X-Linked Disorders

All sex-linked disorders are X-linked, and almost all are recessive. Several genes are located in the "male-specific region of Y"; all of these are related to spermatogenesis. *Males with mutations affecting the Y-linked genes are usually infertile, and hence there is no Y-linked inheritance.* As discussed later, a few additional genes with homologues on the X chromosome have been mapped to the Y chromosome, but only a few rare disorders resulting from mutations in such genes have been described.

X-linked recessive inheritance accounts for a small number of well-defined clinical conditions. The Y chromosome, for the most part, is not homologous to the X, and so mutant genes on the X do not have corresponding alleles on the Y. Thus, the male is said to be *hemizygous* for X-linked mutant genes, so these disorders are expressed in the male. Other features that characterize these disorders are as follows:

- An affected male does not transmit the disorder to his sons, but all daughters are carriers. Sons of heterozygous women have, of course, one chance in two of receiving the mutant gene.
- The heterozygous female usually does not express the full phenotypic change because of the paired normal allele. Because of the random inactivation of one of the X chromosomes in the female, however, females have a variable proportion of cells in which the mutant X chromosome is active. Thus, it is remotely possible for the normal allele to be inactivated in most cells, permitting full expression of heterozygous X-linked conditions in the female. Much more commonly, the normal allele is inactivated in only some of the cells, and thus the heterozygous female expresses the disorder partially. An illustrative condition is *glucose-6-phosphate dehydrogenase (G6PD) deficiency*. Transmitted on the X chromosome, this enzyme deficiency, which predisposes to red cell hemolysis in patients receiving certain types of drugs (Chapter 14), is expressed principally in males. In the female, a proportion of the red cells may be derived from precursors with inactivation of the normal allele. Such red cells are at the same risk for undergoing hemolysis as are the red cells in the hemizygous male. Thus, the female is not only a carrier of this trait but also is susceptible to drug-induced hemolytic reactions. Because the proportion of defective red cells in heterozygous females depends on the random inactivation of one of the X chromosomes, however, the severity of the hemolytic reaction is almost always less in heterozygous women than in hemizygous men. Most of the X-linked conditions listed in Table 5-3 are covered elsewhere in the text.

There are only a few *X-linked dominant* conditions. They are caused by dominant disease-associated alleles on the X chromosome. These disorders are transmitted by an affected heterozygous female to half her sons and half her daughters and by an affected male parent to all his daughters but none of his sons, if the female parent is unaffected. Vitamin D–resistant rickets is an example of this type of inheritance.

Table 5-3 X-Linked Recessive Disorders

System	Disease
Musculoskeletal	Duchenne muscular dystrophy
Blood	Hemophilia A and B Chronic granulomatous disease Glucose-6-phosphate dehydrogenase deficiency
Immune	Agammaglobulinemia Wiskott-Aldrich syndrome
Metabolic	Diabetes insipidus Lesch-Nyhan syndrome
Nervous	Fragile X syndrome*

*Discussed in this chapter. Others are discussed in appropriate chapters in the text.

KEY CONCEPTS

Transmission Patterns of Single-Gene Disorders

- **Autosomal dominant disorders** are characterized by expression in heterozygous state; they affect males and females equally, and both sexes can transmit the disorder.
- Enzyme proteins are not affected in autosomal dominant disorders; instead, receptors and structural proteins are involved.
- **Autosomal recessive diseases** occur when both copies of a gene are mutated; enzyme proteins are frequently involved. Males and females are affected equally.
- **X-linked disorders** are transmitted by heterozygous females to their sons, who manifest the disease. Female carriers usually are protected because of random inactivation of one X chromosome.

Biochemical and Molecular Basis of Single-Gene (Mendelian) Disorders

Mendelian disorders result from alterations involving single genes. The genetic defect may lead to the formation of an abnormal protein or a reduction in the output of the gene product. Virtually any type of protein may be affected in single-gene disorders and by a variety of mechanisms (Table 5-4). To some extent the pattern of inheritance of the disease is related to the kind of protein affected by the mutation. For this discussion, the mechanisms involved in single-gene disorders can be classified into four categories: (1) *enzyme defects and their consequences*; (2) *defects in membrane receptors and transport systems*; (3) *alterations in the structure, function, or quantity of nonenzyme proteins*; and (4) *mutations resulting in unusual reactions to drugs.*

Enzyme Defects and Their Consequences

Mutations may result in the synthesis of an enzyme with reduced activity or a reduced amount of a normal enzyme. In either case, the consequence is a metabolic block. Figure 5-5 provides an example of an enzyme reaction in which the substrate is converted by intracellular enzymes, denoted as 1, 2, and 3, into an end product through intermediates 1 and 2. In this model the final product exerts feedback control on enzyme 1. A minor pathway producing small quantities of M1 and M2 also exists. The biochemical