Chapter 14

Mendel and the Gene Idea

Lecture Outline

Overview

- Every day we observe heritable variations (such as brown, green, or blue eyes) among individuals in a population.
- These traits are transmitted from parents to offspring.
- One possible explanation for heredity is a "blending" hypothesis.
  - This hypothesis proposes that genetic material contributed by each parent mixes in a manner analogous to the way blue and yellow paints blend to make green.
  - With blending inheritance, a freely mating population will eventually give rise to a uniform population of individuals.
  - Everyday observations and the results of breeding experiments tell us that heritable traits do not blend to become uniform.
- An alternative model, "particulate" inheritance, proposes that parents pass on discrete heritable units, genes, that retain their separate identities in offspring.
  - Genes can be sorted and passed on, generation after generation, in undiluted form.
- Modern genetics began in an abbey garden, where a monk named Gregor Mendel documented a particulate mechanism of inheritance.

A. Gregor Mendel's Discoveries

1. Mendel brought an experimental and quantitative approach to genetics.

- Mendel discovered the basic principles of heredity by breeding garden peas in carefully planned experiments.
- Mendel grew up on a small farm in what is today the Czech Republic.
- In 1843, Mendel entered an Augustinian monastery.
- He studied at the University of Vienna from 1851 to 1853, where he was influenced by a physicist who encouraged experimentation and the application of mathematics to science and by a botanist who stimulated Mendel's interest in the causes of variation in plants.
- These influences came together in Mendel's experiments.
- After university, Mendel taught at the Brunn Modern School and lived in the local monastery.
- The monks at this monastery had a long tradition of interest in the breeding of plants, including peas.
- Around 1857, Mendel began breeding garden peas to study inheritance.
- Pea plants have several advantages for genetic study.

- Pea plants are available in many varieties with distinct heritable features, or **characters,** with different variant **traits.**
- Mendel could strictly control which plants mated with which.
- Each pea plant has male (stamens) and female (carpal) sexual organs.
- In nature, pea plants typically self-fertilize, fertilizing ova with the sperm nuclei from their own pollen.
- However, Mendel could also use pollen from another plant for cross-pollination.

- Mendel tracked only those characters that varied in an "either-or" manner, rather than a "more-or-less" manner.
  - For example, he worked with flowers that were either purple or white.
  - He avoided traits, such as seed weight, that varied on a continuum.
- Mendel started his experiments with varieties that were **true-breeding.**
  - When true-breeding plants self-pollinate, all their offspring have the same traits.
- In a typical breeding experiment, Mendel would cross-pollinate **(hybridize)** two contrasting, true-breeding pea varieties.
  - The true-breeding parents are the **P generation,** and their hybrid offspring are the **F_1 generation.**
- Mendel would then allow the F_1 hybrids to self-pollinate to produce an **F_2 generation.**
- It was mainly Mendel's quantitative analysis of F_2 plants that revealed two fundamental principles of heredity: the law of segregation and the law of independent assortment.

2. By the law of segregation, the two alleles for a character are separated during the formation of gametes.

- If the blending model was correct, the F_1 hybrids from a cross between purple-flowered and white-flowered pea plants would have pale purple flowers.
- Instead, F_1 hybrids all have purple flowers, just as purple as their purple-flowered parents.
- When Mendel allowed the F_1 plants to self-fertilize, the F_2 generation included both purple-flowered and white-flowered plants.
  - The white trait, absent in the F_1, reappeared in the F_2.
- Mendel used very large sample sizes and kept accurate records of his results.
  - Mendel recorded 705 purple-flowered F_2 plants and 224 white-flowered F_2 plants.
  - This cross produced a traits ratio of three purple to one white in the F_2 offspring.
- Mendel reasoned that the heritable factor for white flowers was present in the F_1 plants, but did not affect flower color.
  - Purple flower color is a *dominant* trait, and white flower color is a *recessive* trait.
- The reappearance of white-flowered plants in the F_2 generation indicated that the heritable factor for the white trait was not diluted or "blended" by coexisting with the purple-flower factor in F_1 hybrids.
- Mendel found similar 3-to-1 ratios of two traits among F_2 offspring when he conducted crosses for six other characters, each represented by two different traits.
- For example, when Mendel crossed two true-breeding varieties, one producing round seeds and the other producing wrinkled seeds, all the F_1 offspring had round seeds.
  - In the F_2 plants, 75% of the seeds were round and 25% were wrinkled.

