

- C1. Recessive X-linked traits are distinguished from the other two by their prevalence in males. Dominant X-linked traits (which are exceedingly rare) are always passed from father to daughter and never from father to son. Autosomal recessive and dominant traits are distinguished primarily by the pattern of transmission from parents to offspring. A person with a dominant trait usually has an affected parent unless it is due to a new mutation or incomplete penetrance is observed. Also, two affected parents can have unaffected children, which should never occur with recessive traits. In the case of rare recessive traits, affected children usually have unaffected parents.
- C2. When a disease-causing allele affects a trait, it is causing a deviation from normality, but the gene involved is not usually the only gene that governs the trait. For example, an allele causing hemophilia prevents the normal blood clotting pathway from operating correctly. It follows a simple Mendelian pattern because a single gene affects the phenotype. Even so, it is known that normal blood clotting is due to the actions of many genes.
- C3. A heterogeneous disorder is one that can be caused by mutations in two or more different genes. Hemophilia and thalassemia are two examples. Heterogeneity can confound pedigree analysis because alleles in different genes that cause the same disorder may be inherited in different ways. For example, there are autosomal and X-linked forms of hemophilia. If a pedigree contained individuals with both types of alleles, the data would not be consistent with either an autosomal or X-linked pattern of inheritance.
- C4. Changes in chromosome number, and unbalanced changes in chromosome structure, tend to affect phenotype because they create an imbalance of gene expression. For example, in Down syndrome, there are three copies of chromosome 21 and therefore three copies of all the genes on chromosome 21. This leads to a relative overexpression of genes that are located on chromosome 21 compared to the other chromosomes. Balanced translocations and inversions often are without phenotypic consequences because the total amount of genetic material is not altered, and the level of gene expression is not significantly changed.
- C5. A. False. Dominant alleles require the inheritance of only one copy, and X-linked alleles require the inheritance of only one copy in males.  
B. True.  
C. True.  
D. False. In many cases, it is difficult to assess the relative contributions of genetics and environment. In some cases, however, the environment seems most important. For example, with PKU, a low-phenylalanine diet will prevent harmful symptoms, even if an individual is homozygous for the mutant PKU alleles.
- C6. There are lots of possible answers; here are a few. Dwarfism occurs in people and dogs. Breeds like the dachshund and basset hound are types of dwarfism in dogs. There are diabetic people and mice. There are forms of inherited obesity in people and mice. Hip dysplasia is found in people and dogs.
- C7. Oftentimes, the age of onset coincides with a particular stage of development. Throughout the life span of an individual, from embryonic through adult life, the pattern of gene expression changes. Some genes are turned on only during embryonic stages, some are turned on during fetal stages, some are turned on at birth, some are turned on at adolescence, etc. An individual who is carrying a mutant gene may not manifest any disorder until the time in life when the gene is supposed to be expressed. For example, many genetic diseases manifest themselves after birth. Prior to birth, an individual may develop properly and be born a healthy baby. After birth, the baby begins a new developmental phase, and at this point, new genes may be turned on. If one or both copies of a “newborn” gene (i.e., a gene turned on at birth) are mutant, this may lead to a serious disorder, with an age of onset that occurs during infancy.  
An infectious disease would probably not have a particular age of onset, because people could be exposed to the infectious agent at any time in their lives. Therefore, most infectious diseases do not have a predictable age of onset, although some diseases are more common in children or older people.
- C8. A. Because a person must inherit two defective copies of this gene and it is known to be on chromosome 1, the mode of transmission is autosomal recessive. Both members of this couple must be heterozygous because they have one affected parent (who had to transmit the mutant allele to them) and their phenotypes are normal (so they must have received the normal allele from their other parent). Because both parents are heterozygotes, there is a 1/4 chance of producing a homozygote with Gaucher disease. If we let  $G$  represent the normal allele, and  $g$  the mutant allele:

	♂	G	g
♀	G	GG Normal	Gg Normal
	g	Gg Normal	gg Gaucher's

B. From this Punnett square, we can also see that there is a 1/4 chance of producing a homozygote with both normal copies of the gene.

