Diseases such as congenital birth defects, myocardial infarction, cancer, mental illness, diabetes, and Alzheimer disease cause morbidity and premature mortality in nearly two of every three individuals during their lifetimes (Table 8-1). Many of these diseases “run in families”—they seem to recur in the relatives of affected individuals more frequently than in the general population. And yet their inheritance generally does not follow one of the mendelian patterns seen in the single-gene disorders (described in Chapter 7). Instead, they are thought to result from complex interactions between a number of genetic and environmental factors and therefore are said to follow a multifactorial (or complex) inheritance pattern. The familial clustering can be explained by recognizing that family members share a greater proportion of their genetic information and environmental exposures than do individuals chosen at random in the population. Thus, the relatives of an affected individual are more likely to experience the same gene-gene and gene-environment interactions that led to disease in the proband in the first place than are individuals who are unrelated to the proband. The multifactorial inheritance pattern that results represents an interaction between the collective effect of the genotype at one or, more commonly, multiple loci (polygenic or multigenic effects) either to raise or to lower susceptibility to disease, combined with a variety of environmental exposures that may trigger, accelerate, exacerbate, or protect against the disease process. The gene-gene interactions in polygenic inheritance may be simply additive or much more complicated. For example, there may be synergistic amplification of susceptibility by the genotypes at multiple loci or dampening of the effect of genotype at one locus by the genotypes at other loci. Gene-environment interactions, including systematic exposures or chance encounters with environmental factors in one’s surroundings, add even more complexity to individual disease risk and the pattern of disease inheritance.

In this chapter, we first address the question of how we determine that genes predispose to common diseases and, therefore, that these diseases are, at least in part, “genetic.” We describe how studies of familial aggregation, twin studies, and estimates of heritability are used by geneticists to quantify the relative contributions of genes and environment to diseases and clinically important physiological measures with complex inheritance. Second, we illustrate the general concept of gene-gene interaction, starting with one of the simplest examples, one in which modifier genes affect the occurrence or severity of a mendelian disorder. We then give a few examples of more complicated multifactorial diseases in which knowledge of the alleles and loci that confer disease susceptibility is leading to an increased understanding of the mechanisms by which these alleles interact with each other or the environment to cause disease. Unfortunately, we do not understand the underlying mechanisms of the gene-gene and gene-environment interactions for the majority of complex disorders. Geneticists must therefore continue to rely on empirically derived risk figures to give our patients and their relatives some answers to basic questions about disease risk and approaches to reducing that risk. We provide such risk figures here but expect that, with
time, research will make them obsolete, replaced by more robust measures of individual risk. As the information gained through the Human Genome Project is applied to the problem of diseases with complex inheritance, physicians and genetic counselors in the years ahead will have the information they need to provide accurate molecular diagnosis and risk assessment and to develop rational preventive and therapeutic measures.

**QUALITATIVE AND QUANTITATIVE TRAITS**

We can divide the complex phenotypes of multifactorial disorders into two major categories: qualitative and quantitative traits. A genetic disease that is either present or absent is referred to as a discrete or qualitative trait; one has the disease or not. In contrast are quantitative traits, which are measurable physiological or biochemical quantities such as height, blood pressure, serum cholesterol concentration, and body mass index (a measure of obesity) that underlie many common and devastating illnesses in the population.

**Genetic Analysis of Qualitative Disease Traits**

**Familial Aggregation of Disease**

A primary characteristic of diseases with complex inheritance is that affected individuals may cluster in families (familial aggregation). The converse, however, is not necessarily true: familial aggregation of a disease does not mean that a disease must have a genetic contribution. Family members may develop the same disease or trait by chance alone, particularly if it is a common one in the population. Even if familial aggregation is not due to chance, families share more than their genes; for example, they often have cultural attitudes and behaviors, socioeconomic status, diet, and environmental exposures in common. It is the task of the genetic epidemiologist to determine whether familial aggregation is coincidental or the result of factors common to members of the family and to assess the extent to which those common factors are genetic or environmental. Ultimately, gene mapping studies to locate and identify the particular loci and alleles involved provide the definitive proof of a genetic contribution to multifactorial disease (see Chapter 10).

**Concordance and Discordance**

When two related individuals in a family have the same disease, they are said to be concordant for the disorder. Conversely, when only one member of the pair of relatives is affected and the other is not, the relatives are discordant for the disease. Diseases with complex inheritance result from the impact of environmental factors on individuals with certain genotypes. Discordance for phenotype between relatives who share a genotype at loci that predispose to disease can be explained if the unaffected individual has not experienced the other factors (environmental or chance occurrences) necessary to trigger the disease process and make it manifest. Conversely, concordance for a phenotype may occur even when the two affected relatives have different predisposing genotypes, if the disease in one relative is a genocopy or phenocopy of the disease in the other relative. Lack of penetrance and frequent genocopies and phenocopies contribute to obscuring the inheritance pattern in multifactorial genetic disease.

**Measuring Familial Aggregation in Qualitative Traits**

**Relative Risk \( \lambda_r \)** The familial aggregation of a disease can be measured by comparing the frequency of the disease in the relatives of an affected proband with its frequency (prevalence) in the general population. The relative risk ratio \( \lambda_r \) is defined as:

\[
\lambda_r = \frac{\text{Prevalence of the disease in the relatives of an affected person}}{\text{Prevalence of the disease in the general population}}
\]

(The subscript \( r \) for \( \lambda \) is used here to refer to relatives; in practice, one measures \( \lambda \) for a particular class of relatives, e.g., \( r = s \) for sibs, \( r = p \) for parents.) The value of \( \lambda_r \) is a measure of familial aggregation that depends...
both on the risk of the disease’s recurrence in the family and on the population prevalence; the larger \( \lambda \), is, the greater is the familial aggregation. The population prevalence enters into the calculation because the more common a disease is, the greater is the likelihood that aggregation may be just a coincidence rather than a result of sharing the alleles that predispose to disease. A value of \( \lambda = 1 \) indicates that a relative is no more likely to develop the disease than is any individual in the population. Examples of approximate \( \lambda \) values for various diseases are shown in Table 8-2.

Table 8-2

<table>
<thead>
<tr>
<th>Disease</th>
<th>Relationship</th>
<th>( \lambda )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>Siblings</td>
<td>12</td>
</tr>
<tr>
<td>Autism</td>
<td>Siblings</td>
<td>150</td>
</tr>
<tr>
<td>Manic-depressive (bipolar) disorder</td>
<td>Siblings</td>
<td>7</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>Siblings</td>
<td>35</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>Siblings</td>
<td>25</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Siblings</td>
<td>24</td>
</tr>
</tbody>
</table>


Case-control studies for familial aggregation are subject to many different kinds of errors or bias. One of the most troublesome is ascertainment bias, a difference in the likelihood that affected relatives of the cases will be reported to the epidemiologist as compared with the affected relatives of controls. A proband’s relatives may be more likely than a control’s relatives to know of other family members with the same or similar disease or may be more motivated to respond to questioning because of familiarity with the disease (recall bias). Another confounding factor is the choice of controls. Controls should differ from the cases only in their disease status and not in ethnic background, occupation, gender, or socioeconomic status, any of which may distinguish them as being different from the cases in important ways that have little or nothing to do with the fact that they are not affected by the disease. Finally, an association found in a case-control study does not prove causation. If two factors are not independent of each other, such as ethnic background and dietary consumption of certain foods, a case-control study may find a significant association between the disease and ethnic background when it is actually the dietary habits associated with ethnic background that are responsible. For example, the lower frequency of coronary artery disease among Japanese compared with North Americans becomes less pronounced in first-generation Japanese who emigrated to North America and adopted the dietary customs of their new home.