- Mendel developed a hypothesis to explain these results that consisted of four related ideas. We will explain each idea with the modern understanding of genes and chromosomes.
  1. *Alternative versions of genes account for variations in inherited characters.*
  - The gene for flower color in pea plants exists in two versions, one for purple flowers and one for white flowers.
  - These alternate versions are called **alleles.**
  - Each gene resides at a specific locus on a specific chromosome.
  - The DNA at that locus can vary in its sequence of nucleotides.
  - The purple-flower and white-flower alleles are two DNA variations at the flower-color locus.
  2. *For each character, an organism inherits two alleles, one from each parent.*
  - A diploid organism inherits one set of chromosomes from each parent.
  - Each diploid organism has a pair of homologous chromosomes and, therefore, two copies of each gene.
  - These homologous loci may be identical, as in the true-breeding plants of the P generation.
  - Alternatively, the two alleles may differ.
  3. *If the two alleles at a locus differ, then one, the dominant allele, determines the organism's appearance. The other, the recessive allele, has no noticeable effect on the organism's appearance.*
  - In the flower-color example, the F_1 plants inherited a purple-flower allele from one parent and a white-flower allele from the other.
  - They had purple flowers because the allele for that trait is dominant.
  4. 4. Mendel's **law of segregation** states that the two alleles for a heritable character separate and segregate during gamete production and end up in different gametes.
  - This segregation of alleles corresponds to the distribution of homologous chromosomes to different gametes in meiosis.
  - If an organism has two identical alleles for a particular character, then that allele is present as a single copy in all gametes.
  - If different alleles are present, then 50% of the gametes will receive one allele and 50% will receive the other.
- Mendel's law of segregation accounts for the 3:1 ratio that he observed in the F_2 generation.
- The F_1 hybrids produce two classes of gametes, half with the purple-flower allele and half with the white-flower allele.
- During self-pollination, the gametes of these two classes unite randomly.
- This produces four equally likely combinations of sperm and ovum.
- A **Punnett square** predicts the results of a genetic cross between individuals of known genotype.
- Let us describe a Punnett square analysis of the flower-color example.
- We will use a capital letter to symbolize the dominant allele and a lowercase letter to symbolize the recessive allele.
  - *P* is the purple-flower allele, and *p* is the white-flower allele.
- What will be the physical appearance of the F_2 offspring?
  - One in four F_2 offspring will inherit two white-flower alleles and produce white flowers.

- Half of the F_2 offspring will inherit one white-flower allele and one purple-flower allele and produce purple flowers.
- One in four F_2 offspring will inherit two purple-flower alleles and produce purple flowers.

- Mendel's model accounts for the 3:1 ratio in the F_2 generation.
- An organism with two identical alleles for a character is **homozygous** for that character.
- Organisms with two different alleles for a character is **heterozygous** for that character.
- An organism's traits are called its **phenotype.**
- Its genetic makeup is called its **genotype.**
  - Two organisms can have the same phenotype but have different genotypes if one is homozygous dominant and the other is heterozygous.
- For flower color in peas, the only individuals with white flowers are those that are homozygous recessive (*pp*) for the flower-color gene.
- However, *PP* and *Pp* plants have the same phenotype (purple flowers) but different genotypes (homozygous dominant and heterozygous).
- How can we tell the genotype of an individual with the dominant phenotype?
  - The organism must have one dominant allele, but could be homozygous dominant or heterozygous.
- The answer is to carry out a **testcross.**
  - The mystery individual is bred with a homozygous recessive individual.
  - If any of the offspring display the recessive phenotype, the mystery parent must be heterozygous.

