be either normal or abnormal in a given individual, but in this book, which emphasizes disorders of medical significance, the focus is on abnormal phenotypes—that is, genetic disorders.

A **single-gene disorder** is one that is determined by the alleles at a single locus. A variant allele, which arose by mutation at some time in the recent or remote past and is usually relatively rare, replaces a wild-type allele on one or both chromosomes. When a person has a pair of identical alleles, he or she is said to be **homozygous** (a **homozygote**); when the alleles are different, he or she is **heterozygous** (a **heterozygote** or carrier). The term **compound heterozygote** is used to describe a genotype in which two different mutant alleles of the same gene are present, rather than one normal and one mutant. These terms (homozygous, heterozygous, and compound heterozygous) can be applied either to a person or to a genotype. The term **mutation** is used in medical genetics in two senses: sometimes to indicate a new genetic change that has not been previously known in a kindred and sometimes merely to indicate a disease-causing allele. Mutation and mutant, however, are not used to refer to the human beings who carry mutant alleles that arose by mutation.

Single-gene disorders are characterized by their patterns of transmission in families. To establish the pattern of transmission, a usual first step is to obtain information about the family history of the patient and to summarize the details in the form of a **pedigree**, a graphical representation of a family tree, using standard symbols (Fig. 5–1). The member through whom a family with a genetic disorder is first brought to attention (ascertained) is the **proband** (synonyms **propositus** or **index case**) if he or she is affected. The person who brings the family to attention by consulting a geneticist is referred to as the **consultand**; the consultand may be an affected individual or an unaffected relative of a proband. A family may have more than one proband, if ascertained through more than one source. Brothers and sisters are called **sibs**, and a family of sibs forms a **sibship**. The entire family is called a **kindred** (Fig. 5–2). Relatives are classified as **first-degree** (parents, sibs, and offspring of the proband); **second-degree** (grandparents and grandchildren, uncles and aunts, nephews and nieces, and half-sibs); **third-degree** (e.g., first cousins), and so forth, depending on the number of steps (in other words, the number of meioses) in the pedigree between the two relatives. The offspring of first cousins are second cousins, and a child is a "first cousin once removed" of his or her parents' first cousins. Couples who have one or more ancestors in common are **consanguineous**. If there is only one affected member in a family, he or she is an **isolated** case or, if the disorder is determined to be due to new mutation in the propositus, a **sporadic** case (see Fig. 5–2).

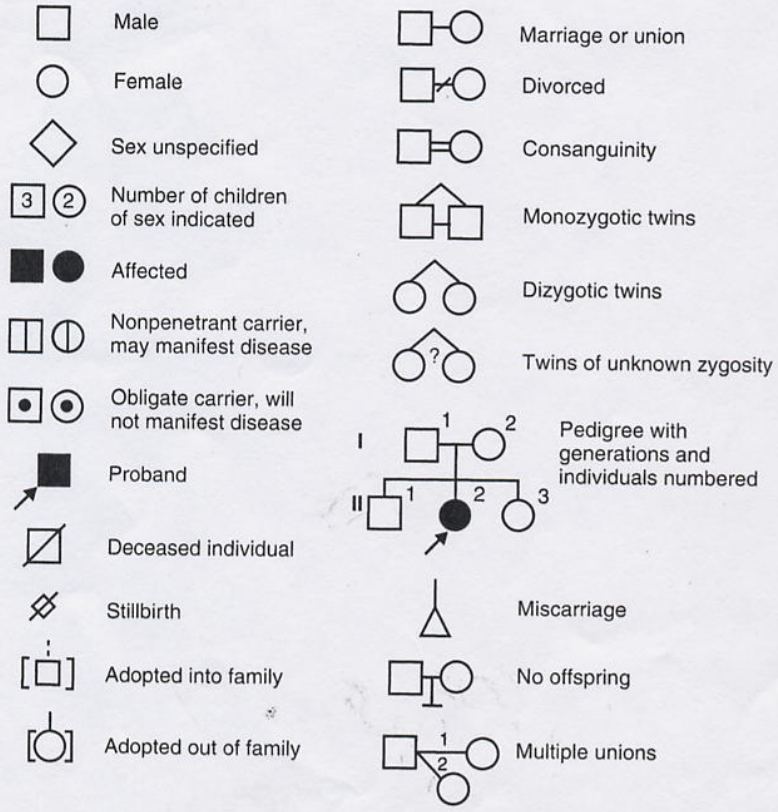

Figure 5–1. Symbols commonly used in pedigree charts. Although there is no uniform system of pedigree notation, the symbols used here are according to recent recommendations made by professionals in the field of genetic counseling. (From Bennett RL, Steinhaus KA, Uhrich SB et al (1995) Recommendations for standardized pedigree nomenclature. J Genet Counsel 4:267–279.)