- Many genes exist in populations in more than two allelic forms.
- The ABO blood groups in humans are determined by three alleles, I^A, I^B, and i.
  - Both the I^A and I^B alleles are dominant to the i allele.
  - The I^A and I^B alleles are codominant to each other.
- Because each individual carries two alleles, there are six possible genotypes and four possible blood types.
  - Individuals that are I^AI^A or I^Ai are type A and have type A carbohydrates on the surface of their red blood cells.
  - Individuals that are I^BI^B or I^Bi are type B and have type B carbohydrates on the surface of their red blood cells.
  - Individuals that are I^AI^B are type AB and have both type A and type B carbohydrates on the surface of their red blood cells.
  - Individuals that are ii are type O and have neither carbohydrate on the surface of their red blood cells.
- Matching compatible blood groups is critical for blood transfusions because a person produces antibodies against foreign blood factors.
  - If the donor's blood has an A or B carbohydrate that is foreign to the recipient, antibodies in the recipient's blood will bind to the foreign molecules, cause the donated blood cells to clump together, and can kill the recipient.
- The genes that we have covered so far affect only one phenotypic character.
- However, most genes are **pleiotropic,** affecting more than one phenotypic character.
  - For example, the wide-ranging symptoms of sickle-cell disease are due to a single gene.
- Considering the intricate molecular and cellular interactions responsible for an organism's development, it is not surprising that a gene can affect a number of characteristics.
- In **epistasis,** a gene at one locus alters the phenotypic expression of a gene at a second locus.
  - For example, in mice and many other mammals, coat color depends on two genes.
  - One, the epistatic gene, determines whether pigment will be deposited in hair or not.
    - Presence (C) is dominant to absence (c) of pigment.
  - The second gene determines whether the pigment to be deposited is black (B) or brown (b).
    - The black allele is dominant to the brown allele.
  - An individual that is cc has a white (albino) coat regardless of the genotype of the second gene.
- A cross between two black mice that are heterozygous ($BbCc$) will follow the law of independent assortment.
- However, unlike the 9:3:3:1 offspring ratio of a normal Mendelian experiment, the offspring ratio is nine black, three brown, and four white.
- All cc mice will be albino, regardless of the alleles they inherit at the B gene.
- Some characters cannot be classified as either-or, as Mendel's genes were.
- **Quantitative characters** vary in a population along a continuum.
- These are usually due to **polygenic inheritance,** the additive effects of two or more genes on a single phenotypic character.
  - For example, skin color in humans is controlled by at least three independent genes.

- Imagine that each gene has two alleles, one light and one dark, which demonstrate incomplete dominance.
- An *AABBCC* individual is very dark; an *aabbcc* individual is very light.

- A cross between two *AaBbCc* individuals (with intermediate skin shade) will produce offspring covering a wide range of shades.
  - Individuals with intermediate skin shades will be most common, but some very light and very dark individuals could be produced as well.
  - The range of phenotypes will form a normal distribution, if the number of offspring is great enough.
- Phenotype depends on environment and genes.
  - A person becomes darker if they tan, despite their inherited skin color.
  - A single tree may have leaves that vary in size, shape, and greenness, depending on exposure to wind and sun.
  - For humans, nutrition influences height, exercise alters build, sun-tanning darkens skin, and experience improves performance on intelligence tests.
  - Even identical twins, who are genetically identical, accumulate phenotypic differences as a result of their unique experiences.
- The relative importance of genes and the environment in influencing human characteristics is a very old and hotly contested debate.
- The product of a genotype is generally not a rigidly defined phenotype, but a range of phenotypic possibilities, the **norm of reaction,** that are determined by the environment.
  - In some cases, the norm of reaction has no breadth, and a given genotype specifies a particular phenotype (for example, blood type).
  - In contrast, a person's red and white blood cell count varies with factors such as altitude, customary exercise level, and presence of infection.
- Norms of reaction are broadest for polygenic characters.
  - For these **multifactorial characters,** environment contributes to their quantitative nature.
- A reductionist emphasis on single genes and single phenotypic characters presents an inadequate perspective on heredity and variation.
- A more comprehensive theory of Mendelian genetics must view organisms as a whole.
- The term *phenotype* can refer not only to specific characters such as flower color or blood group, but also to an organism in its entirety, including all aspects of its physical appearance.
- *Genotype* can refer not just to a single genetic locus, but also to an organism's entire genetic makeup.
- An organism's phenotype reflects its overall genotype and its unique environmental history.