C. We need to apply the binomial expansion to solve this problem. See Chapter 2 for a description of this calculation. In this problem,  $n = 5$ ,  $x = 1$ ,  $p = 0.25$ ,  $q = 0.75$ . The answer is 0.396, or 39.6%.

C9. In this pedigree, every affected member has an affected parent (except I-1, whose parentage is unknown). Also, the disease is found in both males and females. Therefore, this pattern suggests an autosomal dominant mode of transmission. Recessive transmission cannot be ruled out, but it is unlikely because it is a rare disorder and it would be extremely unlikely that unrelated individuals in this pedigree (i.e., I-2, II-1, II-7, III-4, and III-5) would all be heterozygous carriers.

C10. The mode of transmission is autosomal recessive. All of the affected individuals do not have affected parents. Also, the disorder is found in both males and females. If it were X-linked recessive, individual III-1 would have to have an affected father, which she does not.

C11. Since both members of this couple are phenotypically normal, and they have two sons with the disorder, the mother must be a heterozygous carrier, and the father has a normal allele (see the following Punnett square).

	♂	$X^F$	Y
♀	$X^F$	$X^F X^F$ Normal	$X^F Y$ Normal
	$X^f$	$X^F X^f$ Carrier	$X^f Y$ Fabry

From this Punnett square, there is a 50% chance that their daughter is a carrier. If she is a carrier, there is a 50% chance that she will pass the mutant allele to her sons. So, if we multiply 0.5 times 0.5, this gives a value of 0.25, or 25%. This means that there is a 25% chance that she will have an affected son, if she gives birth to a son. Another way to view this calculation, however, is to consider that this female may have sons or daughters. When she gives birth, there is a 25% chance of having a male child with Fabry disease, if she is a carrier. If we do our calculation based on this perspective, the odds of this female having an affected son are 0.5 times 0.25, which equals 0.125, or 12.5%. In other words, there is a 12.5% chance that this female will have an affected son, each time she has a child.

C12. The 13 babies have acquired a new mutation. In other words, during spermatogenesis or oogenesis, or after the egg was fertilized, a new mutation occurred in the fibroblast growth factor gene. These 13 individuals have the same chances of passing the mutant allele to their offspring compared to the 18 individuals who inherited the mutant allele from a parent. The chance is 50%.

C13. Based on this pedigree, it appears to be an X-linked recessive trait (which it is known to be). All of the affected members are males, who had unaffected parents. From this pedigree alone, you could not rule out autosomal recessive, but it is less likely because there are no affected females.

C14. Because this is a dominant trait, the mother must have two normal copies of the gene, and the father (who is affected) is most likely to be a heterozygote. (Note: the father could be a homozygote, but this is extremely unlikely because the dominant allele is very rare.) If we let  $M$  represent the mutant Marfan allele, and  $m$  the normal allele, the following Punnett square can be constructed:

