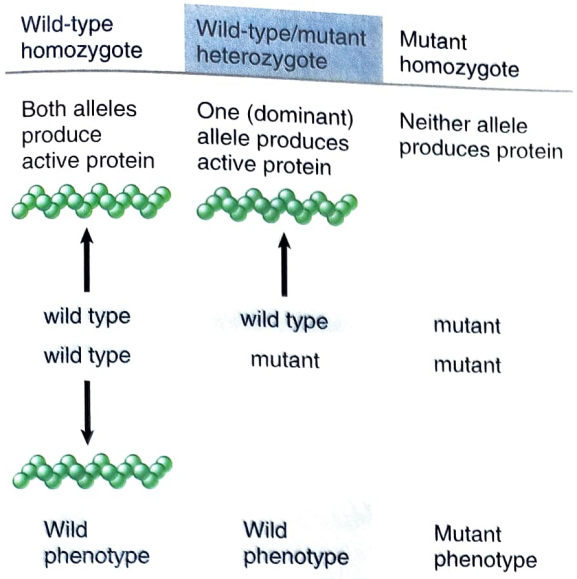

FIGURE 2.2 Genes code for proteins; dominance is explained by the properties of mutant proteins. A recessive allele does not contribute to the phenotype in the wild-type/mutant heterozygote because it produces no protein (or protein that is nonfunctional). If both alleles are the recessive mutant allele, no active protein is produced.

and wild-type alleles. When a heterozygote contains one wild-type allele and one mutant allele, the wild-type allele is able to direct production of the normal gene product. The wild-type allele is therefore dominant. (This assumes that an adequate *amount* of product is made by the single wild-type allele. When this is not true, the smaller amount made by one allele as compared to two alleles results in the intermediate phenotype of a partially dominant allele in a heterozygote.)

2.3 Mutations in the Same Gene Cannot Complement

Key concepts

- A mutation in a gene affects only the product (protein or RNA) coded by the mutant copy of the gene and does not affect the product coded by any other allele.
- Failure of two mutations to complement (produce wild phenotype) when they are present in *trans* configuration in a heterozygote means that they are part of the same gene.

How do we determine whether two mutations that cause a similar phenotype lie in the same gene? If they map close together, they may be alleles. They could, however, also represent mutations in two *different* genes whose proteins are involved in the same function. The **complementation test** is used to determine whether two mutations lie in the same gene or in different genes. The test consists of making a heterozygote for the two mutations.

If the mutations lie in the same gene, the parental genotypes can be represented as:

$$\frac{m_1}{m_1} \text{ and } \frac{m_2}{m_2}$$

The first parent provides an m_1 mutant allele and the second parent provides an m_2 allele, so that the heterozygote has the constitution:

$$\frac{m_1}{m_2}$$

No wild-type gene is present, so the heterozygote has mutant phenotype and the alleles fail to complement. If the mutations lie in different genes, the parental genotypes can be represented as:

$$\frac{m_1+}{m_1+} \text{ and } \frac{+m_2}{+m_2}$$

Each chromosome has a wild-type copy of one gene (represented by the plus sign) and a mutant copy of the other. Then the heterozygote has the constitution:

$$\frac{m_1+}{+m_2}$$

in which the two parents between them have provided a wild-type copy of each gene. The heterozygote has wild phenotype, and thus the two genes are said to *complement*.

The complementation test is shown in more detail in FIGURE 2.3. The basic test consists of the comparison shown in the top part of the figure. If two mutations lie in the same gene, we see a difference in the phenotypes of the *trans* configuration and the *cis* configuration. The *trans* configuration is mutant because each allele has a (different) mutation, whereas the *cis* co nfiguration is wild-type because one allele has two mutations and the other allele has no mutations. The lower part of the figure shows that if the two mutations lie in different genes, we always see a wild phenotype. There is always one wild-type and one mutant allele of each gene, and the configuration is irrelevant. Failure to complement means that two mutations are part of the *same* genetic unit. Mutations that do not complement one another are said to comprise part of the same *complementation group*. Another term used to describe the

