It's the Small Things That Make the Big Differences…
Mendelian Genetics

Mendel and the Garden Pea

- **Heredity** is the tendency for traits to be passed from parent to offspring
  - heritable features are called **characters**
    - **traits** are alternative forms of a character

- Before the discovery of DNA and chromosomes, principles of heredity were first identified by quantitative science (i.e., counting and measuring)
  - **Gregor Mendel** solved the puzzle of heredity

Gregor Mendel

- Gregor Mendel performed experiments with garden peas
  - peas are ideally suited to the study of heredity
    - many varieties are available with easily distinguishable traits that can be quantitified
    - they are small, easy to grow, and produce large numbers of offspring quickly
    - their reproductive organs can be easily manipulated so that pollination can be controlled
    - they can self-fertilize

- Mendel had a specific experimental design
  - he first established **true-breeding** varieties
    - by allowing plants to self-fertilize for several generations, he ensured that each variety contained only one type of trait
    - he named these pure lines the **P generation**
  - he then crossed two varieties exhibiting alternative traits
    - he named the resulting offspring the **F_1 generation**
  - he then allowed the plants from the F_1 generation to self-fertilize
    - he named the resulting offspring the **F_2 generation**

How Mendel conducted his experiments

What Mendel Observed

- Mendel experimented with a variety of traits and repeatedly made the same observations
  - for each pair of contrasting varieties that he crossed, one of the traits disappeared in the F1 generation but reappeared in the F2 generation
    - he called the trait expressed in the F1 generation the **dominant** trait
    - he named the trait not expressed in the F1 generation the **recessive trait**

- Mendel counted the number of each type of plant in the F2 generation
  - he found a consistent proportion in expressed traits for his different crosses

- three-fourths of the F2 individuals expressed the dominant trait while one-fourth expressed the recessive trait
- the dominant:recessive ratio among the F2 plants was always close to 3:1

Seven Characters Mendel Studied in his Experiments

- Mendel reasoned that the recessive trait must somehow be hidden in the F_1 generation but just not expressed

- He allowed the F_2 to self-fertilize and form the F_3 generation

  - he found that one-fourth of the plants from the F_2 that were recessive were true-breeding in the F_3

  - he found that of the three-fourths of the plants from the F_2

    - only one-third were true breeding in the F_3
    - the remaining half showed both traits

- He determined that the ratio of 3:1 ratio that he observed in the F_2 generation was in fact a disguised 1:2:1 ratio

1		2		1
true-breeding dominant	:	not true-breeding dominant	:	true-breeding recessive

The F_2 generation is a disguised 1:2:1 ratio

Mendel Proposes a Theory

- Mendel proposed a simple set of five hypotheses to explain his results

- Hypothesis 1
  - *parents do not transmit traits directly to their offspring*
  - parents transmit information about the trait in the form of what Mendel called factors
    - in modern terms, Mendel's factors as called **genes**

- Hypothesis 2
  - *each parent contains two copies of the factor governing each trait*
  - the two copies of the factor may or may not be the same
    - **homozygous** individuals have two of the same copies
    - **heterozygous** individuals have two different copies

- Hypothesis 3
  - *alternative forms of a factor lead to alternative traits*
  - **alleles** are defined as alternative forms of a factor

- appearance is determined by the alleles a plant receives from its parents
  - this is the plant's **genotype**
  - the expression of the alleles is the appearance or **phenotype**

- Hypothesis 4
  - *the two alleles that an individual possesses do not affect each other*

- Hypothesis 5
  - *the presence of an allele does not ensure that a trait will be expressed in the individual that carrier it*
  - in heterozygotes, only the dominant allele is expressed

Alternative alleles of genes are located on homologous chromosomes

Some Dominant and Recessive Traits in Humans

- By convention, genetic traits are assigned a letter symbol referring to their more common form
  - dominant traits are capitalized while a lower-case letter is reserved for the recessive trait
  - for example, flower color in peas is represented as follows
    - *P* signifies purple
    - *p* signifies white

- The results from a cross between a true-breeding, white-flowered plant (*pp*) and a true breeding, purple-flowered plant (*PP*) can be visualized with a **Punnett square**

- A Punnett square lists the possible gametes from one individual on one side of the square and the possible gametes from the other individual on the opposite side

- The genotypes of potential offspring are represented within the square

A Punnett square analysis

How Mendel analyzed flower color

- Mendel devised the **testcross** in order to determine the genotype of unknown individuals in the F_2 generation
  - the unknown individual is crossed with a homozygous recessive individual
    - if the unknown is homozygous, then all of the offspring will express dominant traits
    - if the unknown is heterozygous, then one-half of the offspring will express recessive traits

How Mendel used the testcross to detect heterozygotes

Mendel's Laws

- Mendel's hypotheses so neatly predict the results of his crosses that they have elevated to laws
  - **Mendel's First Law: Segregation**
    - *the two alleles of a trait separate from each other during the formation of gametes, so that half of the gametes will carry one copy and half will carry the other copy*