	♂	M	m
♀	m	Mm Marfan	mm Normal
	m	Mm Marfan	mm Normal

- A. There is a 50% chance that this couple will have an affected child.
- B. We use the product rule. The odds of having an unaffected child are 50%. So if we multiply  $0.5 \times 0.5 \times 0.5$ , this equals 0.125, or a 12.5% chance of having three unaffected offspring.
- C15.A. The mode of transmission is autosomal recessive. All of the affected individuals do not have affected parents. Also, the disorder is found in both males and females. If it were X-linked recessive, individual III-1 would have to have an affected father, which she does not.
- B. If the disorder is autosomal recessive, individuals II-1, II-2, II-6, and II-7 must be heterozygous carriers because they have affected offspring. Since individuals II-2 and II-6 are heterozygotes, one of their parents (I-1 or I-2) must also be a carrier. Since this is a rare disease, we would assume that only one of them (I-1 or I-2) would be a carrier. Therefore, there is a 50% chance that II-3, II-4, and II-5 are also heterozygotes.
- C16.A. A prion is a protein that behaves like an infectious agent. The infectious form of the prion protein has an abnormal conformation. This abnormal conformation is termed PrP<sup>Sc</sup>, while the normal conformation of the protein is termed PrP<sup>C</sup>. A prion protein in the PrP<sup>Sc</sup> conformation can bind to a prion protein in the PrP<sup>C</sup> conformation and convert it to the PrP<sup>Sc</sup> form. An accumulation of the PrP<sup>Sc</sup> form is what causes the disease symptoms. In the case of mad cow disease, an animal is initially exposed to a small amount of the prion protein in the PrP<sup>Sc</sup> conformation. This PrP<sup>Sc</sup> protein then converts the normal PrP<sup>C</sup> proteins, which are normally found within the cells of the animal, into the PrP<sup>Sc</sup> conformation. The disease symptoms rely on the conversion of the endogenous PrP<sup>C</sup> conformation into the PrP<sup>Sc</sup> form.
- C17. The answer to this question is not actually known. However, we can guess about possible explanations based on the molecular mechanism of the disease. A prion protein can exist in the PrP<sup>Sc</sup> conformation, which is an abnormal conformation that can convert the normal conformation (PrP<sup>C</sup>) into the abnormal conformation (PrP<sup>Sc</sup>). In people with Gerstmann-Straussler-Scheinker disease, the prion protein is predominantly in the PrP<sup>C</sup> conformation, but at a very low rate, it may convert to the PrP<sup>Sc</sup> conformation. One possibility is that the conversion to PrP<sup>Sc</sup> does not occur very often in the cells of younger people.
- This second explanation resembles the game of “tag” in which the person who is “it” can tag someone, and a person who has been tagged also is “it.” Initially, there might be thousands of people playing, and the one person who is “it” might be slow at tagging anyone. However, once that person tags someone, then two people are “it” and then those two people can tag two more people, and then four people are “it.” Initially, the number of people who are “it” will be low and will rise fairly slowly. However, once there are a substantial number of people who are “it,” it becomes difficult for the people who are not “it” to evade the people who are “it.” At this point, the number of people who are not “it” rapidly declines. This same analogy can be applied to the conformations of the prion protein. Initially, when the concentration of PrP<sup>Sc</sup> is low, most of the PrP<sup>C</sup> conformations can avoid an interaction with PrP<sup>Sc</sup>. However, once the PrP<sup>Sc</sup> concentration becomes high, this is more difficult, and all of the PrP<sup>C</sup> conformations will be rapidly converted (in an exponential fashion).
- C18.A. Keep in mind that a conformational change is a stepwise process. It begins in one region of a protein and involves a series of small changes in protein structure. The entire conformational change from PrP<sup>C</sup> to PrP<sup>Sc</sup> probably involves many small changes in protein structure that occur in a stepwise manner. Perhaps the conformational change (from PrP<sup>C</sup> to PrP<sup>Sc</sup>) begins in the vicinity of position 178 and then proceeds throughout the rest of the protein. If there is a methionine at position 129, the complete conformational change (from PrP<sup>C</sup> to PrP<sup>Sc</sup>) can take place. However, perhaps the valine at position 129 somehow blocks one of the steps that are needed to complete the conformational change. (Note: This answer is purely speculative. The actual biochemical mechanism is not known.)

B. Based on the answer to part A, once the PrP<sup>Sc</sup> conformational change is completed, a PrP<sup>Sc</sup> protein can bind to another prion protein in the PrP<sup>C</sup> conformation. Perhaps it begins to convert it (to the PrP<sup>Sc</sup> conformation) by initiating a small change in protein structure in the vicinity of position 178. The conversion would then proceed in a stepwise manner until the PrP<sup>Sc</sup> conformation has been achieved. If a valine is at position 129, this could somehow inhibit one of the steps that are needed to complete the conformational change. If an individual had Val-129 in the polypeptide encoded by the second *PrP* gene, half of their prion proteins would be less sensitive to conversion by PrP<sup>Sc</sup>, compared to individuals who had Met-129. This would explain why individuals with Val-129 in half of the prion proteins would have disease symptoms that would progress more slowly.