C. Mendelian Inheritance in Humans

- While peas are convenient subjects for genetic research, humans are not.
  - The generation time is too long, fecundity is too low, and breeding experiments are unacceptable.
- Yet humans are subject to the same rules governing inheritance as other organisms.
- New techniques in molecular biology have led to many breakthrough discoveries in the study of human genetics.

1. Pedigree analysis reveals Mendelian patterns in human inheritance.

- Rather than manipulate mating patterns of people, geneticists analyze the results of matings that have already occurred.
- In a **pedigree** analysis, information about the presence or absence of a particular phenotypic trait is collected from as many individuals in a family as possible, across generations.
- The distribution of these characters is then mapped on the family tree.
  - For example, the occurrence of widow's peak (*W*) is dominant to a straight hairline (*w*).
  - Phenotypes of family members and knowledge of dominant/recessive relations between alleles allow researchers to predict the genotypes of members of this family.
  - For example, if an individual in the third generation lacks a widow's peak, but both her parents have widow's peaks, then her parents must be heterozygous for that gene.
  - If some siblings in the second generation lack a widow's peak and one of the grandparents (first generation) also lacks one, then we know the other grandparent must be heterozygous, and we can determine the genotype of many other individuals.
- We can use the same family tree to trace the distribution of attached earlobes (*f*), a recessive characteristic.
- Individuals with a dominant allele (*F*) have free earlobes.
- Some individuals may be ambiguous, especially if they have the dominant phenotype and could be heterozygous or homozygous dominant.
- A pedigree can help us understand the past and predict the future.
- We can use normal Mendelian rules, including multiplication and addition, to predict the probability of specific phenotypes.
  - For example, these rules could be used to predict the probability that a child with *WwFf* parents will have a widow's peak and attached earlobes.
    - The chance of having a widow's peak is 3/4 (1/2 [*WW*] + 1/4 [*Ww*]).
    - The chance of having attached earlobes is 1/4 [*ff*].
    - This combination has a probability of $3/4 \times 1/4 = 3/16$.

2. Many human disorders follow Mendelian patterns of inheritance.

- Thousands of genetic disorders, including disabling or deadly hereditary diseases, are inherited as simple recessive traits.
  - These conditions range from relatively mild (albinism) to life-threatening (cystic fibrosis).
- The recessive behavior of the alleles causing these conditions occurs because the allele codes for a malfunctioning protein or for no protein at all.
  - Heterozygotes have a normal phenotype because one normal allele produces enough of the required protein.
- A recessively inherited disorder shows up only in homozygous individuals who inherit a recessive allele from each parent.
- Individuals who lack the disorder are either homozygous dominant or heterozygotes.
- While heterozygotes may lack obvious phenotypic effects, they are **carriers** who may transmit a recessive allele to their offspring.
- Most people with recessive disorders are born to carriers with normal phenotypes.
  - Two carriers have a 1/4 chance of having a child with the disorder, 1/2 chance of having a child who is a carrier, and 1/4 chance of having a child without a defective allele.