- Mendel also investigated the inheritance pattern for more than one factor
  - when crossing individuals who are true-breeding for two different characters, the F1 individual that results is a **dihybrid**
  - after the dihybrid individuals self-fertilize, there are 16 possible genotypes of offspring

Analysis of a dihybrid cross

- Mendel concluded that for the pairs of traits that he studied, the inheritance of one trait does not influence the inheritance of the other trait
  - **Mendel's Second Law: Independent Assortment**
    - *genes located on different chromosomes are inherited independently of one another*

The journey from DNA to phenotype

Why Some Traits Don't Show Mendelian Inheritance

- Often the expression of phenotype is not straightforward

- **Continuous variation**
  - characters can show a range of small differences when multiple genes act jointly to influence a character
    - this type of inheritance is called **polygenic**

Height is a continuously varying character

- **Pleiotropic effects**
  - an allele that has more than one effect on a phenotype is considered **pleiotropic**
  - these effects are characteristic of many inherited disorders, such as cystic fibrosis and sickle-cell anemia

Pleiotropic effects of the cystic fibrosis gene

- **Incomplete dominance**
  - not all alternative alleles are either fully dominant or fully recessive in heterozygotes
    - in such cases, the alleles exhibit **incomplete dominance** and produce a heterozygous phenotype that is intermediate between those of the parents

Incomplete dominance

- **Environmental effects**
  - the degree to which many alleles are expressed depends on the environment
  - for example, some alleles are heat-sensitive
    - arctic foxes only produce fur pigment when temperatures are warm
    - the *ch* allele in Himalayan rabbits and Siamese cats encodes a heat-sensitive enzyme, called tyrosinase, that controls pigment production
      - tyrosinase is inactive at high temperatures

Environmental effects on an allele

- **Epistasis**
  - in some situations, two or more genes interact with each other, such that one gene contributes to or masks the expression of the other gene
  - in **epistasis**, one gene modifies the phenotypic expression produced by the other
  - for example, in corn, to produce and deposit pigment, a plant must possess at least one function copy of each of two genes
    - one gene controls pigment deposition
    - the other gene controls pigment production

How epistasis affects kernel color

The effect of epistatic interactions on coat color in dogs

- **Codominance**
  - a gene may have more than two alleles in a population
    - often, in heterozygotes, there is not a dominant allele but, instead, both alleles are expressed
    - these alleles are said to be **codominant**

- The gene that determines ABO blood type in humans exhibits more than one dominant allele
  - the gene encodes an enzyme that adds sugars to lipids on the membranes of red blood cells
  - these sugars act as recognition markers for cells in the immune system
  - the gene that encodes the enzyme, designated *I,* has three alleles: I^A,I^B, and *i*
    - different combinations of the three alleles produce four different phenotypes, or bloodtypes (A, B, AB, and O)
    - both I^A and I^B are dominant over *i* and also codominant

Multiple alleles controlling the ABO blood groups

Chromosomes Are the Vehicles of Mendelian Inheritance

- **The chromosomal theory of inheritance** was first proposed in 1902 by Walter Sutton
  - supported by several pieces of evidence
    - reproduction involves the initial union of only eggs and sperm
      - each gamete contains only copy of the genetic information
      - since sperm have little cytoplasm, the material contributed must reside in the nucleus
    - chromosomes both segregate and assort independently during meiosis

- A potential problem with the chromosomal theory of inheritance is that there are many more traits that assort independently than there are chromosomes

- Experimental study of the fruit fly, *Drosophila melanogaster*, by Thomas Hunt Morgan provided confirmation of the chromosomal theory of inheritance

- Morgan discovered, in 1910, a mutant male fruit fly who had white eyes instead of the typical red
  - he tried to determine whether this trait would be inherited by the Mendelian pattern
    - he crossed a mutant male with a normal female
    - as predicted, eye color segregated and all the F_1 individuals had red eyes
    - but, in the F_2 generation, only males were white-eyed and not females

- Morgan determined that sex was key to explaining the results of his cross
  - in fruit flies, sex is determined by the number of copies of a particular chromosome, the **X chromosome**, that an individual possesses
    - a fly with two X chromosomes is female
    - in male flies, there is only one X chromosome and that is paired with a **Y chromosome**

- Morgan reasoned that the white-eyed trait resided only on the X chromosome
  - a trait determined by a gene on the sex chromosome is said to be **sex-linked**

Morgan's experiment demonstrating the chromosomal basis of sex linkage

- Morgan's demonstration of sex linkage in *Drosophila* confirmed the chromosomal theory of inheritance that Mendelian traits reside on chromosomes
  - it also explains why Mendel's First Law of Segregation works
    - traits assort independently because chromosomes assort independently

