

# CHAPTER 14

## MENDEL AND THE GENE IDEA

### Introduction

- Every day we observe heritable variations (eyes of brown, green, blue, or gray) among individuals in a population.
- These traits are transmitted from parents to offspring.
- One mechanism for this transmission is the “blending” hypothesis.
  - This hypothesis proposes that the genetic material contributed by each parent mixes in a manner analogous to the way blue and yellow paints blend to make green.
  - Over many generations, a freely mating population should give rise to a uniform population of individuals.
- However, the “blending” hypothesis appears incorrect as everyday observations and the results of breeding experiments contradict its predictions.
- 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 the particulate mechanism of inheritance.

### A. Gregor Mendel’s Discoveries

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

- 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 aroused Mendel’s interest in the causes of variation in plants.
- These influences came together in Mendel’s experiments.
- After the 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 genetics.
  - Pea plants are available in many varieties with distinct heritable features (\_\_\_\_\_ ) with different variants (\_\_\_\_\_).
  - Another advantage of peas is that Mendel had strict control over 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 their own sperm.
  - However, Mendel could also move pollen from one plant to another to cross-pollinate plants.
- In a typical breeding experiment, Mendel would cross-pollinate (\_\_\_\_\_ ) two contrasting, \_\_\_\_\_ pea varieties.
  - The true-breeding parents are the \_\_\_\_\_ and their hybrid offspring are the \_\_\_\_\_.
- 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 the 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 packaged into separate gametes**

- If the blending model were correct, the  $F_1$  hybrids from a cross between purple-flowered and white-flowered pea plants would have pale purple flowers.
- Instead, the  $F_1$  hybrids all have purple flowers, just as purple as the 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  $F_2$ .
- Based on a large sample size, Mendel recorded 705 purple-flowered  $F_2$  plants and 224 white-flowered  $F_2$  plants from the original cross.
- This cross produced a three purple to one white ratio of traits in the  $F_2$  offspring.
- Mendel reasoned that the heritable factor for white flowers was present in the  $F_1$  plants, but it did not affect flower color.
  - Purple flower is a dominant trait and white flower 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 varieties.
- For example, when Mendel crossed two true-breeding varieties, one of which produced round seeds, the other of which produced wrinkled seeds, all the  $F_1$  offspring had round seeds, but among 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.
  - 1) Alternative version of genes (different alleles) account for variations in inherited characters.
    - Different alleles vary somewhat in the sequence of nucleotides at the specific locus of a gene.
      - The purple-flower allele and white-flower allele 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 locus.
    - These homologous loci may be identical, as in the true-breeding plants of the P generation.
    - Alternatively, the two alleles may differ
    - 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.
  - 3) If two alleles differ, then one, the \_\_\_\_\_, is fully expressed in the organism’s appearance.
    - The other, the \_\_\_\_\_, has no noticeable effect on the organism’s appearance.
    - Mendel’s  $F_1$  plants had purple flowers because the purple-flower allele is dominant and the white-flower allele is recessive.
  - 4) The two alleles for each character segregate (separate) during gamete production.
    - This segregation of alleles corresponds to the distribution of homologous chromosomes to different gametes in meiosis.
    - If an organism has identical allele for a particular character, then that allele exists 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.
- The separation of alleles into separate gametes is summarized as Mendel’s \_\_\_\_\_.
- Mendel’s law of segregation accounts for the 3:1 ratio that he observed in the  $F_2$  generation.
- The  $F_1$  hybrids will 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 can produce four equally likely combinations of sperm and ovum.
- A \_\_\_\_\_ predicts the results of a genetic cross between individuals of known genotype.
- A Punnett square analysis of the flower-color example demonstrates Mendel's model.
  - 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 too.
- Mendel's model accounts for the 3:1 ratio in the  $F_2$  generation.
- An organism with two identical alleles for a character is \_\_\_\_\_ for that character.
- Organisms with two different alleles for a character is \_\_\_\_\_ for that character.
- A description of an organism's traits is its \_\_\_\_\_.
- A description of its genetic makeup is its \_\_\_\_\_.
  - 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, both  $PP$  and  $Pp$  plants have the same phenotype (purple) but different genotypes (homozygous and heterozygous).
- The only way to produce a white phenotype is to be homozygous recessive ( $pp$ ) for the flower-color gene.
- It is not possible to predict the genotype of an organism with a dominant phenotype.
  - The organism must have one dominant allele, but it could be homozygous dominant or heterozygous.
- A \_\_\_\_\_, breeding a homozygous recessive with dominant phenotype, but unknown genotype, can determine the identity of the unknown allele.

