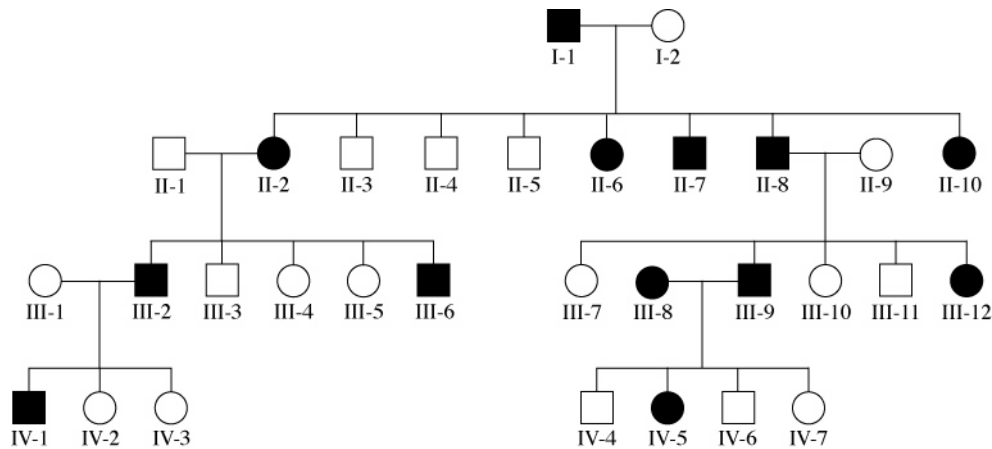


S1. The pedigree shown here concerns a human disease known as familial hypercholesterolemia.



This disorder is characterized by an elevation of serum cholesterol in the blood. Though relatively rare, this genetic abnormality can be a contributing factor to heart attacks. At the molecular level, this disease is caused by a defective gene that encodes a protein called the low-density lipoprotein receptor (LDLR). In the bloodstream, serum cholesterol is bound to a carrier protein known as low-density lipoprotein (LDL). LDL binds to LDLR so that cells can absorb cholesterol. When LDLR is defective, it becomes more difficult for the cells to absorb cholesterol. This explains why the levels of blood cholesterol remain high. Based on the pedigree, what is the most likely pattern of inheritance of this disorder?

**Answer:** The pedigree is consistent with a dominant pattern of inheritance. An affected individual always has an affected parent. Also, individuals III-8 and III-9, who are both affected, produced unaffected offspring. If this trait was recessive, two affected parents should always produce affected offspring. However, because the trait is dominant, two heterozygous parents can produce homozygous unaffected offspring. The ability of two affected parents to have unaffected offspring is a striking characteristic of dominant inheritance. On average, we would expect that two heterozygous parents should produce 25% unaffected offspring. In the family containing IV-4, IV-5, IV-6, and IV-7, there are actually three out of four unaffected offspring. This higher-than-expected proportion of unaffected offspring is not too surprising because the family is a very small group and may deviate substantially from the expected value due to random sampling error.

S2. One way to identify a human cellular oncogene is to use human DNA from a malignant cell to transform a mouse cell. A mouse cell that has been transformed by human DNA will have a human oncogene incorporated into its genome; it also is likely to have *Alu* sequences that are closely linked to this human oncogene. (Note: As discussed in chapter 10, the human genome contains *Alu* sequences interspersed every 5,000 to 6,000 bp. *Alu* sequences are not found in the mouse genome.) Discuss how the *Alu* sequence can provide a way to clone human oncogenes.

**Answer:** One approach is transposon tagging, described in chapter 17. When a mouse cell is transformed with a human DNA fragment containing an oncogene, that fragment is likely to contain an *Alu* sequence as well. To clone the human oncogene, the chromosomal DNA can be isolated from the transformed mouse cells, digested with a restriction enzyme, and cloned into vectors to create a library of DNA fragments. The members of the library that carry the human oncogene can be identified using a probe complementary to the *Alu* sequence because this sequence is not found in the mouse genome. Using this strategy, researchers have identified several human cellular oncogenes. In human bladder carcinoma, for example, the human cellular oncogene called *ras* has been identified this way.

S3. Oncogenes sometimes result from the genetic rearrangements (e.g., translocations) that produce gene fusions. An example is the Philadelphia chromosome that causes the *bcr* gene to fuse with the *abl* gene. Suggest two different reasons why a gene fusion could create an oncogene.

**Answer:** An oncogene is derived from a genetic change that abnormally activates the expression of a gene that plays a role in cell division. When a genetic change creates a gene fusion, this can abnormally activate the expression of the gene in two ways.

The first way is at the level of transcription. The promoter and part of the coding sequence of one gene may become fused with the coding sequence of another gene. For example, the promoter and part of the coding sequence of the *bcr* gene may fuse with the coding sequence of the *abl* gene. After this has occurred, the *abl* gene may be abnormally activated because it is now under the control of the *bcr* promoter, rather than its own normal promoter. If the *bcr* promoter is much stronger than the *abl* promoter, or if it is turned on in different cells compared to the *abl* promoter, this may lead to the overexpression of the *abl* protein compared to its normal level of expression.

A second way that a gene fusion can cause abnormal activation is at the level of protein structure. The fusion protein has parts of two different polypeptides. For example, the *abl/bcr* fusion protein has parts of the *abl* polypeptide and the *bcr* polypeptide. Perhaps the *abl* portion of the fusion protein affects the structure of the *bcr* portion of the polypeptide in such a way that the *bcr* portion becomes abnormally active, or vice versa.