3. By the law of independent assortment, each pair of alleles segregates independently into gametes.

- Mendel's first experiments followed only a *single* character, such as flower color.
  - All F_1 progeny produced in these crosses were **monohybrids,** heterozygous for one character.
  - A cross between two heterozygotes is a *monohybrid cross.*
- Mendel identified the second law of inheritance by following *two* characters at the same time.
- In one such **dihybrid cross,** Mendel studied the inheritance of seed color and seed shape.
  - The allele for yellow seeds (*Y*) is dominant to the allele for green seeds (*y*).
  - The allele for round seeds (*R*) is dominant to the allele for wrinkled seeds (*r*).
- Mendel crossed true-breeding plants that had yellow, round seeds (*YYRR*) with true-breeding plants that has green, wrinkled seeds (*yyrr*).
- One possibility is that the two characters are transmitted from parents to offspring as a package.
  - The *Y* and *R* alleles and *y* and *r* alleles stay together.
- If this were the case, the F_1 offspring would produce yellow, round seeds.
- The F_2 offspring would produce two phenotypes (yellow + round; green + wrinkled) in a 3:1 ratio, just like a monohybrid cross.
  - This was not consistent with Mendel's results.
- An alternative hypothesis is that the two pairs of alleles segregate independently of each other.

- The presence of a specific allele for one trait in a gamete has no impact on the presence of a specific allele for the second trait.

- In our example, the F_1 offspring would still produce yellow, round seeds.
- However, when the F_1s produced gametes, genes would be packaged into gametes with all possible allelic combinations.
  - Four classes of gametes (*YR*, *Yr*, *yR*, and *yr*) would be produced in equal amounts.
- When sperm with four classes of alleles and ova with four classes of alleles combined, there would be 16 equally probable ways in which the alleles can combine in the F_2 generation.
- These combinations produce four distinct phenotypes in a 9:3:3:1 ratio.
- This was consistent with Mendel's results.
- Mendel repeated the dihybrid cross experiment for other pairs of characters and always observed a 9:3:3:1 phenotypic ratio in the F_2 generation.
- Each character appeared to be inherited independently.
- If you follow just one character in these crosses, you will observe a 3:1 F_2 ratio, just as if this were a monohybrid cross.
- The independent assortment of each pair of alleles during gamete formation is now called Mendel's **law of independent assortment.**
- Mendel's law of independent assortment states that *each pair of alleles segregates independently during gamete formation.*
- Strictly speaking, this law applies only to genes located on different, nonhomologous chromosomes.
- Genes located near each other on the same chromosome tend to be inherited together and have more complex inheritance patterns than those predicted for the law of independent assortment.

4. The laws of probability govern Mendelian inheritance.

- Mendel's laws of segregation and independent assortment reflect the same laws of probability that apply to tossing coins or rolling dice.
- The probability scale ranges from 0 (an event with no chance of occurring) to 1 (an event that is certain to occur).
  - The probability of tossing heads with a normal coin is 1/2.
  - The probability of rolling a 3 with a six-sided die is 1/6, and the probability of rolling any other number is $1 - 1/6 = 5/6$.
- When tossing a coin, the outcome of one toss has no impact on the outcome of the next toss.
- Each toss is an independent event, just like the distribution of alleles into gametes.
  - Like a coin toss, each ovum from a heterozygous parent has a 1/2 chance of carrying the dominant allele and a 1/2 chance of carrying the recessive allele.
  - The same odds apply to the sperm.
- We can use the *multiplication rule* to determine the chance that two or more independent events will occur together in some specific combination.
  - Compute the probability of each independent event.
  - Multiply the individual probabilities to obtain the overall probability of these events occurring together.