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

- Mendel's experiments that followed the inheritance of flower color or other characters focused on only a single character via \_\_\_\_\_ crosses.
- He conducted other experiments in which he followed the inheritance of two different characters, a \_\_\_\_\_ cross.
- In one dihybrid cross experiment, 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 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 one specific allele for one trait 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  $F_1$ 's 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<sub>2</sub> 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<sub>2</sub> generation.
- Each character appeared to be inherited independently.
- The independent assortment of each pair of alleles during gamete formation is now called Mendel's \_\_\_\_\_.
- One other aspect that you can notice in the dihybrid cross experiment is that if you follow just one character, you will observe a 3:1 F<sub>2</sub> ratio for each, just as if this were a monohybrid cross.

#### **4. Mendelian inheritance reflects rules of probability**

- 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 ranged from zero (an event with no chance of occurring) to one (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 rule of multiplication to determine the chance that two or more independent events will occur together in some specific combination.
  - Compute the probability of each independent event.
  - Then, 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  $1/2 \times 1/2 = 1/4$ .
  - Similarly, the probability that a heterozygous pea plant (*Pp*) will produce a white-flowered offspring (*pp*) depends on an ovum with a white allele mating with a sperm with a white allele.
  - This probability is  $1/2 \times 1/2 = 1/4$ .
- The rule of multiplication also applies to dihybrid crosses.
  - For a heterozygous parent (*YyRr*) the probability of producing a *YR* gamete is  $1/2 \times 1/2 = 1/4$ .
  - We can use this to predict the probability of a particular F<sub>2</sub> genotype without constructing a 16-part Punnett square.
  - The probability that an F<sub>2</sub> plant will have a *YYRR* genotype from a heterozygous parent 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<sub>1</sub> 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 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 finding 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 would 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  $pp = 1/2 \times 1/2 = 1/4$ .
  - The probability of producing  $yy = 1/2 \times 1 = 1/2$ .
  - The probability of producing  $Rr = 1/2 \times 1 = 1/2$ .
  - Therefore, the probability of all three being present ( $ppyyRr$ ) in one offspring is  $1/4 \times 1/2 \times 1/2 = 1/16$ .
- For  $ppYyrr$ :  $1/4 \times 1/2 \times 1/2 = 1/16$ .
- For  $Ppyyrr$ :  $1/2 \times 1/2 \times 1/2 = 2/16$
- For  $PPyyrr$ :  $1/4 \times 1/2 \times 1/2 = 1/16$
- For  $ppyyrr$ :  $1/4 \times 1/2 \times 1/2 = 1/16$
- Therefore, the chance of at least two recessive traits is  $6/16$ .

## **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 probabilities that it will fit a specific genotype or phenotype.
- Mendel's experiments succeeded because he counted so many offspring and was able to discern this statistical feature 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 rule of probability.
- These laws apply not just to garden peas, but to all other 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 (but one) 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.
- However, some alleles show \_\_\_\_\_ where heterozygotes show a distinct intermediate phenotype, not seen in homozygotes.
  - This is not blended inheritance because the traits are separable (particulate) as seen in further crosses.
  - Offspring of a cross between heterozygotes will show three phenotypes: both parentals 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 offspring.
- Incomplete and \_\_\_\_\_ are part of a spectrum of relationships among alleles.