Determining the Relative Contributions of Genes and Environment to Complex Disease

Concordance and Allele Sharing Among Relatives

The more closely related two individuals are in a family, the more alleles they have in common, inherited from their common ancestors. Conversely, the more distantly related the relative is to the proband, the fewer the alleles shared between the proband and the relative. One approach to dissecting the contribution of genetic influences from environmental effects in multifactorial disease is to compare disease concordance in relatives who are more or less closely related to the proband. When genes are important contributors to a disease, the frequency of disease concordance increases as the degree of relatedness increases. The most extreme examples of two individuals having alleles in common are identical (monozygotic) twins (see later in this chapter), who have the same alleles at every locus. The next most closely related individuals in a family are first-degree relatives, such as a parent and child or a pair of sibs, including fraternal ( dizygotic) twins. In a parent-child pair, the child has one allele in common with each parent at every locus, that is, the allele the
child inherited from that parent. For a sibpair (including dizygotic twins), the situation is slightly different. A pair of sibs inherits the same two alleles at a locus 2.5% of the time, no alleles in common 2.5% of the time, and one allele in common 50% of the time (Fig. 8-1). At any one locus, the average number of alleles one sibling is expected to share with another is given by:

\[0.25 \times 2 + 0.5 \times 1 + 0.25 \times 0 = 1\] allele

For example, if genes predispose to a disease, one would expect \(\lambda_i\) to be greatest for monozygotic twins, then to decrease for first-degree relatives such as sibs or parent-child pairs, and to continue to decrease as allele sharing decreases among the more distant relatives in a family (Table 8-3).

**Unrelated Family Member Controls**

The more closely related two individuals are, the more likely they are to share home environment as well as genes. One way to separate family environment from genetic influence is to compare the incidence of disease in unrelated family members (adoptees, spouses) with that in biological relatives. In one study of MS, for example, \(\lambda_i = 20\) to 40 in first-degree biological relatives (parents, children, and sibs) but \(\lambda_i = 1\) for siblings or children adopted into the family, suggesting that most of the familial aggregation in MS is genetic rather than environmental in origin. These values of \(\lambda_i\) translate into a risk for MS for the monozygotic twin of an affected individual, who shares 100% of his genetic information with his twin, that is 190 times the risk for MS in an adopted child or sibling of an MS proband, who shares with the affected individual much of the same environmental exposures but none of the genetic information.

**Twin Studies**

Another common method for separating genetic from environmental influences on disease is to study twins, both monozygotic (MZ) and dizygotic (DZ). Twins are “experiments of nature” that come closest to providing an opportunity to assess environmental and genetic influences separately in humans. DZ twins reared together allow geneticists to measure disease concordance in relatives who grow up in similar environments but do not share all their genes, whereas MZ twins provide an opportunity to compare relatives with identical genotypes who may or may not be reared together in the same environment. Studies of twins have played a significant role in helping geneticists to assess the relative contributions of genes and environment to disease causation.

MZ twins arise from the cleavage of a single fertilized zygote into two separate zygotes early in embryogenesis (see Fig. 14-12). As a result, MZ twins have identical genotypes at every locus and are always of the same sex. They occur in approximately 0.3% of all births, without significant differences among different ethnic groups. DZ twins arise from the simultaneous

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**Table 8-3**

<table>
<thead>
<tr>
<th>Relationship to Proband</th>
<th>Proportion of Alleles in Common with Proband</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monozygotic twin</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative</td>
<td>1/2</td>
</tr>
<tr>
<td>Second-degree relative</td>
<td>1/4</td>
</tr>
<tr>
<td>Third-degree relative</td>
<td>1/8</td>
</tr>
</tbody>
</table>

See Chapter 7, Figure 7-2, for description of degrees of relationship.
fertilization of two eggs by two sperm; genetically, DZ twins are siblings who share a womb and, like all siblings, share, on average, 50% of the alleles at all loci. DZ twins are of the same sex half the time and of opposite sex the other half. DZ twins occur with a frequency that varies as much as 5-fold in different populations, from a low of 0.2% among Asians to more than 1% of births in parts of Africa and among African Americans.

Disease Concordance in Monozygotic Twins An examination of how frequently MZ twins are concordant for a disease is a powerful method for determining whether genotype alone is sufficient to produce a particular disease. For example, if one MZ twin has sickle cell disease, the other twin will also have sickle cell disease. In contrast, when one MZ twin has type 1 diabetes mellitus (previously known as insulin-dependent or juvenile diabetes), only about 40% of the other twins will also have type 1 diabetes. Disease concordance less than 100% in MZ twins is strong evidence that nongenetic factors play a role in the disease. Such factors could include environmental influences, such as exposure to infection or diet, as well as other effects, such as somatic mutation, effects of aging, and differences in X inactivation in one female twin compared with the other.

Concordance of Monozygotic Versus Dizygotic Twins MZ and same-sex DZ twins share a common intrauterine environment and are generally reared together in the same household by the same parents. Thus, a comparison of concordance for a disease between MZ and same-sex DZ twins shows how frequently disease occurs when relatives who experience the same prenatal and possibly postnatal environment have all their genes in common, compared with only 50% of their genes in common. Greater concordance in MZ versus DZ twins is strong evidence of a genetic component to the disease (Table 8-4). This conclusion is strongest for conditions with early onset, such as birth defects. For late-onset diseases, such as neurodegenerative disease of late adulthood, the assumption that MZ and DZ twins are exposed to similar environments throughout their adult lives becomes less valid, and thus a difference in concordance provides less strong evidence for genetic factors in disease causation.

Twins Reared Apart If MZ twins are separated at birth and raised apart, geneticists have the opportunity to observe disease concordance in individuals with identical genotypes reared in different environments. Such studies have been used primarily in research in psychiatric disorders, substance abuse, and eating disorders, in which strong environmental influences within the family are believed to play a role in the development of disease. For example, in one study of alcoholism, five of six MZ twin pairs reared apart were concordant for alcoholism, a concordance rate at least as high as that seen among MZ twins reared together, suggesting that shared genetic factors are far more important than shared environment.

Limitations of Twin Studies As useful as twin studies are for dissecting genetic and environmental factors in disease, they must be interpreted with care for several reasons. First, MZ twins do not have precisely identical genes or gene expression despite starting out with identical genotypes at the time the zygote cleaves in two to create the MZ twins. For example, somatic rearrangements in the immunoglobulin and T-cell receptor loci will differ between MZ twins in various lymphocyte subsets (see Chapter 3). In addition, on the X chromosome, random X inactivation after cleavage into two female MZ zygotes produces significant differences in the expression of alleles of X-linked genes in different tissues (see Chapter 6).

Second, environmental exposures may not be the same for twins, especially once the twins reach adulthood and leave their childhood home. Even intrauterine environment may not be the same. For example, MZ twins frequently share a placenta, and there may be a disparity between the twins in blood supply, intrauterine development, and birth weight.

