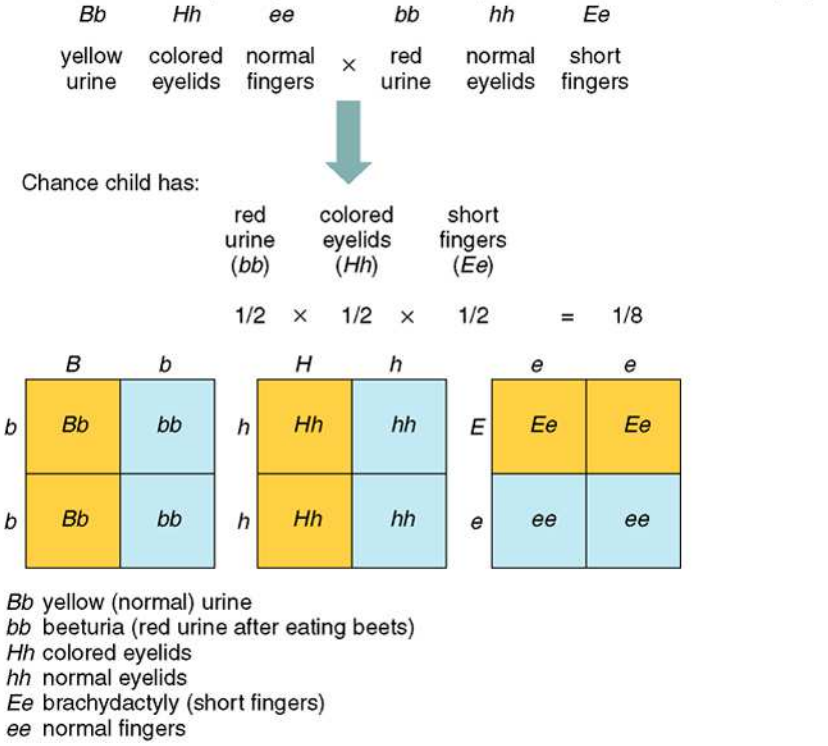
2. Law of Independent Assortment

- One gene does not influence transmission of another gene
    - Genes independent from each other
        - Not Linked
    - Creates non-P_1 phenotypes in F_2

3. Probability Calculations

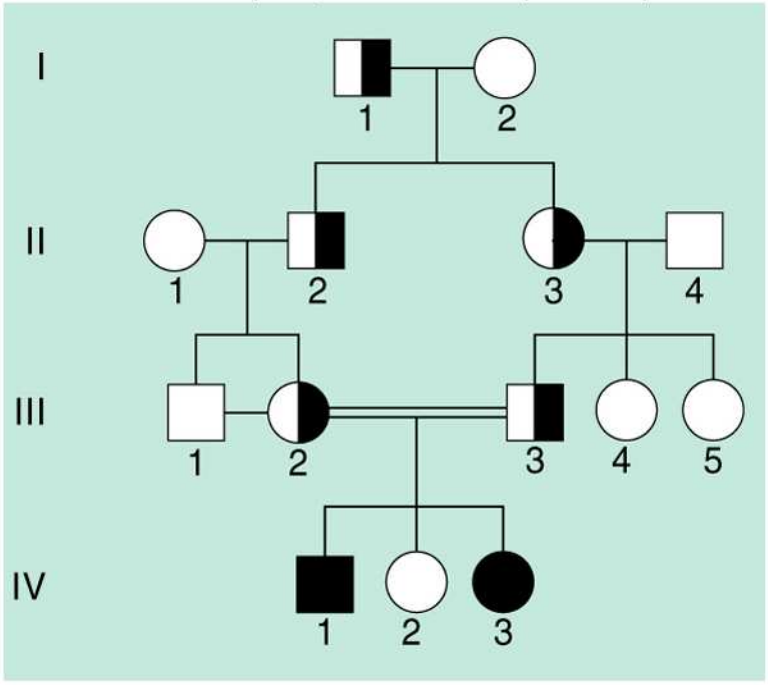
- Determine probability of any trait
    - fraction between 0 and 1
        - phenotype or genotype
- Multiply probabilities
    - Only works for independent events
    - any number of unlinked genes





D. Pedigrees

- Chart of familial relationships
    - Includes genealogy
    - Includes medically important traits
        - phenotypes, or better, genotypes



C.

Symbols

= Normal female, male

= Female, male who expresses trait

= Female, male who carries an allele for the trait but does not express it (carrier)

= Dead female, male

= Sex unspecified

= Stillbirth

= Pregnancy

= Spontaneous abortion (miscarriage)

= Terminated pregnancy (shade if abnormal)

Lines

= Generation

= Parents

= Adoption

= Siblings

= Identical twins

= Fraternal twins

= Parents closely related (by blood)

= Former relationship

= Person who prompted pedigree analysis (proband)