C19. An oncogene is abnormally activated to cause cancer while a tumor-suppressor gene is inactivated to cause cancer. *Ras* and *src* are examples of oncogenes and *Rb* and *p53* are tumor-suppressor genes.

C20. A proto-oncogene is a normal cellular gene that typically plays a role in cell division. It can be altered by mutation to become an oncogene and thereby cause cancer. At the level of protein function, a proto-oncogene can become an oncogene by synthesizing too much of a protein or synthesizing the same amount of a protein that is abnormally active.

C21. A retroviral oncogene is a cancer-causing gene found within the genome of a retrovirus. It is not necessary for viral infection and proliferation. Oncogene-defective viral strains are able to infect cells and multiply normally. It is thought that retroviruses have acquired oncogenes due to their life cycle. It may happen that a retrovirus will integrate next to a cellular proto-oncogene. Later in its life cycle, it may transcribe this proto-oncogene and thereby incorporate it into its viral genome. The high copy number of the virus or additional mutations may lead to the overexpression of the proto-oncogene and thereby cause cancer.

C22. The predisposition to develop cancer is inherited in a dominant fashion because the heterozygote has the higher predisposition. The mutant allele is actually recessive at the cellular level. But, because we have so many cells in our bodies, it becomes relatively likely that a defective mutation will occur in the single normal gene and lead to a cancerous cell. Some heterozygous individuals may not develop the disease as a matter of chance. They may be lucky and not get a defective mutation in the normal gene. Or, perhaps their immune system is better at destroying cancerous cells once they arise.

C23. Conversion of a proto-oncogene to an oncogene can occur by missense mutations, gene amplifications, translocations, and viral insertions. Examples are given in Table 22.7. The genetic changes are expected to increase the amount of the encoded protein or alter its function in a way that makes it more active.

C24. If an oncogene was inherited, it may cause uncontrollable cell growth at an early stage of development and thereby cause an embryo to develop improperly. This could lead to an early spontaneous abortion and thereby explain why we do not observe individuals with inherited oncogenes. Another possibility is that inherited oncogenes may adversely affect gamete survival, which would make it difficult for them to be passed from parent to offspring. A third possibility would be that oncogenes could affect the fertilized zygote in a way that would prevent the correct implantation in the uterus.

C25. A. No, because E2F is inhibited.

B. Yes, because E2F is not inhibited.

C. Yes, because E2F is not inhibited.

D. No, because there is no E2F.

C26. The role of p53 is to sense DNA damage and prevent damaged cells from proliferating. Perhaps, prior to birth, the fetus is in a protected environment so that DNA damage may be minimal. In other words, the fetus may not really need p53. After birth, agents such as UV light may cause DNA damage. At this point, p53 is important. A p53 knockout is more sensitive to UV light because it cannot repair its DNA properly in response to this DNA-damaging agent, and it cannot kill cells that have become irreversibly damaged.

C27. A. True.

B. True.

C. False, most cancer cells are caused by mutations that result from environmental mutagens.

D. True.

C28. The p53 protein is a regulatory transcription factor; it binds to DNA and influences the transcription rate of nearby genes. This transcription factor (1) activates genes that promote DNA repair; (2) activates genes that arrest cell division and represses genes that are required for cell division; and (3) activates genes that promote apoptosis. If a cell is exposed to DNA damage, it has a greater potential to become malignant. Therefore, an organism wants to avoid the proliferation of such a cell. When exposed to an agent that causes DNA damage, a cell will try to repair the damage. However, if the damage is too extensive, the p53 protein will stop the cell from dividing and program it to die. This helps to prevent the proliferation of cancer cells in the body.