Third, measurements of disease concordance in MZ twins give an average estimate that may not be accurate if the relevant predisposing alleles or environmental factors are different in different twin pairs. Suppose the genotype of one pair of twins generates a greater risk for disease than does the genotype of another pair; the observed concordance will be an average that really applies to neither pair of twins. As
a more extreme example, the disease may not always be genetic in origin, that is, nongenetic phenocopies may exist. If genotype alone causes the disease in some pairs of twins (MZ twin concordance 100%) and a nongenetic phenocopy affects one twin of the pair in another group of twins (MZ twin concordance 0%), twin studies will show an intermediate level of concordance greater than 0% and less than 100% that really applies to neither form of the disease.

Finally, ascertainment bias is a problem, particularly when one twin with a particular disease is asked to recruit the other twin to participate in a study (volunteer-based ascertainment), rather than if they are ascertained first as twins and only then is their health status examined (population-based ascertainment). Volunteer-based ascertainment can give biased results because twins, particularly MZ twins who may be emotionally close, are more likely to volunteer if they are concordant than if they are not, which inflates the concordance rate. In properly designed studies, however, twins offer an unusual opportunity to study disease occurrence when genetic influences are held constant (measuring disease concordance in MZ twins reared together or apart) or when genetic differences are present but environmental influences are similar (comparing disease concordance in MZ versus DZ twins).

Genetic Analysis of Quantitative Traits

Measurable physiological quantities, such as blood pressure, serum cholesterol concentration, and body mass index, vary among different individuals and are important determinants of health and disease in the population. Such variation is usually due to differences in genotype as well as nongenetic (i.e., environmental) factors. The challenge to geneticists is to determine the extent to which genes contribute to this variability, to identify these genes, and to ascertain the alleles responsible.

The Normal Distribution

As is often the case with physiological quantities measured in a population, a graph of the number of individuals in the population (y-axis) having a particular quantitative value (x-axis) produces the familiar bell-shaped curve known as the normal (gaussian) distribution (Fig. 8-2). In a graph of the population frequency of a normally distributed value, the position of the peak of the graph and the shape of the graph are governed by two quantities, the mean (μ) and the variance (σ^2), respectively. The mean is the arithmetic average of the values, and because more people have values for the trait near the average, the curve has its peak at the mean value. The variance (or its square root, the standard deviation, σ), is a measure of the degree of spread of values to either side of the mean and therefore determines the breadth of the curve. Any physiological quantity that can be measured is a quantitative phenotype, with a mean and a variance. The variance of a measured quantity in the population is called the total phenotypic variance.

The Normal Range

The concept of the normal range of a physiological quantity is fundamental to clinical medicine. For example, extremely tall or short stature, hypertension, hypercholesterolemia, and obesity are all considered abnormal when a value sits clearly outside the normal range. In assessing health and disease in children, height, weight, head circumference, and other measurements are compared with the “normal” expected mea-
Familial Aggregation of Quantitative Traits

Just as familial aggregation, as measured by $\lambda$, and case-control studies, is used to assess the role of heredity in qualitative disease traits, family studies can also be used to determine the role of heredity in quantitative traits. Quantitative traits, however, are not either present or absent; they are measurements. Consequently, one cannot simply compare the prevalence of disease in relatives versus controls or the degree of concordance in twins. Instead, geneticists measure the correlation of particular physiological quantities among relatives, that is, the tendency for the actual values of a physiological measurement to be more similar among relatives than among the general population. The coefficient of correlation (symbolized by the letter $r$) is a statistical measure applied to a pair of measurements, such as, for example, a person's blood pressure and the mean blood pressures of that person's siblings. Accordingly, a positive correlation exists between the blood pressure measurements in a group of patients and the blood pressure measurements of their relatives if it is found that the higher a patient's blood pressure, the higher are the blood pressures of that patient's siblings. A negative correlation exists when the greater the increase in the patient's measurement, the lower the measurement in the patient's relatives. The measurements are still correlated, but in the opposite direction. The value of $r$ can range from 0 when there is no correlation to +1 for perfect positive correlation and to −1 for perfect negative correlation.

Figure 8-3 shows a graph of the average height of more than 200 parent couples plotted against the average height of their nearly 1000 adult children. There is a positive but not perfect correlation ($r = -0.6$) between the average parental height and the mean height of their children.

The correlation among relatives can be used to estimate genetic influence on a quantitative trait if you assume that the degree of similarity in the values of the trait measured among relatives is proportional to the number of alleles they share at the relevant loci.
for that trait. The more closely related the individuals are in a family, the more likely they are to share alleles at loci that determine a quantitative trait and the more strongly correlated will be their values. However, just as with disease traits that are found to aggregate in families because relatives share genes and environmental factors, correlation of a particular physiological value among relatives reflects the influence of both heredity and common environmental factors. A correlation does not indicate that genes are wholly responsible for whatever correlation there is.

**Heritability**

The concept of heritability (symbolized as \( h^2 \)) was developed to quantify the role of genetic differences in determining variability of quantitative traits. Heritability is defined as the fraction of the total phenotypic variance of a quantitative trait that is caused by genes and is therefore a measure of the extent to which different alleles at various loci are responsible for the variability in a given quantitative trait seen across a population. The higher the heritability, the greater is the contribution of genetic differences among people in causing variability of the trait. The value of \( h^2 \) varies from 0, if genes contribute nothing to the total phenotypic variance, to 1, if genes are totally responsible for the phenotypic variance.

Heritability of a trait is a somewhat theoretical concept; it is estimated from the correlation between measurements of that trait among relatives of known degrees of relatedness, such as parents and children, siblings, or, as described next, MZ and DZ twins. There are, however, a number of practical difficulties in measuring and interpreting \( h^2 \). One is that relatives share more than their genes; they also share environmental exposures, and so the correlation between relatives may not reflect simply their familial genetic relationship. Second, even when the heritability of a trait is high, it does not reveal the underlying mechanism of inheritance of the trait, such as the number of loci involved or how the various alleles at those loci interact. Finally, as tempting as it is to think of heritability as an intrinsic quality of a particular quantitative trait, it cannot be considered in isolation from the population group and living conditions in which the estimate is being made.

**Estimating Heritability from Twin Studies**

Just as twin data may be used to assess the separate roles of genes and environment in qualitative disease traits, they can also be used to estimate the heritability of a quantitative trait. The variance in the values of a physiological measurement made in a set of MZ twins (who share 100% of their genes) is compared with the variance in the values of that measurement made in a set of DZ twins (who share 50% of their genes, on average). The formula for calculating \( h^2 \) is given by

\[
b^2 = \frac{\text{Variance in DZ pairs} - \text{Variance in MZ pairs}}{\text{Variance in DZ pairs}}
\]

If the variability of the trait is determined chiefly by environment, the variance within pairs of DZ twins will be similar to that seen within pairs of MZ twins, and the numerator, and therefore \( b^2 \) itself, will approach 0. If the variability is determined exclusively by genetic makeup, variance of MZ pairs is zero, and \( b^2 \) is 1.

Adult stature has been studied by geneticists for decades as a model of how genetic and environmental contributions to a quantitative trait can be apportioned. Large numbers of measurements have been collected (from military recruits, for example). A graph of the frequency of various heights in the population (see Fig. 8-2) demonstrates a bell-shaped curve that fits the normal distribution. By use of the twin method in samples of northern European extraction, \( b^2 \) for stature is estimated to be approximately 0.8, indicating that most of the variability in height among individuals is due to genotypic differences between them, not differences in environmental exposures. Thus, genes play a far greater role in determining adult height than does environment.