Numbers

Roman numerals = generations

Arabic numerals = individuals in a generation

- Recessive alleles

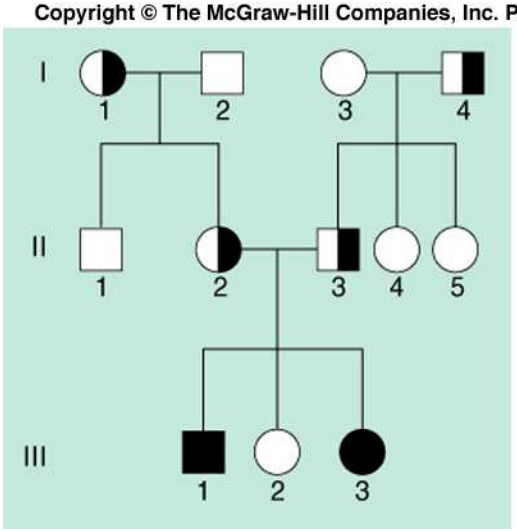


Table 4.4

Criteria for an Autosomal Recessive Trait

1. Males and females are affected.
2. Affected males and females can transmit the gene, unless it causes death before reproductive age.
3. The trait can skip generations.
4. Parents of an affected individual are heterozygous or have the trait.

- Dominant alleles

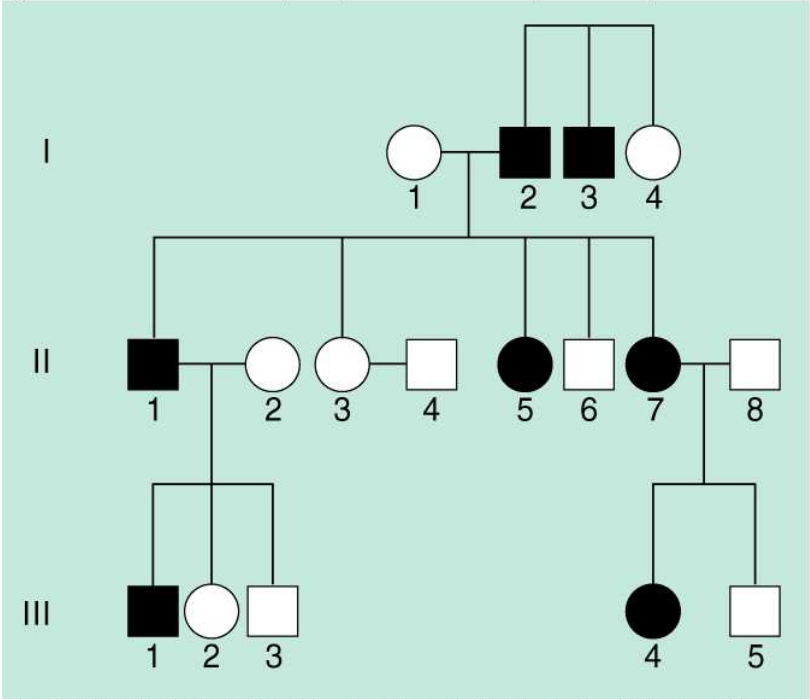
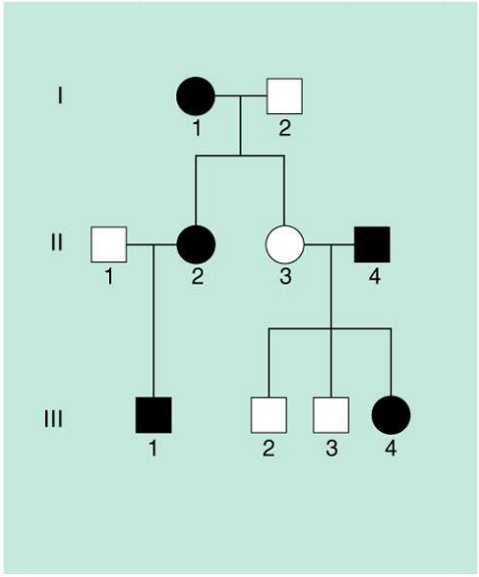


Table 4.3

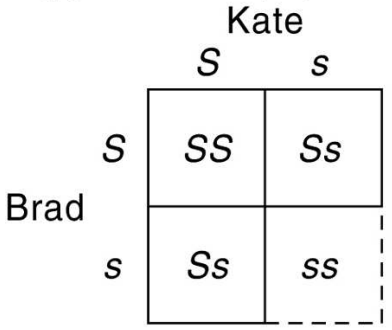
Criteria for an Autosomal Dominant Trait

1. Males and females can be affected. Male-to-male transmission can occur.
2. Males and females transmit the trait with equal frequency.
3. Successive generations are affected.
4. Transmission stops if a generation arises in which no one is affected.

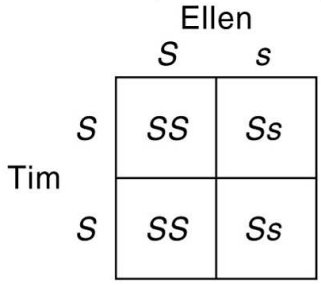
- Uses
  - Identifying mutant genes



  - Risk of transmitting inherited illness



b. Probability that Ellen is a carrier: $^2/_3$



c. If Ellen is a carrier, chance that fetus is a carrier: $^1/_2$

Total probability = $^2/_3 \times {}^1/_2 = {}^1/_3$