

Understanding Modes of Inheritance

Genetic diseases are either **single-gene** or **multifactorial**, depending on the genetic cause. Some common diseases are caused by single-gene or chromosomal disorders — e.g., breast cancer resulting from mutations in the *BRCA1* or *BRCA2* gene; or mental retardation and cleft palate caused by a small deletion in the chromosome 22 (22q11 deletion syndrome). However, most common diseases are multifactorial, caused by a combination of genetic and non-genetic factors.

Knowledge about different modes of inheritance contributes to:

- Accurate interpretation of family history
- Effective use of genetic testing

This Web site provides an overview of different modes of inheritance and links to relevant teaching cases.

Multifactorial Disorders

Multifactorial disorders are conditions caused by the interaction or additive effect of genetic and non-genetic factors. Most common disorders — such as nonspecific developmental delay, asthma, congenital heart disease, dementia, coronary heart disease, venous thrombosis, and diabetes mellitus — fall into this category.

For some of these disorders (e.g., coronary heart disease) much is known about both the genetic and the environmental risks. For others (e.g., asthma and diabetes mellitus) more is known about environmental risks than about genetic risks. Over the next decade, however, it is anticipated that genetic research will rapidly increase knowledge about genetic contributors to common diseases. Some of these genetic risk factors will become the basis for genetic tests — e.g., the test for Factor V Leiden, a mutation with a prevalence of 1% to 5% associated with an increased risk of venous thrombosis.

A major challenge for clinical medicine will be assessment of the clinical utility of such tests; that is, will such tests improve health outcome and if so, how and with what additional risks? (**Multifactorial disorders: related**

teaching cases)

"Non-Genetic" Disorders

Even disorders that we think of as "environmental" are influenced to some extent by genetic factors. For example:

- **Chicken pox** is highly contagious, and the likelihood of developing chicken pox is almost entirely determined by exposure. About 97% of adults in temperate climates have antibodies to chicken pox by their early 20s. The likelihood of infection is 60-87% for household contacts, and similarly high for people with five minutes or more of face-to-face contact with an affected person, or indoor contact for less than one hour. However, a small fraction of people seem to be resistant to chicken pox infection. Recent studies indicate that resistance is due to a mutation in the *CCR5* gene, a cell-surface receptor. People who are homozygous for this receptor mutation are also resistant to HIV infection.
- Most **lung cancer** is caused by exposure to cigarette smoke and other inhaled carcinogens such as asbestos; however, only about 15% of smokers develop lung cancer. To be sure, some die of other smoking-related causes before they have a chance to develop lung cancer. However, a growing body of evidence indicates that a smoker's risk for developing lung cancer is variable and is influenced by the smoker's profile of normal variants for several metabolic enzymes. The highest risk probably occurs with certain combinations of normal variants that result in longer exposure to cigarette carcinogens. Thus, if everyone had the same environmental exposure, susceptibility to lung cancer would be determined by genetic factors alone. A noted epidemiologist pointed out that if we lived in a world in which everyone smoked ten cigarettes a day, we would think of lung cancer as a genetic disease [[Rose 1987](#)].

These examples illustrate the two ways in which genetic variation can influence the health risk of environmental exposures: **providing protection** or **amplifying the risk**. It is likely that both mechanisms play a role in the genetic contribution to most common diseases.

Single-Gene Disorders

Single-gene disorders are disorders caused by mutation of a single gene.

Most are rare, but their frequency ranges widely — from 1/500 to less than 1/50,000. This curriculum emphasizes the more common single-gene disorders, because these are more likely to be seen in primary care practice.

Single-gene disorders follow rules of inheritance that are determined by:

1. Whether manifestation of the disease occurs with one copy of the mutation or two copies; and
2. Whether the mutation is located on an autosome (i.e., the 22 paired human chromosomes) or on the sex chromosomes (the X and the Y).

The resulting patterns are [autosomal dominant](#), [autosomal recessive](#), and [X-linked recessive](#). Recognizing these patterns of inheritance is an important element of the accurate interpretation of family history.