As another example, a comparison of MZ twins reared together or apart with DZ twins reared together or apart is a classic way of measuring heritability of complex traits. Studies of the body mass index of twins showed a high heritability value (\( b^2 = .70 \) to .80), indicating that there is a strong influence of heredity on this trait.

One has to make a number of simplifying assumptions when using twins to estimate heritability. The first is that MZ and same-sex DZ twins reared together differ only in that they share all (MZ) or, on average, half (DZ) of their genes, although their experiences and environmental exposures are identical. In analyzing the heritability of stature or body mass index, such assumptions may not be too far off the mark, but they are much more difficult to justify in estimating the heritability of more complicated quantitative measurements, such as scores on personality profiles and IQ tests. Another important caveat is that one may not always be able to extrapolate heritability estimated from twins to the population as a whole, to different ethnic groups, or even to the same group if socioeconomic conditions change over time.

**Limitations of Studies of Familial Aggregation, Disease Concordance, and Heritability**

Familial aggregation studies, the analysis of twin concordance, and estimates of heritability do not specify
which loci and alleles are involved, how many loci there are, or how a particular genotype and set of environmental influences interact to cause a disease or to determine the value of a particular physiological parameter. In most cases, all we can show is that there is a genetic contribution but little else.

Historically, geneticists lacked the tools needed to study families and populations directly to identify the factors involved in most multifactorial disease. Instead, they attempted to understand the underlying mechanisms by which complex diseases are inherited by creating theoretical models. In these models, geneticists would specify a set of alleles at various unknown loci, a number of environmental factors, and the nature of the interactions among these factors and then test the models for how well they could predict the inheritance pattern of a disease observed in actual families. A good match between theoretical prediction and observation would suggest that the theoretical model is a good approximation of the true underlying mechanism of disease. Unfortunately, many different models can fit an inheritance pattern to a first approximation, making it difficult to know which model, if any, is closest to the correct underlying mechanism. The powerful genetic analysis tools that have come out of the Human Genome Project now make it possible to analyze families and populations directly to find specific genes and alleles that contribute to disease susceptibility. Empirical studies designed to identify how particular alleles at specific loci interact with relevant environmental factors to alter susceptibility to complex disease are a central focus of the field of genetic epidemiology (to be discussed more fully in Chapter 10). The field is developing rapidly, and it is clear that the genetic basis of many more complex diseases in humans will be elucidated in the coming years.

### GENETIC AND ENVIRONMENTAL MODIFIERS OF SINGLE-GENE DISORDERS

As discussed in Chapter 7, differences in one’s genotype can explain variation in the phenotype in many single-gene disorders. In cystic fibrosis (CF), for example, whether or not a patient has pancreatic insufficiency requiring enzyme replacement can be largely explained by which mutant alleles are present in the CFTR gene. The correlation may be imperfect, however, for other alleles, loci, and phenotypes. With CF again as an example, the variation in the degree of pulmonary disease remains unexplained even after correction for allelic heterogeneity. It has been proposed that the genotypes at other genetic loci could act as genetic modifiers, that is, genes whose alleles have an effect on the severity of pulmonary disease seen in CF patients. For example, reduction in FEV₁ (forced expiratory volume after 1 second) is a commonly used measure of deterioration in pulmonary function in CF patients. FEV₁, calculated as percentage of the value expected for CF patients (a CF-specific FEV₁ percent), can be considered a quantitative trait and compared in MZ versus DZ twins to get an estimate of the heritability of the severity of lung disease in CF patients independent of the CFTR genotype (since twins have the same CF mutations). The decrease in CF-specific FEV₁ percent was found to correlate better in MZ versus DZ twins, with a heritability of 0.5, suggesting that modifier genes play a role in determining this measure of lung disease. On the other hand, since the heritability was not 1, the analysis also shows that environmental factors are likely to be important in influencing lung disease severity in CF patients with identical genotypes at the CFTR locus.

The specific loci harboring alleles responsible for modifying the severity of pulmonary disease in CF are currently not completely known. Two candidates are MBL2, a gene that encodes a serum protein called mannose-binding lectin, and the TGFβ1 locus encoding the cytokine transforming growth factor β (TGFβ). Mannose-binding lectin is a plasma protein in the innate immune system that binds to carbohydrates on the surface of many pathogenic organisms and aids in their destruction by phagocytosis and complement activation. A number of common alleles that result in reduced blood levels of the lectin exist at the MBL2 locus in European populations. Lower levels of

### Characteristics of Inheritance of Complex Diseases

- Genes contribute to diseases with complex inheritance, but these diseases are not single-gene disorders and do not demonstrate a simple mendelian pattern of inheritance.
- Diseases with complex inheritance often demonstrate familial aggregation because relatives of an affected individual are more likely to have disease-predisposing alleles in common with the affected person than are unrelated individuals.
- Pairs of relatives who share disease-predisposing genotypes at relevant loci may still be discordant for phenotype (show lack of penetrance) because of the crucial role of nongenetic factors in disease causation. The most extreme examples of lack of penetrance despite identical genotypes are discordant monozygotic twins.
- The disease is more common among the close relatives of the proband and becomes less common in relatives who are less closely related and therefore share fewer predisposing alleles. Greater concordance for disease is expected among monozygotic versus dizygotic twins.
manganese-binding lectin appear associated with worse outcomes, perhaps because of difficulties with containing respiratory tract infection and inflammation. Alleles at the TGFβ1 locus that result in higher TGFβ production are also associated with worse outcome, perhaps because TGFβ promotes lung scarring and fibrosis after inflammation.

**EXAMPLES OF MULTIFACTORIAL TRAITS FOR WHICH GENETIC AND ENVIRONMENTAL FACTORS ARE KNOWN**

**Digenic Retinitis Pigmentosa**

The simplest example of a multigenic trait (i.e., one determined by the additive effect of the genotypes at multiple loci) has been found in a few families of patients with a form of retinal degeneration called retinitis pigmentosa (Fig. 8-4). Two rare mutations in two different unlinked genes encoding proteins found in the photoreceptor are present in these families. Patients heterozygous either for a particular missense mutation in one gene, encoding the photoreceptor membrane protein peripherin, or for a null allele in the other gene, encoding a related photoreceptor membrane protein called Rom1, do not develop the disease. However, patients heterozygous for both mutations do develop the disease. Thus, this disease is caused by the simplest form of multigenic inheritance, inheritance due to the effect of mutant alleles at two loci without any known environmental factors that influence disease occurrence or severity. These two photoreceptor proteins are associated noncovalently in the stacks of membranous disks found in photoreceptors in the retina. Thus, in patients with digenic retinitis pigmentosa, the deleterious effect of each mutation alone is insufficient to cause disease, but their joint presence is sufficient to cross a threshold of cell damage, photoreceptor death, and loss of vision.