- The probability that two coins tossed at the same time will land heads up is 1/2 × 1/2 = 1/4.
- Similarly, the probability that a heterozygous pea plant (*Pp*) will self-fertilize to produce a white-flowered offspring (*pp*) is the chance that a sperm with a white allele will fertilize an ovum with a white allele.
- This probability is 1/2 × 1/2 = 1/4.

- The rule of multiplication also applies to dihybrid crosses.
  - For a heterozygous parent (*YyRr*) the probability of producing a *YR* gamete is 1/2 × 1/2 = 1/4.
  - We can use this to predict the probability of a particular F_2 genotype without constructing a 16-part Punnett square.
  - The probability that an F_2 plant from heterozygous parents will have a *YYRR* genotype is 1/16 (1/4 chance for a *YR* ovum and 1/4 chance for a *YR* sperm).
- The rule of addition also applies to genetic problems.
- Under the *rule of addition,* the probability of an event that can occur two or more different ways is the sum of the separate probabilities of those ways.
  - For example, there are two ways that F_1 gametes can combine to form a heterozygote.
    - The dominant allele could come from the sperm and the recessive from the ovum (probability = 1/4).
    - Or the dominant allele could come from the ovum and the recessive from the sperm (probability = 1/4).
    - The probability of obtaining a heterozygote is 1/4 + 1/4 = 1/2.
- We can combine the rules of multiplication and addition to solve complex problems in Mendelian genetics.
- Let's determine the probability of an offspring having two recessive phenotypes for at least two of three traits resulting from a trihybrid cross between pea plants that are *PpYyRr* and *Ppyyrr*.
  - There are five possible genotypes that fulfill this condition: *ppyyRr*, *ppYyrr*, *Ppyyrr*, *PPyyrr*, and *ppyyrr*.
  - We can use the rule of multiplication to calculate the probability for each of these genotypes and then use the rule of addition to pool the probabilities for fulfilling the condition of at least two recessive traits.
- The probability of producing a *ppyyRr* offspring:
  - The probability of producing *pp* = 1/2 × 1/2 = 1/4.
  - The probability of producing *yy* = 1/2 × 1 = 1/2.
  - The probability of producing *Rr* = 1/2 × 1 = 1/2.
  - Therefore, the probability of all three being present (*ppyyRr*) in one offspring is 1/4 × 1/2 × 1/2 = 1/16.
- For *ppYyrr*: 1/4 × 1/2 × 1/2 = 1/16.
- For *Ppyyrr*: 1/2 × 1/2 × 1/2 = 1/8 or 2/16.
- For *PPyyrr*: 1/4 × 1/2 × 1/2 = 1/16.
- For *ppyyrr*: 1/4 × 1/2 × 1/2 = 1/16.
- Therefore, the chance that a given offspring will have at least two recessive traits is 1/16 + 2/16 + 1/16 + 1/16 = 6/16.

5. Mendel discovered the particulate behavior of genes: a review.

- While we cannot predict with certainty the genotype or phenotype of any particular seed from the F_2 generation of a dihybrid cross, we can predict the probability that it will have a specific genotype or phenotype.
- Mendel's experiments succeeded because he counted so many offspring, was able to discern the statistical nature of inheritance, and had a keen sense of the rules of chance.
- Mendel's laws of independent assortment and segregation explain heritable variation in terms of alternative forms of genes that are passed along according to simple rules of probability.
- These laws apply not just to garden peas, but to all diploid organisms that reproduce by sexual reproduction.
- Mendel's studies of pea inheritance endure not only in genetics, but as a case study of the power of scientific reasoning using the hypothetico-deductive approach.