Human Chromosomes

- Each human somatic cell normally has 46 chromosomes, which in meiosis form 23 pairs
  - 22 of the 23 pairs are perfectly matched in both males and females and are called **autosomes**

- 1 pair are the **sex chromosomes**
  - females are designated XX while males are designated XY
  - the genes on the Y chromosome determine "maleness"

- Sometimes errors occur during meiosis
  - **nondisjunction** is the failure of chromosome to separate correctly during either meiosis I or meiosis II
    - this leads to **aneuploidy**, an abnormal chromosome number
    - most of these abnormalities cause a failure to develop or an early death before adulthood
    - in contrast individuals with an extra copy of chromosome 21 or, more rarely, chromosome 22 can survive to adulthood
      - however, these individuals have delayed development and mental impairment
      - **Down syndrome** is caused by having an extra copy of chromosome 21

Nondisjunction in anaphase I
Down Syndrome

- Nondisjunction may also affect the sex chromosomes
  - nondisjunction of the X chromosome creates three possible viable conditions
    - XXX female
      - usually taller than average but other symptoms vary
    - XXY male (Klinefelter syndrome)
      - sterile male with many female characteristics and diminished mental capacity
    - XO female (Turner syndrome)
      - sterile female with webbed neck and diminished stature

Nondisjunction of the X chromosome

- Nondisjunction of the Y chromosome also occurs
  - in such cases, YY gametes are formed, leading to XYY males
  - these males are fertile and of normal appearance

The Role of Mutations in Human Heredity

- Accidental changes in genes are called **mutations**
  - mutations occur only rarely and almost always result in recessive alleles
    - not eliminated from the population because they are not usually expressed in most individuals (heterozygotes)
    - in some cases, particular mutant alleles have become more common in human populations and produce harmful effects called **genetic disorders**

Some Important Genetic Disorders

- To study human heredity, scientists examine crosses that have already been made
  - the identiy which relatives exhibit a trait by looking at family trees or **pedigree**
  - often one can determine whether a trait is sex-linked or autosomal and whether the trait's phenotype is dominant or recessive
    - for example, hemophilia is a sex-linked trait

A general pedigree

The Royal hemophilia pedigree

- **Sickle-cell anemia** is a recessive hereditary disorder
  - affected individuals are homozygous recessive and carry a mutated gene that produces a defective version of hemoglobin
    - the hemoglobin sticks together inappropriately and produces a stiff red blood cell with a sickle-shape
    - the cells cannot move through the blood vessels easily and tends to clot
      - this causes sufferers to have intermittent illness and shortened life spans

- The sickle-cell mutation to hemoglobin affects the stickiness of the hemoglobin protein surface but not its oxygen-binding ability
- Heterozygous individuals have some of their red blood cells become sickled when oxygen levels become low
  - this may explain why the sickle-cell allele is so frequent among people of African descent
    - the presence of the allele increases resistance to malaria infection

Sickle-cell Anemia

- **Tay-Sachs disease** is another disease caused by a recessive allele
  - it is an incurable disorder in which the brain deteriorates
  - sufferers rarely live beyond five years of age

- **Huntington's disease** is a genetic disorder caused by a dominant allele
  - it causes progressive deterioration of brain cells
  - every individual who carries the allele expresses the disorder but most persons do not know they are affected until they are more than 30 years old

Huntington's disease is a dominant genetic disorder

Genetic Counseling and Therapy

- **Genetic counseling** is the process of identifying parents at risk of producing children with genetic defects and of assessing the genetic state of early embryos

- One method of genetic counseling focuses on identify high-risk pregnancies
  - through pedigree analysis, one can identify the chances of both parents being heterozygote carriers of an allele for a recessive genetic disorder
  - high-risk pregnancies are also identified when the mothers are more than 35 years old

- Genetic counselors also utilize genetic screening
  - **amniocentesis** is when amniotic fluid is sampled and isolated fetal cells are then grown in culture and analyzed
  - **chorionic villus sampling** is when fetal cells from the chorion in the placenta are removed for analysis

Amniocentesis

- Genetic counselors look at three things from the cell cultures obtained from either amniocentesis or chorionic villus sampling
  - **chromosomal karyotype**
    - analysis can reveal aneuploidy or gross chromosomal alterations
  - **enzyme activity**
    - in some cases, it is possible to test directly for the proper functioning of enzymes associated with genetic disorders
  - **genetic markers**
    - test for the presence of mutations at the same place on chromosomes where disorder-causing mutations are found

- **DNA screening** is the most recent form of genetic counseling and screens DNA for the presence of key genes
  - utilizing information from the Human Genome Project, the DNA of patients is assessed for copies of genes that lead to hereditary disorders, such as cystic fibrosis and muscular dystrophy
  - in addition, parents conceiving by in vitro fertilization (i.e., test-tube babies) can screen zygotes for potential genetic anomalies
    - this procedure is called **preimplantation screening**

Pre-implantation genetic diagnosis