**Venous Thrombosis**

Another example of gene-gene interaction predisposing to disease is found in the group of conditions referred to as hypercoagulable states, in which venous or arterial clots form inappropriately and cause life-threatening complications. With hypercoagulability, however, there is a third factor, an environmental influence that, in the presence of the predisposing genetic factors, increases the risk of disease even more. One such disorder is idiopathic cerebral vein thrombosis, a disease in which clots form in the venous system of the brain, causing catastrophic occlusion of cerebral veins in the absence of an inciting event such as infection or tumor. It affects young adults, and although quite rare (<1 per 100,000 in the population), it carries with it a high mortality rate (5% to 30%). Three relatively common factors (two genetic and one environmental) that lead to abnormal coagulability of the clotting system are each known to individually increase the risk for cerebral vein thrombosis: a common missense mutation in a clotting factor, factor V; another common variant in the untranslated region of the gene for the clotting factor prothrombin; and the use of oral contraceptives (Fig. 8-5).

A mutant allele of factor V (factor V Leiden, FVL), in which arginine is replaced by glutamine at position 506 (Arg506Gly), has an allele frequency of approx-
mately 2.5% in white people but is rarer in other population groups. This alteration affects a cleavage site used to degrade factor V, thereby making the protein more stable and able to exert its procoagulant effect for a longer duration. Heterozygous carriers of FVL, approximately 5% of the white population, have a risk of cerebral vein thrombosis that, although still quite low, is seven times higher than that in the general population; homozygotes have a risk that is 80 times higher. The second genetic risk factor, a mutation in the prothrombin gene, changes a G to an A at position 20210 in the 3’ untranslated region of the gene (prothrombin g.20210G>A). Approximately 2.4% of white individuals are heterozygotes, but it is rare in other ethnic groups. This change appears to increase the level of prothrombin mRNA, resulting in increased translation and elevated levels of the protein. Being heterozygous for the prothrombin 20210G>A allele raises the risk of cerebral vein thrombosis 3-fold to 6-fold. Finally, the use of oral contraceptives causes a procoagulant effect through increased levels of the clotting factors in the blood. Although using oral contraceptives and being heterozygous for FVL cause only a modest increase in risk compared with either factor alone, oral contraceptive use in a heterozygote for prothrombin 20210G>A has an increased relative risk for cerebral vein thrombosis between 30 and 150! Thus, each of these three factors, two genetic and one environmental, on its own increases the risk for an abnormal hypercoagulable state; having two of these factors at the same time raises the risk for a rare, devastating illness of the cerebral vascular system even more.

These FVL and prothrombin 20210G>A alleles, as well as an allele for a heat-sensitive methylene tetrahydrofolate reductase (see later discussion), have also been implicated as serious predisposing genetic risk factors for \textit{placental artery thrombosis}. Carrying one of these mutations raises the risk an average of 5-fold above the general population risk for this rare but severe obstetrical complication. The resulting placental dysfunction is associated with severe preeclampsia, premature separation of the placenta from the uterine wall, intrauterine growth retardation, and stillbirth.

There is much interest in the role of FVL and prothrombin 20210G>A alleles in \textit{deep venous thrombosis} (DVT) of the lower extremities, a condition that is far more common than idiopathic cerebral venous or placental artery thrombosis. Lower extremity DVT occurs in approximately 1 in 1000 individuals per year, with mortality, primarily due to pulmonary embolus, of up to 10%, depending on age and the presence of other medical conditions. Many environmental factors are known to increase the risk for DVT and include trauma, surgery (particularly orthopedic surgery), malignant disease, prolonged periods of immobility, oral contraceptive use, and advanced age. FVL increases the relative risk of a first episode of DVT 7-fold in heterozygotes and 80-fold in homozygotes; heterozygotes who use oral contraceptives see their risk increased to 30-fold compared with controls. Heterozygotes for prothrombin 20210G>A also have an increase in their relative risk for DVT of 2-fold to 3-fold; double heterozygotes for FVL and prothrombin 20210G>A have a relative increased risk 20-fold above that of the general population. Interestingly, heterozygosity for either FVL or prothrombin 20210G>A alone has little effect on the risk of a recurrence of DVT after the first episode, but together they act synergistically and increase the risk of recurrence 2-fold to 3-fold.

The interaction of these genetic factors with the use of oral contraceptives has led to a proposal that physicians screen all women for the predisposing factor V and prothrombin gene mutations before prescribing birth control pills. Although carriers of the FVL and prothrombin 20210G>A alleles have an increased risk for thrombotic events above that of noncarriers, a risk that increases even more if oral contraceptives are used, these alleles are frequent in the population, as is oral contraceptive use, while the incidence of thrombotic events is small. One can only conclude, therefore, that these factors must not cause significant disease in everyone who uses birth control pills or is heterozygous for one of these alleles. If that were the case, thrombosis
would be far more frequent than it is. For example, nearly 1 in 40 white women is heterozygous for prothrombin 20210G>A, yet fewer than 1 in 1000 of these heterozygotes will develop cerebral venous thrombosis when using oral contraception.

The effect of FVL and prothrombin 20210G>A provides a clear example of the difference between increasing susceptibility to an illness and actually causing the illness, and between relative risk and absolute risk conferred by a particular genotype. A risk factor can increase risk, but still not be a good predictor in any one individual of whether one will develop the complication (see Chapter 17). As a result, there is significant controversy as to whether being a woman of childbearing age contemplating oral contraceptive use is enough to justify the expense and potential for complications for employment or insurance (in societies that lack genetic discrimination protection) of testing for FVL or prothrombin 20210G>A, unless an additional warning sign is present, such as a personal or family history of unexplained or recurrent venous thrombosis. Thus, consensus recommendations for testing for FVL or prothrombin 20210G>A (see Box) do not include screening all young women contemplating starting oral contraceptives in the absence of personal or family history of thrombosis.

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### *Consensus Recommendations for Testing for Factor V Leiden or Prothrombin 20210G>A*

- Any venous thrombosis in an individual younger than 50 years
- Venous thrombosis in unusual sites (such as hepatic, mesenteric, and cerebral veins)
- Recurrent venous thrombosis
- Venous thrombosis and a strong family history of thrombotic disease
- Venous thrombosis in pregnant women or women taking oral contraceptives
- Relatives of individuals with venous thrombosis younger than 50 years
- Myocardial infarction in female smokers younger than 50 years

---

### Hirschsprung Disease

A more complicated set of interacting genetic factors has been described in the pathogenesis of a developmental abnormality of the parasympathetic nervous system in the gut known as Hirschsprung disease (HSCR) [Case 20]. In HSCR, there is complete absence of some or all of the intrinsic ganglion cells in the myenteric and submucosal plexuses of the colon. An aganglionic colon is incapable of peristalsis, resulting in severe constipation, symptoms of intestinal obstruction, and massive dilatation of the colon (megacolon) proximal to the aganglionic segment. The disorder affects approximately 1 in 5000 newborns. HSCR occurs most commonly as an isolated defect involving a single, short segment of colon, but it can also involve long, continuous colonic segments and can also occur as one element of a broader constellation of congenital abnormalities including deafness and pigmentary abnormalities of hair and eyes (the Waardenburg-Shah syndrome).

The hereditary pattern of HSCR has many of the characteristics of a disorder with complex genetics. The relative risk ratio for infants, λ, is very high (approximately 200), but MZ twins do not show perfect concordance. HSCR can occur through multiple generations or can affect multiple siblings in a family, or both, suggesting an autosomal dominant or recessive disorder, but recurrence risks are not strictly 50% or 25% as one might expect for autosomal dominant or autosomal recessive disease traits. Finally, males have a 2-fold higher risk for developing HSCR compared with females within the same family.