- At the other extreme from complete dominance is \_\_\_\_\_ 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 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 gangliosides (a lipid) which accumulate in the brain, harming brain cells, and ultimately leading to death.
  - Children with two Tay-Sachs alleles have the disease.
  - Heterozygotes with one working allele and homozygotes with two working alleles are “normal” at the *organismal* level, but heterozygotes produce less functional enzymes.
  - However, both the Tay-Sachs and functional alleles produce equal numbers of enzyme molecules, codominant at the molecular level.
- *Dominant* alleles do not somehow subdue a recessive allele.
- It is in the pathway from genotype to phenotype that dominance and recessiveness come into play.
  - For example, wrinkled seeds in pea plants with two copies of the recessive allele are due to the accumulation of monosaccharides and excess water in seeds because of the lack of a key enzyme.
    - The seeds wrinkle when they dry.
  - Both homozygous dominants and heterozygotes produce enough enzymes to convert all the monosaccharides into starch and form smooth seeds when they dry.
- Because an allele is dominant does not necessarily mean that it is more common in a population than the recessive allele.
  - For example, polydactyly, in which individuals are born with extra fingers or toes, is due to an allele dominant to the recessive allele for five digits per appendage.
  - However, the recessive allele is far more prevalent than the dominant allele in the population.
    - 399 individuals out of 400 have five digits per appendage.
- Dominance/recessiveness relationships have three important points.
  - 1) They range from complete dominance, through various degrees of incomplete dominance, to codominance.
  - 2) They reflect the mechanisms by which specific alleles are expressed in the phenotype and do not involve the ability of one allele to subdue another at the level of DNA.
  - 3) They do not determine or correlate with the relative abundance of alleles in a population.
- Most genes have more than two alleles in a population.
- 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  $I^A I^A$  or  $I^A i$  are type A and place type A oligosaccharides on the surface of their red blood cells.
  - Individuals that are  $I^B I^B$  or  $I^B i$  are type B and place type B oligosaccharides on the surface of their red blood cells.
  - Individuals that are  $I^A I^B$  are type AB and place both type A and type B oligosaccharides on the surface of their red blood cells.
  - Individuals that are  $ii$  are type O and place neither oligosaccharide 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 oligosaccharide 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 \_\_\_\_\_, 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 an organism's characteristics.
- In \_\_\_\_\_, 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).
  - The second 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 ratio is nine black, three brown, and four white.
- Some characters do not fit the either-or basis that Mendel studied.
- \_\_\_\_\_ vary in a population along a continuum.
- These are usually due to \_\_\_\_\_, 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 different genes.
  - Imagine that each gene has two alleles, one light and one dark, that demonstrate incomplete dominance.
  - An AABBCC individual is dark and aabbcc is light.
- A cross between two AaBbCc individuals (intermediate skin shade) would produce offspring covering a wide range of shades.
  - Individuals with intermediate skin shades would be the most likely offspring, but very light and very dark individuals are possible as well.
  - The range of phenotypes forms a normal distribution.
- Phenotype depends on environment and genes.
  - A single tree has 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 the skin, and experience improves performance on intelligence tests.
  - Even identical twins, genetic equals, 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 \_\_\_\_\_, that are determined by the environment.
  - In some cases the norm of reaction has no breadth (for example, blood type).
- Norms of reactions are broadest for polygenic characters.
  - For these \_\_\_\_\_, 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.

- Phenotype has been used to this point in the context of single characters, but it is also used to describe all aspects of an organism.
- 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 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 too low, and breeding experiments are unacceptable.
- Yet, humans are subject to the same rules regulating 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 \_\_\_\_\_ analysis, information about the presence/absence of a particular phenotypic trait is collected from as many individuals in a family as possible and 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 ( $w$ ).
  - The relationship among alleles can be integrated with the phenotypic appearance of these traits 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 almost all 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 to predict the future.
- We can use the 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  $3/4 + 1/4 = 3/16$ .