B. Extending Mendelian Genetics

1. The relationship between genotype and phenotype is rarely simple.

- In the 20th century, geneticists have extended Mendelian principles not only to diverse organisms, but also to patterns of inheritance more complex than Mendel described.
- In fact, Mendel had the good fortune to choose a system that was relatively simple genetically.
  - Each character that Mendel studied is controlled by a single gene.
  - Each gene has only two alleles, one of which is completely dominant to the other.
- The heterozygous F_1 offspring of Mendel's crosses always looked like one of the parental varieties because one allele was dominant to the other.
- The relationship between genotype and phenotype is rarely so simple.
- The inheritance of characters determined by a single gene deviates from simple Mendelian patterns when alleles are not completely dominant or recessive, when a gene has more than two alleles, or when a gene produces multiple phenotypes.
- We will consider examples of each of these situations.
- Alleles show different degrees of dominance and recessiveness in relation to each other.
- One extreme is the **complete dominance** characteristic of Mendel's crosses.
- At the other extreme from complete dominance is **codominance,** in which two alleles affect the phenotype in separate, distinguishable ways.
  - For example, the M, N, and MN blood groups of humans are due to the presence of two specific molecules on the surface of red blood cells.
  - People of group M (genotype MM) have one type of molecule on their red blood cells, people of group N (genotype NN) have the other type, and people of group MN (genotype MN) have both molecules present.
  - The MN phenotype is not intermediate between M and N phenotypes but rather exhibits both the M and the N phenotype.
- Some alleles show **incomplete dominance,** in which heterozygotes show a distinct intermediate phenotype not seen in homozygotes.
  - This is not blending inheritance because the traits are separable (particulate), as shown in further crosses.
  - Offspring of a cross between heterozygotes show three phenotypes: each parental and the heterozygote.

- The phenotypic and genotypic ratios are identical: 1:2:1.

- A clear example of incomplete dominance is seen in flower color of snapdragons.
  - A cross between a white-flowered plant and a red-flowered plant will produce all pink F_1 offspring.
  - Self-pollination of the F_1 offspring produces 25% white, 25% red, and 50% pink F_2 offspring.
- The relative effects of two alleles range from complete dominance of one allele, through incomplete dominance of either allele, to codominance of both alleles.
- It is important to recognize that a dominant allele does not somehow subdue a recessive allele.
- Alleles are simply variations in a gene's nucleotide sequence.
  - When a dominant allele coexists with a recessive allele in a heterozygote, they do not interact at all.
- To illustrate the relationship between dominance and phenotype, let us consider Mendel's character of round versus wrinkled pea seed shape.
  - Pea plants with wrinkled seeds have two copies of the recessive allele.
  - The seeds are wrinkled due to the accumulation of monosaccharides because of the lack of a key enzyme that converts them to starch.
  - Excess water enters the seed due to the accumulation of monosaccharides.
    - The seeds wrinkle when the excess water dries.
  - Both homozygous dominants and heterozygotes produce enough enzymes to convert all the monosaccharides into starch.
  - As a result, they do not fill with excess water and form smooth seeds as they dry.
- For any character, dominance/recessiveness relationships depend on the level at which we examine the phenotype.
  - For example, humans with **Tay-Sachs disease** lack a functioning enzyme to metabolize certain lipids. These lipids accumulate in the brain, harming brain cells, and ultimately leading to death.
  - Children with two Tay-Sachs alleles (homozygotes) have the disease.
  - Both heterozygotes with one working allele and homozygotes with two working alleles are healthy and normal at the *organismal* level.
  - The activity level of the lipid-metabolizing enzyme is reduced in heterozygotes. At the *biochemical* level, the alleles show incomplete dominance.
  - Heterozygous individuals produce equal numbers of normal and dysfunctional enzyme molecules. At the *molecular* level, the Tay-Sachs and functional alleles are codominant.
- A dominant allele is not necessarily more common in a population than the recessive allele.
  - For example, one baby in 400 is born with polydactyly, a condition in which individuals are born with extra fingers or toes.
  - Polydactyly is due to a dominant allele.
  - However, the recessive allele is far more prevalent than the dominant allele.
    - 399 individuals out of 400 have five digits per appendage.
- 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.