Mendelian Disorders

Virtually all Mendelian disorders are the result of mutations in single genes that have large effects. It is not necessary to detail Mendel's laws here, since every student in biology, and possibly every garden pea, has learned about them at an early age. Only some comments of medical relevance are made.

It is estimated that every individual is a carrier of five to eight deleterious genes, a number originally estimated from studies of populations that appears to be borne out by genomic sequencing of normal individuals. Most of these are recessive and therefore do not have serious phenotypic effects. About 80% to 85% of these mutations are familial. The remainder represents new mutations acquired de novo by an affected individual.

Some autosomal mutations produce partial expression in the heterozygote and full expression in the homozygote. Sickle cell anemia is caused by substitution of normal hemoglobin (HbA) by hemoglobin S (HbS). When an individual is homozygous for the mutant gene, all the hemoglobin is of the abnormal, HbS, type, and even with normal saturation of oxygen the disorder is fully expressed (i.e., sickling deformity of all red cells and hemolytic anemia). In the heterozygote, only a proportion of the hemoglobin is HbS (the remainder being HbA), and therefore red cell sickling occurs only under unusual circumstances, such as exposure to lowered oxygen tension. This is referred to as the *sickle cell trait* to differentiate it from full-blown sickle cell anemia.

Although Mendelian traits are usually described as dominant or recessive, in some cases both of the alleles of a gene pair contribute to the phenotype—a condition called *codominance.* Histocompatibility and blood group antigens are good examples of codominant inheritance.

A single mutant gene may lead to many end effects, termed *pleiotropism*; conversely, mutations at several genetic loci may produce the same trait (*genetic heterogeneity).* Sickle cell anemia is an example of pleiotropism. In this hereditary disorder not only does the point mutation in the gene give rise to HbS, which predisposes the red cells to hemolysis, but also the abnormal red cells tend to cause a logjam in small vessels, inducing, for example, splenic fibrosis, organ infarcts, and bone changes. The numerous differing end-organ derangements are all related to the primary defect in hemoglobin synthesis. On the other hand, profound childhood deafness, an apparently homogeneous clinical entity, results from many different types of autosomal recessive mutations. Recognition of genetic heterogeneity not only is important in genetic counseling but also is relevant in the understanding of the pathogenesis of some common disorders, such as diabetes mellitus.

Transmission Patterns of Single-Gene Disorders

Mutations involving single genes typically follow one of three patterns of inheritance: autosomal dominant, autosomal recessive, and X-linked. The general rules that govern the transmission of single-gene disorders are well known; only a few salient features are summarized. Single-gene disorders with nonclassic patterns of inheritance are described later.

Autosomal Dominant Disorders

Autosomal dominant disorders are manifested in the heterozygous state, so at least one parent of an index case is usually affected; both males and females are affected, and both can transmit the condition. When an affected person marries an unaffected one, every child has one chance in two of having the disease. In addition to these basic rules, autosomal dominant conditions are characterized by the following:

- *With every autosomal dominant disorder, some proportion of patients do not have affected parents.* Such patients owe their disorder to new mutations involving either the egg or the sperm from which they were derived. Their siblings are neither affected nor at increased risk for disease development. The proportion of patients who develop the disease as a result of a new mutation is related to the effect of the disease on reproductive capability. If a disease markedly reduces reproductive fitness, most cases would be expected to result from new mutations. Many new mutations seem to occur in germ cells of relatively older fathers.
- *Clinical features can be modified by variations in penetrance and expressivity.* Some individuals inherit the mutant gene but are phenotypically normal. This is referred to as *incomplete penetrance.* Penetrance is expressed in mathematical terms. Thus, 50% penetrance indicates that 50% of those who carry the gene express the trait. In contrast to penetrance, if a trait is seen in all individuals carrying the mutant gene but is expressed differently among individuals, the phenomenon is called *variable expressivity.* For example, manifestations of neurofibromatosis type 1 range from brownish spots on the skin to multiple skin tumors and skeletal deformities. The mechanisms underlying incomplete penetrance and variable expressivity are not fully understood, but they most likely result from effects of other genes or environmental factors that modify the phenotypic expression of the mutant allele. For example, the phenotype of a patient with sickle cell anemia (resulting from mutation at the β-globin locus) is influenced by the genotype at the α-globin locus, because the latter influences the total amount of hemoglobin made (Chapter 14). The influence of environmental factors is exemplified by individuals heterozygous for familial hypercholesterolemia. The expression of the disease in the form of atherosclerosis is conditioned by the dietary intake of lipids.
- In many conditions the age at onset is delayed; symptoms and signs may not appear until adulthood (as in Huntington disease).

The biochemical mechanisms of autosomal dominant disorders depend upon the nature of the mutation and the type of protein affected. Most mutations lead to the reduced production of a gene product or give rise to a dysfunctional or inactive protein. Whether such a mutation gives rise to dominant or recessive disease depends on whether the remaining copy of the gene is capable of compensating for the loss. Thus, understanding the reasons why particular loss-of-function mutations give rise to dominant vs. recessive disease patterns requires an understanding of the biology. Many autosomal dominant