- Genetic disorders are not evenly distributed among all groups of humans.
- This results from the different genetic histories of the world's people during times when populations were more geographically and genetically isolated.
- **Cystic fibrosis** strikes one of every 2,500 whites of European descent.
  - One in 25 people of European descent is a carrier for this condition.
  - The normal allele for this gene codes for a membrane protein that transports Cl^- between cells and extracellular fluid.
  - If these channels are defective or absent, there are abnormally high extracellular levels of chloride.
  - This causes the mucus coats of certain cells to become thicker and stickier than normal.
  - This mucus buildup in the pancreas, lungs, digestive tract, and elsewhere causes poor absorption of nutrients, chronic bronchitis, and bacterial infections.
  - Without treatment, affected children die before five, but with treatment, they can live past their late 20s or even 30s.
- **Tay-Sachs disease** is another lethal recessive disorder.
  - It is caused by a dysfunctional enzyme that fails to break down specific brain lipids.
  - The symptoms begin with seizures, blindness, and degeneration of motor and mental performance a few months after birth.
  - Inevitably, the child dies after a few years.
  - Among Ashkenazic Jews (those from central Europe), this disease occurs in one of 3,600 births, about 100 times greater than the incidence among non-Jews or Mediterranean (Sephardic) Jews.
- The most common inherited disease among people of African descent is **sickle-cell disease,** which affects one of 400 African-Americans.
  - Sickle-cell disease is caused by the substitution of a single amino acid in hemoglobin.
  - When oxygen levels in the blood of an affected individual are low, sickle-cell hemoglobin aggregate into long rods that deform red blood cells into a sickle shape.
  - This sickling creates a cascade of symptoms, demonstrating the pleiotropic effects of this allele, as sickled cells clump and clog capillaries throughout the body.
- Doctors can use regular blood transfusions to prevent brain damage and new drugs to prevent or treat other problems.
- At the organismal level, the nonsickle allele is incompletely dominant to the sickle-cell allele.
  - Carriers are said to have *sickle-cell trait.*
  - These individuals are usually healthy, although some suffer some symptoms of sickle-cell disease under blood oxygen stress.
- At the molecular level, the two alleles are codominant as both normal and abnormal (sickle-cell) hemoglobins are synthesized.
- About one in ten African-Americans has sickle-cell trait.
  - The high frequency of heterozygotes is unusual for an allele with severe detrimental effects in homozygotes.
  - Individuals with one sickle-cell allele have increased resistance to malaria, a parasite that spends part of its life cycle in red blood cells.
  - In tropical Africa, where malaria is common, the sickle-cell allele is both a boon and a bane.

    - Homozygous normal individuals die of malaria and homozygous recessive individuals die of sickle-cell disease, while carriers are relatively free of both.
- The relatively high frequency of sickle-cell trait in African-Americans is a vestige of their African roots.
- Normally it is relatively unlikely that two carriers of the same rare, harmful allele will meet and mate.
- However, consanguineous matings between close relatives increase the risk.
    - Individuals who share a recent common ancestor are more likely to carry the same recessive alleles.
- Most societies and cultures have laws or taboos forbidding marriages between close relatives.
- Although most harmful alleles are recessive, a number of human disorders are due to dominant alleles.
- For example, *achondroplasia,* a form of dwarfism, has an incidence of one case in 25,000 people.
    - Heterozygous individuals have the dwarf phenotype.
    - Those who are not achondroplastic dwarfs, 99.99% of the population, are homozygous recessive for this trait.
    - This provides another example of a trait for which the recessive allele is far more prevalent than the dominant allele.
- Lethal dominant alleles are much less common than lethal recessives.
    - If a lethal dominant kills an offspring before it can mature and reproduce, the allele will not be passed on to future generations.
    - In contrast, a lethal recessive allele can be passed on by heterozygous carriers who have normal phenotypes.
- A lethal dominant allele can escape elimination if it causes death at a relatively advanced age, after the individual has already passed on the lethal allele to his or her children.
- One example is **Huntington's disease,** a degenerative disease of the nervous system.
    - The dominant lethal allele has no obvious phenotypic effect until an individual is about 35 to 45 years old.
    - The deterioration of the nervous system is irreversible and inevitably fatal.
- Any child born to a parent who has the allele for Huntington's disease has a 50% chance of inheriting the disease and the disorder.
- In the United States, this devastating disease afflicts one in 10,000 people.
- Recently, molecular geneticists have used pedigree analysis of affected families to track the Huntington's allele to a locus near the tip of chromosome 4.
    - This has led to the development of a test that can detect the presence of the Huntington's allele in an individual's genome.
- While some diseases are inherited in a simple Mendelian fashion due to alleles at a single locus, many other disorders have a multifactorial basis.
    - These may have a genetic component plus a significant environmental influence.
    - Multifactorial disorders include heart disease; diabetes; cancer; alcoholism; and certain mental illnesses, such as schizophrenia and manic-depressive disorder.
    - The genetic component of such disorders is typically polygenic.
- At present, little is understood about the genetic contribution to most multifactorial diseases.

