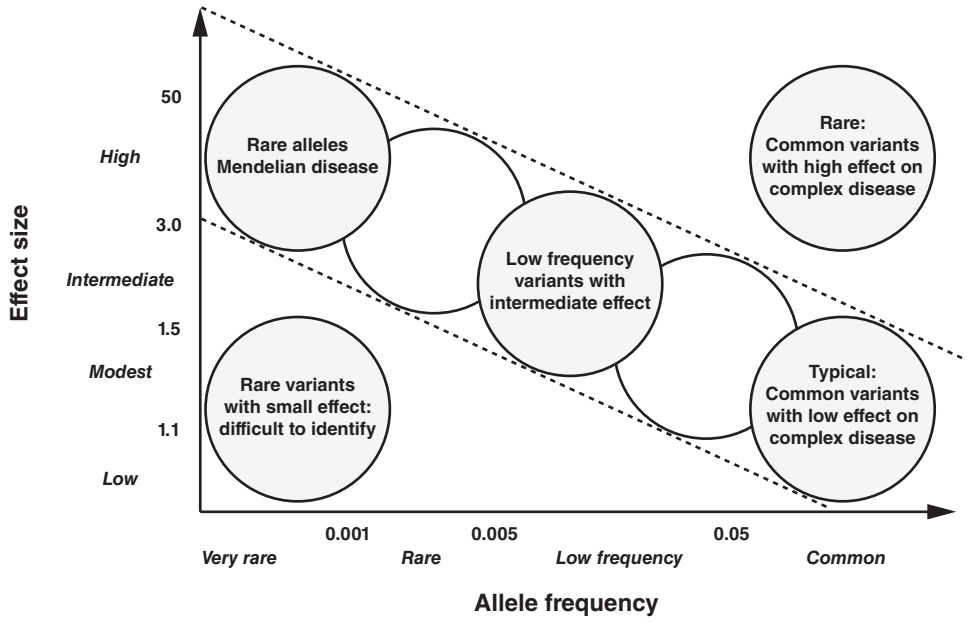

FIGURE 82-14 Relationship between allele frequency and effect size in monogenic and polygenic disorders. In classic Mendelian disorders, the allele frequency is typically low but has a high impact (single gene disorder). This contrasts with polygenic disorders that require the combination of multiple low impact alleles that are frequently quite common in the general population.

pedigree of the first-degree relatives (e.g., parents, siblings, and children), because they share 50% of genes with the patient. Standard symbols for pedigrees are depicted in Fig. 82-11. The family history should include information about ethnic background, age, health status, and deaths, including infants. Next, the physician should explore whether there is a family history of the same or related illnesses to the current problem. An inquiry focused on commonly occurring disorders such as cancers, heart disease, and diabetes mellitus should follow. Because of the possibility of age-dependent expressivity and penetrance, the family history will need intermittent updating. If the findings suggest a genetic disorder, the clinician should assess whether some of the patient's relatives may be at risk of carrying or transmitting the disease. In this circumstance, it is useful to confirm and extend the pedigree based on input from several family members. This information may form the basis for genetic counseling, carrier detection, early intervention, and disease prevention in relatives of the index patient (Chap. 84).

In instances where a diagnosis at the molecular level may be relevant, it is important to identify an appropriate laboratory that can perform the appropriate test. Genetic testing is available for a rapidly growing number of monogenic disorders through commercial laboratories. For uncommon disorders, the test may only be performed in a specialized research laboratory. Approved laboratories offering testing for inherited disorders can be identified in continuously updated online resources (e.g., GeneTests; Table 82-1). If genetic testing is considered, the patient and the family should be counseled about the potential implications of positive results, including psychological distress and the possibility of discrimination. The patient or caretakers should be informed about the meaning of a negative result, technical limitations, and the possibility of false-negative and inconclusive results. For these reasons, genetic testing should only be performed after obtaining *informed consent*. Published ethical guidelines address the specific aspects that should be considered when testing children and adolescents. Genetic testing should usually be limited to situations in which the results may have an impact on medical management.

IDENTIFYING THE DISEASE-CAUSING GENE

Genomic medicine aims to enhance the quality of medical care through the use of genotypic analysis (DNA testing) to identify genetic predisposition to disease, to select more specific pharmacotherapy, and to design individualized medical care based on genotype. Genotype can be deduced by analysis of protein (e.g., hemoglobin, apoprotein E), mRNA, or DNA. However, technologic advances have made DNA analysis particularly useful because it can be readily applied.

DNA testing is performed by mutational analysis or linkage studies in individuals at risk for a genetic disorder known to be present in a family. Mass screening programs require tests of high sensitivity and specificity to be cost-effective. Prerequisites for the success of genetic screening programs include the following: that the disorder is potentially serious; that it can be influenced at a presymptomatic stage by changes in behavior, diet, and/or pharmaceutical manipulations; and that the screening does not result in any harm or discrimination. Screening in Jewish populations for the autosomal recessive neurodegenerative storage disease Tay-Sachs has reduced the number of affected individuals. In contrast, screening for sickle cell trait/disease in African Americans has led to unanticipated problems of discrimination by health insurers and employers. Mass screening programs harbor additional potential problems. For example, screening for the most common genetic alteration in cystic fibrosis, the ΔF508 mutation with a frequency of ~70% in northern Europe, is feasible and seems to be effective. One has to keep in mind, however, that there is pronounced allelic heterogeneity and that the disease can be caused by about 2000 other mutations. The search for these less common mutations would substantially increase costs but not the effectiveness of the screening program as a whole. Next-generation genome sequencing permits comprehensive and cost-effective mutational analyses after selective enrichment of candidate genes. For example, tests that sequence all the common genes causing hereditary deafness are already commercially available. Occupational screening programs aim to detect individuals with increased risk for certain professional activities (e.g., α_1 antitrypsin deficiency and smoke or dust exposure). Integrating genomic data into electronic medical records is evolving and may provide significant decision support at the point of care, for example, by providing the clinician with genomic data and decision algorithms for the prescription of drugs that are subject to pharmacogenetic influences.

Mutational Analyses DNA sequence analysis is now widely used as a diagnostic tool and has significantly enhanced diagnostic accuracy. It is used for determining carrier status and for prenatal testing in monogenic disorders (Chap. 84). Numerous techniques,