Mutations in many different genes may cause the disease. In some families, HSCR affecting long colonic segments is inherited in a mendelian manner. Under these circumstances, the birth defects are most commonly due to mutations in the RET gene located at 10q11.2, encoding RET, a tyrosine kinase receptor. A small minority of families with mendelian inheritance of HSCR has mutations in the gene encoding one of the ligands that binds to RET, such as the glial cell line–derived neurotrophic factor (GDNF). Other individuals have been described with mutations in either one of another pair of genes, the EDNRB gene at 13q22 encoding the G protein–coupled endothelin receptor B, and the EDN3 gene encoding its ligand, endothelin 3, at 20q13. Endothelin receptor B and RET can signal independently along parallel pathways, as well as interact with each other to promote development of colonic ganglion cells.

Although a variety of different mutations in the coding exons of RET can cause HSCR affecting multiple individuals in a family, the penetrance of these RET alleles is far from complete. In some families, penetrance requires that an individual have both a RET mutation and a mutation in GDNF. The most likely explanation for these observations is that some mutant alleles of RET still provide residual function sufficient to prevent development of the disease unless additional dysfunction in another component of the relevant signaling pathways also occurs.

The multifactorial nature of HSCR was brought into even sharper focus when the genetic basis of the most common form of HSCR, involving only a short
segment of colon, was analyzed in families that did not show any obvious mendelian inheritance pattern for the disorder. When a set of 67 pairs of siblings concordant for HSCR were analyzed to see which loci and which sets of alleles at these loci each sib had in common with an affected brother or sister, alleles at three loci were found to be significantly shared—the 10q11.2 region, where RET is located, and two other regions, located at 3p21 and 19q12—although the particular genes responsible in these two regions are not currently known (Fig. 8-6). Most of the concordant sibpairs (55 of 67) were found to share alleles at all three loci. In particular, all of these 55 pairs of siblings had a common DNA variant in the first intron of the RET gene that reduced the function of a regulatory element. This variant is common in certain populations, with a frequency of approximately 25% of whites and approximately 40% of Asians. Because most people with the variant do not have HSCR, it must have very low penetrance and must interact with the other genetic loci to cause disease. A minority of concordant sibpairs (12 of 67) was found to share alleles at only two of the three loci, whereas none of the concordant affected sibpairs shared alleles at only one or none of the loci. Thus, HSCR is a multifactorial disease that results from the additive effects of susceptibility alleles at RET, EDNRB, and a number of other loci. The identification of a common, low-penetrant DNA variation in a noncoding enhancer within an intron of RET serves to illustrate that the gene variants responsible for modifying expression of a multifactorial trait may be subtle in how they exert their effects on gene expression and, as a consequence, on disease penetrance and expressivity. It is also sobering to realize that the underlying genetic mechanisms for this relatively well defined congenital malformation have turned out to be so surprisingly complex; still, they are likely to be far simpler than are the mechanisms involved in the more common complex diseases, such as diabetes.

Type 1 Diabetes Mellitus

There are two major types of diabetes mellitus, type 1 (insulin dependent; IDDM) and type 2 (non–insulin dependent; NIDDM), representing about 10% and 88% of all cases, respectively. They differ in typical onset age, MZ twin concordance, and association with particular alleles at the major histocompatibility complex (MHC; see Chapter 9). Familial aggregation is seen in both types of diabetes, but in any given family, usually only type 1 or type 2 is present.

Type 1 diabetes has an incidence in the white population of about 1 in 500 (0.2%) but is lower in African and Asian populations. It usually manifests in childhood or adolescence. It results from autoimmune destruction of the β cells of the pancreas, which normally produce insulin. A large majority of children who will go on to have type 1 diabetes develop multiple autoantibodies early in childhood against a variety of endogenous proteins, including insulin, well before they develop overt disease.

MHC Association in Type 1 Diabetes

There is strong evidence for genetic factors in type 1 diabetes: concordance among MZ twins is approximately 40%, which far exceeds the 5% concordance in DZ twins. The risk for type 1 diabetes in siblings of an affected proband is approximately 7%, resulting in an estimated λs = 7%/0.2% = −33. It has been known for a long time that the MHC locus (see Chapter 9) is a major genetic factor in type 1 diabetes, as suggested by the finding that about 95% of all patients with type 1
diabetes (in comparison with about half the normal population) are heterozygous for certain alleles, HLA-DR3 or HLA-DR4, at the HLA class II locus in the MHC.

The original studies showing an association between HLA-DR3 and HLA-DR4 with IDDM relied on the standard method in use at that time for distinguishing between different HLA alleles, one that was based on immunological reactions in a test tube. This method has now been superseded by direct determination of the DNA sequence of different alleles. Sequencing of the MHC in a large number of individuals has revealed that the DR3 and DR4 “alleles” are not single alleles at all. Both DR3 and DR4 can be subdivided into a dozen or more alleles located at a locus now termed DRB1, defined at the level of DNA sequence. Furthermore, it has also become clear that the association between certain DRB1 alleles and IDDM was due, in part, to alleles at another class II locus, DQB1, located about 80 kb away from DRB1, that formed a common haplotype (due to linkage disequilibrium; see Chapter 10) with each other. DQB1 encodes the \( \beta \) chain, one of the chains that forms a dimer to make up the class II DQ protein. It appears that the presence of aspartic acid (Asp) at position 57 of the DQ \( \beta \) chain (see Fig. 9-7) is closely associated with resistance to type 1 diabetes, whereas other amino acids at this position (alanine, valine, or serine) confer susceptibility. About 90% of patients with type 1 diabetes are homozygous for DQB1 alleles that do not encode Asp at position 57. Given that the DQ molecule, and position 57 of the \( \beta \) chain in particular, is critical in peptide antigen binding and presentation to the T cell for response, it is likely that differences in antigen binding, determined by which amino acid is at position 57 of the \( \beta \) chain of DQ, contribute directly to the autoimmune response that destroys the insulin-producing cells of the pancreas. Other loci and alleles in the MHC, however, are also important, as can be seen from the fact that some patients with type 1 diabetes do have an aspartic acid at this position in the DQ \( \beta \) chain.

**Genes Other than Class II MHC Loci in Type 1 Diabetes**

The MHC haplotype alone accounts for only a portion of the genetic contribution to the risk for type 1 diabetes in siblings of a proband. Family studies in type 1 diabetes (Table 8-5) suggest that even when siblings share the same MHC class II haplotypes, the risk of disease is approximately 17%, still well below the MZ twin concordance rate of approximately 40%. Thus, there must be other genes, elsewhere in the genome, that also predispose to the development of type 1 diabetes, assuming MZ twins and sibs have similar environmental exposures. Besides the MHC, variation at more than a dozen loci has been proposed to increase susceptibility to type 1 diabetes, but substantial evidence is available for only three. These include a variable number tandem repeat polymorphism in the promoter of the insulin gene itself and single nucleotide polymorphisms in the immune regulatory gene CTLA4 and in the PTPN22 gene encoding a protein phosphatase (see Chapter 9). Identification of other susceptibility genes for type 1 diabetes, both within and outside the MHC, remains the target of intensive investigation. At present, the nature of the nongenetic risk factors in type 1 diabetes is largely unknown.

Genetic factors alone, however, do not cause type 1 diabetes, because the MZ twin concordance rate for type 1 diabetes is only approximately 40%, not 100%. Until a more complete picture develops of the genetic and nongenetic factors that cause type 1 diabetes, risk counseling must remain empirical (see Table 8-5).