### 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 range from relatively mild (albinism) to life-threatening (cystic fibrosis).
- The recessive behavior of the alleles occurs because the allele codes for either a malfunctioning protein or 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 one recessive allele from each parent.
- Individuals who lack the disorder are either homozygous dominant or heterozygotes.
- While heterozygotes may have no clear phenotypic effects, they are \_\_\_\_\_ 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 a carrier, and 1/4 free.
- 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.
- One such disease is \_\_\_\_\_ which strikes one of every 2,500 whites of European descent.
  - One in 25 whites is a carrier.
  - The normal allele codes for a membrane protein that transports Cl<sup>-</sup> between cells and the environment.
  - If these channels are defective or absent, there are abnormally high extracellular levels of chloride that causes the mucus coats of certain cells to become thicker and stickier than normal.
  - This mucus build-up in the pancreas, lungs, digestive tract, and elsewhere favors bacterial infections.
  - Without treatment, affected children die before five, but with treatment can live past their late 20's.
- \_\_\_\_\_ 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 blacks is \_\_\_\_\_ .
  - It affects one of 400 African Americans.
  - It 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 crystallizes into long rods.
  - This deforms red blood cells into a sickle shape.
- This sickling creates a cascade of symptoms, demonstrating the pleiotropic effects of this allele.
- Doctors can use regular blood transfusions to prevent brain damage and new drugs to prevent or treat other problems.
  - At the organismal level, the non-sickle allele is incompletely dominant to the sickle-cell allele.
  - Carriers are said to have the sickle-cell trait.
  - These individuals are usually healthy, although some suffer some symptoms of sickle-cell disease under blood oxygen stress.
- At the molecule level, the two alleles are codominant as both normal and abnormal hemoglobins are synthesized.
- The high frequency of heterozygotes with the sickle-cell trait is unusual for an allele with severe detrimental effects in homozygotes.
  - Interestingly, 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, homozygous recessive individuals die of sickle-cell disease, and carriers are relatively free of both.
- Its relatively high frequency 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, those between close relatives, increase the risk.

- These 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, many human disorders are due to dominant alleles.
- For example, *achondroplasia*, a form of dwarfism, has an incidence of one case in 10,000 people.
  - Heterozygous individuals have the dwarf phenotype.
  - Those who are not achondroplastic dwarfs, 99.99% of the population, are homozygous recessive for this trait.
- Lethal dominant alleles are much less common than lethal recessives because if a lethal dominant kills an offspring before it can mature and reproduce, the allele will not be passed on to future generations.
- 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 \_\_\_\_\_, 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.
- Recently, molecular geneticists have used pedigree analysis of affected families to track down the Huntington's allele to a locus near the tip of chromosome 4.
- 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 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 is typically polygenic.
- At present, little is understood about the genetic contribution to most multifactorial diseases
  - The best public health strategy is education about the environmental factors and healthy behavior.

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

- A preventative 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 and both John and Carol had brothers who died of the disease.
  - While neither John and Carol nor their parents have the disease, their parents must have been carriers ( $Aa \times Aa$ ).
  - 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 =  $2/3$  (chance that John is a carrier)  $\times$   $2/3$  (chance that Carol is a carrier)  $\times$   $1/4$  (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 both are carriers.
  - 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.
  - While the chance that John and Carol's first four children will have the disorder ( $1/4 \times 1/4 \times 1/4 \times 1/4$ ), the likelihood of having a fifth child with the disorder is one chance in sixty four, still  $1/4$ .
- Most children with recessive disorders are born to parents with a normal phenotype.

- A key to assessing risk is identifying if prospective parents are carriers of the recessive trait.
- Recently developed tests for several disorders can distinguish between normal phenotypes in heterozygotes from homozygous dominants.
- The results allow individuals with a family history of a genetic disorder to make informed decisions about having children.
- However, issues of confidentiality, discrimination, and adequate information and counseling arise.
- Tests are also available to determine in utero if a child has a particular disorder.
- One technique, \_\_\_\_\_, can be used beginning at the 14th to 16th week of pregnancy to assess the presence of 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, \_\_\_\_\_ can allow 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 in about 1% of cases.
  - These include maternal bleeding or fetal death.
  - 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 tests 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.