



CHAPTER 2 : DIAGNOSIS OF A GENETIC DISEASE

All diseases have a genetic component. However, the extent to which genes contribute to disease varies and much remains to be learned. Advances in understanding the genetic mechanisms behind these disease enables 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 such as family history that may be suggestive of a genetic disease, the different uses of genetic testing, and the different types of genetic diseases

All diseases have a genetic component. Mutations may be inherited or developed in response to environmental stresses such as viruses or toxins. The ultimate goal is to use this information to treat, cure, or, if possible, prevent the development of disease.

2.1 HISTORY AND PHYSICAL EXAMINATION

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

1. a physical examination
2. a detailed medical family history
3. clinical and laboratory testing if available.

While 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.



IMAGE CREDIT: U.S. Department of Energy Human Genome Program, <http://www.ornl.gov/hgmis>.

2.2 RED FLAGS FOR GENETIC DISEASE

There are several factors that raise 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 on Pedigree and Family-History Taking). The occurrence of the same condition in more than one family member (particularly first-degree relatives), multiple miscarriages, stillbirths, and childhood deaths are all suggestive of a genetic disease. Additionally, family history of common adult conditions (heart disease, cancer, dementia) that occur in two or more relatives at relatively young ages may also suggest a genetic predisposition.

Other clinical symptoms that are suggestive of a genetic disease include developmental delay/mental retardation and congenital abnormalities. Dysmorphologies often involving the heart and facies as well as growth problems are suggestive of a genetic disorder caused by an inherited mutation, spontaneous mutation, teratogen exposure, or unknown factors. While these clinical features may be caused by a number of factors, genetic conditions should also 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 facies, and heart defect). Some physical features may appear unique or slightly different than the average such as wide-set or droopy eyes, flat face, short fingers, and tall stature. While 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 ruling in/out a genetic disease.



While many genetic conditions appear during childhood, a genetic condition should not entirely be ruled out in adolescents or adults. Often a genetic disease 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 manifests in disease. In these cases, a detailed family history and physical examination should be performed and a referral to a genetics specialist if indicated.

2.3 USES OF GENETIC TESTING

Genetic tests can be used for many different purposes. Table 2.1 lists some of the major uses of genetic testing.

- The most widespread use of genetic testing is **newborn screening** [See Chapter 4 for more information about Newborn Screening]. Almost every newborn in the U.S. is screened for several 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 to learn if they carry—and thus risk passing to their children—a recessive allele for genetic diseases such as cystic fibrosis, sickle cell anemia, and Tay-Sachs disease. This type of testing is typically offered to individuals who have a family history of a genetic disorder and to 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 risk of having a child with a genetic condition.
- **Prenatal diagnostic testing** is used to detect changes in a fetus's 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 E for more information about Prenatal Diagnosis.]
- 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.
- **Predictive or predispositional** genetic 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 disorders with a genetic basis, such as certain types of cancer.

Table 2.1
Uses of Genetic Tests

- Newborn Screening
- Carrier Testing
- Prenatal Diagnosis
- Diagnostic/Prognostic
- Predictive/Predispositional

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 that is being measured. In general, three major types of genetic testing are available—cytogenetic, biochemical, and molecular testing to detect abnormalities in chromosome structure, protein function, or DNA sequence, respectively.

2.4.1 Cytogenetic Testing. Cytogenetics involves the examination of whole chromosomes for abnormalities. Chromosomes of a dividing human cell can be clearly analyzed under a microscope. White blood cells, specifically T lymphocytes, are the most readily accessible cells for cytogenetic analysis since they are easily collected from blood and are capable of rapid division in cell culture. Cells from other tissues such as bone marrow (for leukemia), amniotic fluid (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.

Table 2.2 Types of Protein Changes Resulting in Altered Function

- No protein made
- Too much or too little protein made
- Mis-folded protein made
- Altered active site or other critical region
- Incorrectly modified protein
- Incorrectly localized protein (build-up of protein)
- Incorrectly assembled

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 exist to fulfill the multiple functions, such as enzymes, transporters, structural proteins, regulatory proteins, receptors, and hormones. A mutation in any type of protein can result in disease if the mutation ultimately results in failure of the protein to correctly function (see Table 2.2 for how proteins may be altered in a genetic disease).

Clinical testing for a biochemical disease utilizes techniques that examine the protein instead of the gene. Depending on the function, tests can be developed to directly measure 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. Because proteins are more unstable than DNA and can degrade quickly, the sample must be collected and 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 not known and a biochemical test cannot be developed. A DNA test can be performed on any tissue sample and require very small amounts of sample. For some genetic diseases, many different mutations can occur in the same gene and result in the disease, making molecular testing challenging. For example, more than 1,000 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) can cause cystic fibrosis (CF). It would be impractical to sequence the entire CFTR gene to identify the causative mutation since the gene is quite large. However, since the majority of CF cases are caused by approximately 30 mutations, this group of mutations is first tested before more comprehensive testing is performed.

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