### Table 8-5

**Empirical Risks for Counseling in Type 1 Diabetes**

<table>
<thead>
<tr>
<th>Relationship to Affected Individual</th>
<th>Risk for Development of Type 1 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ twin</td>
<td>40%</td>
</tr>
<tr>
<td>Sibling</td>
<td>7%</td>
</tr>
<tr>
<td>Sibling with no DR haplotypes in common</td>
<td>1%</td>
</tr>
<tr>
<td>Sibling with 1 DR haplotype in common</td>
<td>5%</td>
</tr>
<tr>
<td>Sibling with 2 DR haplotypes in common</td>
<td>17% (20%-25% if shared haplotype is DR3/DR4)</td>
</tr>
<tr>
<td>Child</td>
<td>4%</td>
</tr>
<tr>
<td>Child of affected mother</td>
<td>3%</td>
</tr>
<tr>
<td>Child of affected father</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Alzheimer Disease**

Alzheimer disease (AD) is a fatal neurodegenerative disease that affects 1% to 2% of the United States population. It is the most common cause of dementia in the elderly and is responsible for more than half of all cases of dementia. As with other dementias, patients experience a chronic, progressive loss of memory and other intellectual functions, associated with death of cortical neurons. Age, gender, and family history are the most significant risk factors for AD. Once a person reaches 65 years of age, the risk for any dementia, and AD in particular, increases substantially with age and female sex (Table 8-6).

AD can be diagnosed definitively only postmortem, on the basis of neuropathological findings of characteristic protein aggregates (\( \beta \)-amyloid plaques and neurofibrillary tangles; see Chapter 12). The most important constituent of these plaques is a small (39 to 42–amino
acids) peptide, Aβ, derived from cleavage of a normal neuronal protein, the amyloid protein precursor. The secondary structure of Aβ gives the plaques the staining characteristics of amyloid proteins.

In addition to these rare autosomal dominant forms of the disease (see Table 12-9), in which disease onset is in the third to fifth decade, there is a common form of AD with onset after the age of 60 years (late onset). This form has no obvious mendelian inheritance pattern but does show familial aggregation and an elevated relative risk ratio \( (\lambda = 4-5) \) typical of disorders with complex inheritance. Individuals with a first-degree relative with AD have an approximately 3-fold to 4-fold increased risk of developing AD as well. Twin studies have been inconsistent but suggest MZ concordance of about 50% and DZ concordance of about 18%.

The ε4 Allele of Apolipoprotein E

The first significant genetic factor associated with common late-onset AD was the apolipoprotein E (APOE) locus. Apolipoprotein E is a protein component of the low-density lipoprotein (LDL) particle and is involved in clearing LDL through an interaction with high-affinity receptors in the liver. Apolipoprotein E is also a constituent of amyloid plaques in AD and is known to bind the Aβ peptide. The APOE gene maps to chromosome 19 and has three alleles, ε2, ε3, and ε4, due to substitutions of arginine for two different cysteine residues in the protein (see Table 12-10).

When the genotypes at the APOE locus were analyzed in AD patients and controls, a genotype with at least one ε4 allele was found two to three times more frequently among the patients compared with controls (Table 8-7) in both the general United States and Japanese populations, with much less of an association in the Hispanic and African American populations. Even more striking is that the risk for AD appears to increase further if both APOE alleles are ε4, through an effect on the age at onset of AD; patients with two ε4 alleles have an earlier onset of disease than do those with only one. In a study of patients with AD and unaffected controls (Fig. 8-7), the age at which AD developed in the affected patients was earliest for ε4/ε4 homozygotes, next for ε4/ε3 heterozygotes, and significantly less for the other genotypes.

In the population in general, the ε4 allele is clearly a predisposing factor that increases the risk for development of AD by shifting the age at onset to an earlier age. AD develops before most patients die of other life-threatening illnesses of the elderly. Despite this

<p>| Table 8-6 |
|-------------------|-------------------|
| <strong>Cumulative Age- and Sex-Specific Risks for Alzheimer Disease and Dementia</strong> |</p>
<table>
<thead>
<tr>
<th>Time Interval Past 65 Years of Age</th>
<th>Risk for Development of AD (%)</th>
<th>Risk for Development of Any Dementia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 to 80 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6.3</td>
<td>10.9</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>65 to 100 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>32.8</td>
</tr>
<tr>
<td>Female</td>
<td>28.1</td>
<td>45</td>
</tr>
</tbody>
</table>


**Figure 8-7** ▪ Chance of remaining unaffected by Alzheimer disease as a function of age for different APOE genotypes. At one extreme is the ε4/ε4 homozygote who has a less than 10% chance of remaining free of the disease by the age of 80 years, whereas an ε2/ε3 heterozygote has a more than 80% chance of remaining disease free at the age of 80 years. (Modified from Strittmatter WJ, Roses AD: Apolipoprotein E and Alzheimer’s disease. Annu Rev Neurosci 19: 53-77, 1996.)

| Table 8-7 |
|-------------------|-------------------|
| **Association of Apolipoprotein E ε4 Allele with Alzheimer Disease** |
| Genotype           | AD United States | AD Japan |
| ε4/ε4; ε4/ε3; or ε4/ε2 | 0.64            | 0.17      |
| ε3/ε3; ε2/ε3; or ε2/ε2 | 0.36            | 0.53      |

*Frequency of genotypes with and without the ε4 allele among Alzheimer disease (AD) patients and controls from the United States and Japan.
increased risk, other genetic and environmental factors must be important because many ε4/ε4 homozygotes live to extreme old age with no evidence for AD, and 50% to 75% of all heterozygotes carrying one ε4 allele never develop AD. There is also an association between the presence of the ε4 allele and neurodegenerative disease after head injury (as seen in professional boxers), indicating that at least one environmental factor, brain trauma, interacts with the ε4 allele in the pathogenesis of AD. Thus, the ε4 variant of ApoE represents a prime example of a predisposing allele: it predisposes to a complex trait in a powerful way but does not predestine any individual carrying the allele to develop the disease. Additional genes as well as environmental effects are also clearly involved but remain to be identified. Testing of asymptomatic people for the ε4 allele remains inadvisable because knowing that one is a heterozygote or homozygote for the ε4 allele does not mean one will develop AD, nor is there any intervention currently known that can affect the chance one will or will not develop AD (see Chapter 17).

### Multifactorial Congenital Malformations

Several common congenital malformations, occurring as isolated defects and not as part of a syndrome, seem to recur in families. The familial aggregation and elevated risk of recurrence in relatives of an affected individual are all characteristic of a complex trait (Tables 8-8 to 8-10). Some of the more important congenital malformations with complex inheritance are neural tube defects, cleft lip with or without cleft palate, and congenital heart malformations.