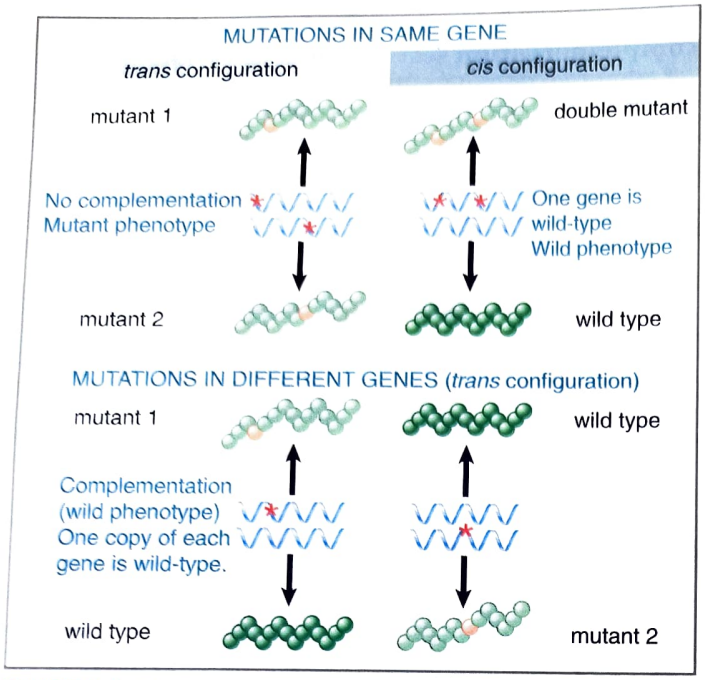

FIGURE 2.3 The cistron is defined by the complementation test. Genes are represented by spirals; red stars identify sites of mutation.

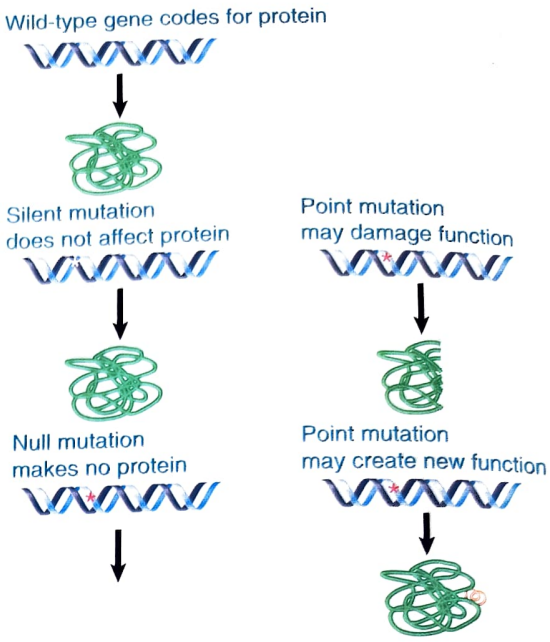

FIGURE 2.4 Mutations that do not affect protein sequence or function are silent. Mutations that abolish all protein activity are null. Point mutations that cause loss-of-function are recessive; those that cause gain-of-function are dominant.

unit defined by the complementation test is the **cistron**. This is the same as the gene. Basically these three terms all describe a stretch of DNA that functions as a unit to give rise to an RNA or protein product. The properties of the gene with regard to complementation are explained by the fact that this product is a single molecule that behaves as a functional unit.

2.4 Mutations May Cause Loss-of-Function or Gain-of-Function

Key concepts

- Recessive mutations are due to loss-of-function by the protein product.
- Dominant mutations result from a gain-of-function.
- Testing whether a gene is essential requires a null mutation (one that completely eliminates its function).
- Silent mutations have no effect, either because the base change does not change the sequence or amount of protein, or because the change in protein sequence has no effect.

The various possible effects of mutation in a gene are summarized in FIGURE 2.4.

When a gene has been identified, insight into its function in principle can be gained by generating a mutant organism that entirely lacks the gene. A mutation that completely eliminates gene function—usually because the gene has been deleted—is called a **null mutation**. If a gene is essential, a null mutation is lethal when homozygous or hemizygous.

To determine what effect a gene has upon the phenotype, it is essential to characterize a null mutant. Generally, if a null mutant fails to affect a phenotype, we may safely conclude that the gene function is not necessary. Some genes have overlapping functions, though, and removal of one gene is not sufficient to significantly affect the phenotype. Null mutations, or other mutations that impede gene function (but do not necessarily abolish it entirely), are called **loss-of-function mutations**. A loss-of-function mutation is recessive (as in the example of Figure 2.2). Loss-of-function mutations that affect protein activity but retain sufficient activity so that the phenotype is not altered are referred to as *leaky mutations*. Sometimes a mutation has the opposite effect and causes a protein to acquire a new function or expression pattern; such a change is called a **gain-of-function mutation**. A gain-of-function mutation is dominant.

Not all mutations in protein-coding genes lead to a detectable change in the phenotype. Mutations without apparent effect are called **silent mutations**. They comprise two types: One type involves base changes in DNA that do not cause any change in the amino acid present

LEWIN'S GENES X

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