- The best public health strategy is education about relevant environmental factors and promotion of healthy behavior.

3. Technology is providing new tools for genetic testing and counseling.

- A preventive approach to simple Mendelian disorders is sometimes possible.
- The risk that a particular genetic disorder will occur can sometimes be assessed before a child is conceived or early in pregnancy.
- Many hospitals have genetic counselors to provide information to prospective parents who are concerned about a family history of a specific disease.
- Consider a hypothetical couple, John and Carol, who are planning to have their first child.
- In both of their families' histories, a recessive lethal disorder is present. Both John and Carol had brothers who died of the disease.
  - While not one of John, Carol, or their parents have the disease, their parents must have been carriers (*Aa* × *Aa*).
  - John and Carol each have a 2/3 chance of being carriers and a 1/3 chance of being homozygous dominant.
  - The probability that their first child will have the disease is 2/3 (chance that John is a carrier) × 2/3 (chance that Carol is a carrier) × 1/4 (chance that the offspring of two carriers is homozygous recessive) = 1/9.
  - If their first child is born with the disease, we know that John and Carol's genotype must be *Aa* and they are both carriers.
  - In that case, the chance that their next child will also have the disease is 1/4.
- Mendel's laws are simply the rules of probability applied to heredity.
  - Because chance has no memory, the genotype of each child is unaffected by the genotypes of older siblings.
  - The chance that John and Carol's first three children will have the disorder is 1/4 × 1/4 × 1/4 = 1/64. Should that outcome happen, the likelihood that a fourth child will also have the disorder is still 1/4.
- Because most children with recessive disorders are born to parents with a normal phenotype, the key to assessing risk is identifying whether prospective parents are carriers of the recessive trait.
- Recently developed tests for several disorders can distinguish normal phenotypes in heterozygotes from homozygous dominants.
  - These results allow individuals with a family history of a genetic disorder to make informed decisions about having children.
  - However, issues of confidentiality, discrimination, and counseling may arise.
- Tests are also available to determine *in utero* if a child has a particular disorder.
- One technique, **amniocentesis,** can be used from the 14th to 16th week of pregnancy to assess whether the fetus has a specific disease.
  - Fetal cells extracted from amniotic fluid are cultured and karyotyped to identify some disorders.
  - Other disorders can be identified from chemicals in the amniotic fluids.
- A second technique, **chorionic villus sampling (CVS)** allows faster karyotyping and can be performed as early as the eighth to tenth week of pregnancy.
  - This technique extracts a sample of fetal tissue from the chorionic villi of the placenta.

- This technique is not suitable for tests requiring amniotic fluid.

- Other techniques, *ultrasound* and *fetoscopy,* allow fetal health to be assessed visually *in utero.*
  - Both fetoscopy and amniocentesis cause complications such as maternal bleeding or fetal death in about 1% of cases.
  - Therefore, these techniques are usually reserved for cases in which the risk of a genetic disorder or other type of birth defect is relatively great.
- If fetal tests reveal a serious disorder, the parents face the difficult choice of terminating the pregnancy or preparing to care for a child with a genetic disorder.
- Some genetic traits can be detected at birth by simple tests that are now routinely performed in hospitals.
- One test can detect the presence of a recessively inherited disorder, phenylketonuria (PKU).
  - This disorder occurs in one in 10,000 to 15,000 births.
  - Individuals with this disorder accumulate the amino acid phenylalanine and its derivative phenylpyruvate in the blood to toxic levels.
    - This leads to mental retardation.
  - If the disorder is detected, a special diet low in phenylalanine usually promotes normal development.
  - Unfortunately, few other genetic diseases are so treatable.