Inheritance Patterns for Single-Gene Disorders

- **Autosomal dominant disorders** are disorders that occur when a mutation is present in one copy of a gene carried on an autosome. The other gene copy in the affected person is normal. Children of a person with an autosomal dominant disorder have a 50% chance of inheriting the mutation; males and females are equally likely to inherit the mutation and to be affected. Family history typically reveals the disorder in sequential generations.

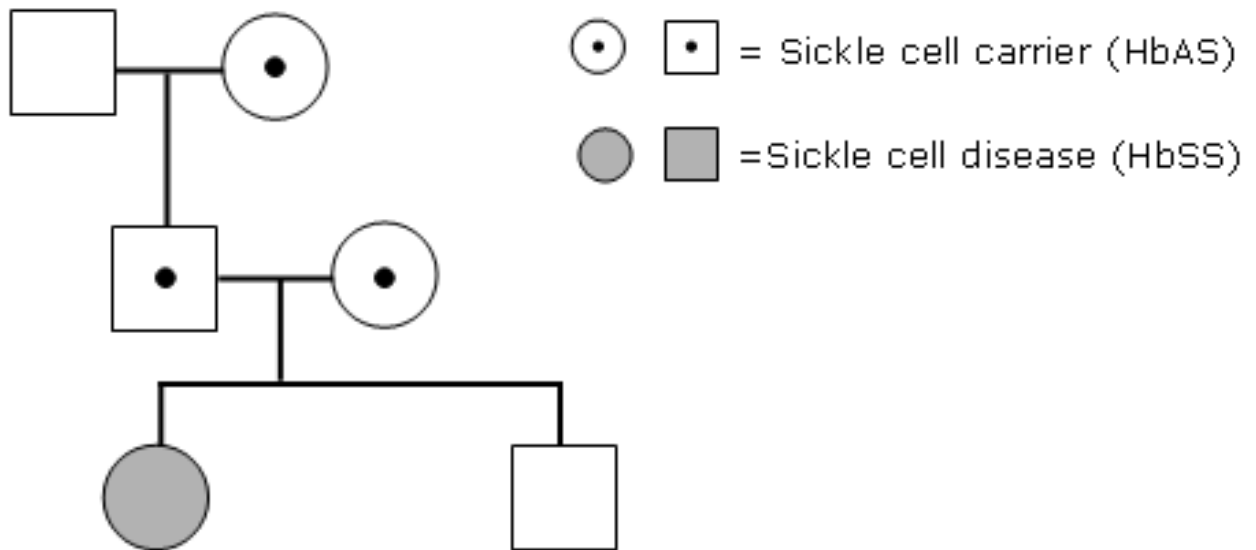
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- **Autosomal recessive disorders** are disorders in which two mutations — one in each gene, for a gene on an autosome — are necessary to cause disease. **Heterozygotes** (such as parents of an affected individual) carry one copy of the mutated gene, are asymptomatic, and are considered **carriers**. If two carriers have children, each child has a 25% chance of inheriting both mutations and having the disease, a 50% chance of one mutation and being an unaffected carrier, and a 25% chance of inheriting both normal alleles.

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Example: Sickle cell disease



- **X-linked recessive disorders** are disorders in which a mutation occurs in a gene on the X chromosome. A single mutation is sufficient to cause disease in a male; women with a single mutation are **heterozygotes** and are considered **carriers**. Carriers may be asymptomatic or symptomatic, depending on the level of X-chromosome inactivation in relevant tissues. Sons of carriers have a 50% risk of being affected; daughters of carriers have a 50% risk of being carriers.

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Chromosomal Disorders

Chromosomal disorders are disorders resulting from a deficiency, excess, or structural abnormality in a chromosome. Aneuploidy (an extra chromosome or a missing chromosome) is a common chromosomal abnormality. Structural abnormalities involve loss (deletion) or excess (duplication) of part of a chromosome.

Small chromosomal deletions (microdeletions) result in loss of a number of contiguous segments of the chromosome. Microdeletion syndromes can be inherited as autosomal dominant conditions, if the clinical manifestations of the condition are compatible with reproduction (**Chromosomal disorders: related teaching cases**).