Advances in understanding the genetic mechanisms behind disease enable the development of early diagnostic tests, new treatments, or interventions to prevent disease onset or minimize disease severity. This chapter provides information about the importance of clinical signs that may be suggestive of a genetic disease, family history, the different uses of genetic testing, and the different types of genetic diseases.

Mutations may be inherited or developed in response to environmental stresses such as viruses or toxins. The ultimate goal of this manual is to use this information to treat, cure, or, if possible, prevent the development of disease.
2.1 History and Physical Examination

Diagnosing genetic disease requires a comprehensive clinical examination composed of three major elements:

1. Physical examination
2. Detailed medical family history
3. Clinical and laboratory testing, if appropriate and available

Although primary care providers may not always be able to make a definitive diagnosis of a genetic disease, their role is critical in collecting a detailed family history, considering the possibility of a genetic disease in the differential diagnosis, ordering testing as indicated, and when available, appropriately referring patients to genetic specialists.

2.2 Red Flags for Genetic Disease

Several factors indicate the possibility of a genetic disease in a differential diagnosis. One major factor is the occurrence of a condition among family members that is disclosed when the family history is obtained (see Chapter 3, Pedigree and Family History-taking). The occurrence of the same condition such as multiple miscarriages, stillbirths, or childhood deaths in more than one family member (particularly first-degree relatives) is suggestive of a genetic disease. Additionally, family history of common adult conditions (e.g., heart disease, cancer, and dementia) that occur in two or more family members at relatively young ages may also suggest a genetic predisposition.

Other clinical symptoms suggestive of a genetic disease include developmental delay, mental retardation, and congenital abnormalities. Dysmorphologies (unusual physical features), as well as growth problems, can be suggestive of a genetic disorder. Although these clinical features may be caused by a number of factors, genetic conditions should be considered as part of the differential diagnosis, particularly if the patient expresses several clinical features together that might be indicative of a syndrome (e.g., mental retardation, distinct facial features, and a heart defect or heart defects). Some physical features such as wide-set or droopy eyes, flat face, short fingers, and tall stature may appear unique or slightly different than the average. Even though these rare and seemingly mild features may not immediately be suggestive of a genetic disease to a primary care provider, an evaluation by a genetics specialist may be helpful in identifying the presence of a genetic disease.

Genetic conditions should not be ruled out in adolescents or adults, though many genetic conditions appear during childhood. Genetic diseases can remain undetected for several years until an event such as puberty or pregnancy triggers the onset of symptoms or the accumulation of toxic metabolites results in disease later in life.
2.3 Uses of Genetic Testing

Genetic tests can be used for many different purposes, some of which are listed in Table 2.1.

- **Newborn screening** is the most widespread use of genetic testing. (See Chapter 4 for more information about newborn screening.) Almost every newborn in the United States is screened for a number of genetic diseases. Early detection of these diseases can lead to interventions to prevent the onset of symptoms or minimize disease severity.

- **Carrier testing** can be used to help couples learn if they carry—and thus risk passing to their children—an allele (variant form of the same gene) for a recessive condition such as cystic fibrosis, sickle cell anemia, or Tay-Sachs disease. This type of testing is typically offered to individuals who have a family history of a genetic disorder or people in ethnic groups with an increased risk of specific genetic conditions. If both parents are tested, the test can provide information about a couple’s chance of having a child with a specific genetic condition.

- **Prenatal diagnostic testing** is used to detect changes in a fetus’ genes or chromosomes. This type of testing is offered to couples with an increased risk of having a baby with a genetic or chromosomal disorder. A tissue sample for testing can be obtained through amniocentesis or chorionic villus sampling (see Appendix H).

- Genetic tests may be used to confirm a diagnosis in a symptomatic individual or used to monitor prognosis of a disease or response to treatment (see Appendix G).

- **Predictive or predispositional testing** can identify individuals at risk of getting a disease prior to the onset of symptoms. These tests are particularly useful if an individual has a family history of a specific disease and an intervention is available to prevent the onset of disease or minimize disease severity. Predictive testing can identify mutations that increase a person’s risk of developing conditions with a genetic basis such as certain types of cancer.

2.4 Types of Genetic Testing

Several different methods are currently used in genetic testing laboratories. The type of test will depend on the type of abnormality being measured. In general, three major types of genetic testing are available: cytogenetic, biochemical, and molecular.

2.4.1 Cytogenetic Testing. Cytogenetics involves the examination of whole chromosomes for abnormalities. Chromosomes of a dividing human cell can be analyzed clearly under a microscope. White blood cells, specifically T lymphocytes, are the most readily accessible cells for cytogenetic analysis because they are easily collected from blood and are capable of rapid division in cell culture. Cells from tissues such as bone marrow (for leukemia), amniotic fluid (for prenatal diagnosis), and other tissue biopsies can also be cultured for cytogenetic analysis. Following several days of cell culture, chromosomes are fixed, spread on microscope slides, and then stained. The staining methods for routine analysis allow each of the chromosomes to be individually identified. The distinct bands of each chromosome revealed by staining allow for analysis of chromosome structure.
2.4.2 Biochemical Testing. The enormous numbers of biochemical reactions that routinely occur in cells require different types of proteins. Several classes of proteins such as enzymes, transporters, structural proteins, regulatory proteins, receptors, and hormones exist to fulfill multiple functions. A mutation in any type of protein can result in disease if the mutation results in failure of the protein to function correctly. (See Table 2.2 for types of protein alterations that may result in disease.)

Clinical testing for a biochemical disease uses techniques that examine the protein instead of the gene. Tests can be developed to measure directly protein activity (enzymes), level of metabolites (indirect measurement of protein activity), and the size or quantity of protein (structural proteins). These tests require a tissue sample in which the protein is present, typically blood, urine, amniotic fluid, or cerebrospinal fluid. Since proteins are less stable than DNA and can degrade quickly, the sample must be collected, stored properly, and shipped promptly according to the laboratory’s specifications.

2.4.3 Molecular Testing. For small DNA mutations, direct DNA testing may be the most effective method, particularly if the function of the protein is unknown and a biochemical test cannot be developed. A DNA test can be performed on any tissue sample and requires very small amounts of sample. Some genetic diseases can be caused by many different mutations, making molecular testing challenging. For example, more than 1,000 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene can cause cystic fibrosis (CF). It would be impractical to examine the entire sequence of the CFTR gene routinely to identify the causative mutation because the gene is quite large. However, since the majority of CF cases are caused by approximately 30 mutations, this smaller group of mutations is tested before more comprehensive testing is performed. (See Appendix I for more information on genetic testing methodologies.)

Table 2.2 Types of Protein Changes Resulting in Altered Function

- No protein made
- Too much or too little protein made
- Misfolded protein made
- Altered active site or other critical region
- Incorrectly modified protein
- Incorrectly localized protein (buildup of protein)
- Incorrectly assembled protein

SELECTED REFERENCES

American College of Medical Genetics
www.acmg.net


GeneTests
www.genetests.org