#### Neural Tube Defects

Anencephaly and spina bifida are neural tube defects (NTDs) that frequently occur together in families and are considered to have a common pathogenesis (Fig. 8-8; also see Table 8-9). In anencephaly, the forebrain, overlying meninges, vault of the skull, and skin are all absent. Many infants with anencephaly are stillborn, and those born alive survive a few hours at most. About two thirds of affected infants are female. In spina bifida, there is failure of fusion of the arches of the

![Table 8-8: Some Common Congenital Malformations with Multifactorial Inheritance](image)

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Population Incidence (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft lip with or without cleft palate</td>
<td>0.4–1.7</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>0.4</td>
</tr>
<tr>
<td>Congenital dislocation of hip</td>
<td>2*</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>4–8</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>1.7</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>0.5</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>1.0</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>0.5</td>
</tr>
<tr>
<td>Neural tube defects</td>
<td>2–10</td>
</tr>
<tr>
<td>Spina bifida and anencephaly</td>
<td>Variable</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>1*, 5*</td>
</tr>
</tbody>
</table>

*Per 1000 males.

Table 8-9: Recurrence Risks (%) for Cleft Lip with or without Cleft Palate and for Neural Tube Malformations*

<table>
<thead>
<tr>
<th>Affected Relatives</th>
<th>Cleft Lip with or without Cleft Palate</th>
<th>Anencephaly and Spina Bifida</th>
</tr>
</thead>
<tbody>
<tr>
<td>No sibs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither parent</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>One parent</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>Both parents</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>One sib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither parent</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>One parent</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Both parents</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Two sibs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither parent</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>One parent</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Both parents</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>One sib and one second-degree relative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither parent</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>One parent</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Both parents</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>One sib and one third-degree relative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither parent</td>
<td>4</td>
<td>5.5</td>
</tr>
<tr>
<td>One parent</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Both parents</td>
<td>44</td>
<td>42</td>
</tr>
</tbody>
</table>

*These recurrence risks within families were calculated before the widespread introduction of maternal folic acid supplementation during pregnancy (see later).


<table>
<thead>
<tr>
<th>Table 8-10: Empirical Risks for Cleft Lip with or without Cleft Palate in Relatives of Affected Probands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Affected</td>
</tr>
<tr>
<td>General population</td>
</tr>
<tr>
<td>First-degree relatives</td>
</tr>
<tr>
<td>Second-degree relatives</td>
</tr>
<tr>
<td>Third-degree relatives</td>
</tr>
</tbody>
</table>
vertebrae, typically in the lumbar region. There are varying degrees of severity, ranging from spina bifida occulta, in which the defect is in the bony arch only, to spina bifida aperta, in which a bone defect is also associated with meningocele (protrusion of meninges) or meningomyelocele (protrusion of neural elements as well as meninges through the defect; see Fig. 8-8).

As a group, NTDs are a leading cause of stillbirth, death in early infancy, and handicap in surviving children. Their incidence at birth is variable, ranging from almost 1% in Ireland to 0.2% or less in the United States. The frequency also appears to vary with social factors and season of birth and oscillates widely over time (with a marked decrease in recent years; see later discussion).
A small proportion of NTDs have known specific causes, for example, amniotic bands (fibrous connections between the amnion and fetus caused by early rupture of the amnion, which may disrupt structures during their embryological development), some single-gene defects with pleiotropic expression, some chromosome disorders, and some teratogens. Most NTDs, however, are isolated defects of unknown cause.

**Maternal Folic Acid Deficiency and Neural Tube Defects** NTDs were long believed to follow a multifactorial inheritance pattern determined by multiple genetic and environmental factors. It was therefore a stunning discovery to find that the single greatest factor in causing NTDs is a vitamin deficiency. The risk of NTDs was found to be inversely correlated with maternal serum folic acid levels during pregnancy, with a threshold of 200 µg/L, below which the risk of NTD becomes significant. Along with reduced blood folate levels, elevated homocysteine levels were also seen in the mothers of children with NTDs, suggesting that a biochemical abnormality was present at the step of recycling of tetrahydrofolate to methylate homocysteine to methionine (see Fig. 12-7). Folic acid levels are strongly influenced by dietary intake and can become depressed during pregnancy even with a typical intake of approximately 230 µg/day. The impact of folic acid deficiency is exacerbated by a genetic variant of the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), caused by a common missense mutation that makes the enzyme less stable than normal. Instability of this enzyme hinders the recycling of tetrahydrofolate and interferes with the methylation of homocysteine to methionine. The mutant allele is so common in many populations that between 5% and 15% of the population is homozygous for the mutation. In studies of infants with NTDs and their mothers, it was found that mothers of infants with NTDs were twice as likely as controls to be homozygous for the mutant allele encoding the unstable enzyme. Not all mothers of NTD infants with low folic acid levels are homozygous for the mutant allele of MTHFR, however, indicating that low folic acid levels may be caused by other unknown genetic factors or by simple dietary deficiency alone. How this enzyme defect contributes to NTDs and whether the abnormality is a direct result of elevated homocysteine levels, depressed methionine levels, or some other metabolic derangement remains undefined.

**Prevention of Neural Tube Defects** The discovery of folic acid deficiency in NTDs has led to a remarkable public health initiative to educate women to supplement their diets with folic acid 1 month before conception and continuing for 2 months after conception during the period when the neural tube forms. Dietary supplementation with 400 to 800 µg of folic acid per day for women who plan their pregnancies has been shown to reduce the incidence of NTDs by more than 75%. Much active discussion is ongoing as to whether the entire food supply should be supplemented with folic acid as a public health measure to avoid the problem of women failing to supplement their diets individually during pregnancy.

Parents of children with an NTD potentially are at increased risk for a recurrence in future pregnancies (see Table 8-9). These risks are now more potential than real since they can be substantially modified by dietary folic acid supplementation.

NTDs also rank high among the conditions for which prenatal diagnosis is possible; anencephaly and most cases of open spina bifida can be identified prenatally by detection of excessive levels of *alpha-fetoprotein* (AFP) and other fetal substances in the amniotic fluid and by ultrasonographic scanning (see Chapter 15 for further discussion). However, less than 5% of all patients with NTDs are born to women with previous affected children. For this reason, screening of all pregnant women for NTDs by measurements of AFP and other fetal substances in maternal serum is becoming more widespread. Thus, we can anticipate that a combination of preventive folic acid therapy and maternal AFP screening will provide major public health benefits by drastically reducing the incidence of NTDs.

**Cleft Lip and Cleft Palate**

Cleft lip with or without cleft palate, or CL(P), is one of the most common congenital malformations, affecting 1.4 per thousand newborns worldwide. There is considerable variation in frequency in different ethnic groups: about 1.7 per 1000 in Japanese, 1.0 per 1000 in whites, and 0.4 per 1000 in African Americans. Relatively high rates are also seen in some North American populations of Asian descent, for example, in Indians of the southwest United States and the west coast of Canada. The concordance rate is approximately 30% in MZ twins and approximately 2% (the same as the risk for non-twin sibs) in DZ twins (see Table 8-4). CL(P), which is usually etiologically distinct from isolated cleft palate without cleft lip, originates as a failure of fusion of the frontal process with the maxillary process at about the 35th day of gestation. About 60% to 80% of those affected with CL(P) are males. CL(P) is heterogeneous and includes forms in which the clefting is only one feature of a syndrome that includes other anomalies—*syndromic CL(P)*—as well as forms that are not associated with other birth defects—*nonsyndromic CL(P)*. Syndromic CL(P) can be inherited as a mendelian single-gene disorder or can be caused by chromosome disorders (especially trisomy 13 and 4p−) (see Chapter 6) or teratogenic exposure...
(rubella embryopathy, thalidomide, or anticonvulsants) (see Chapter 14). Nonsyndromic CL(P) can also be inherited as a single-gene disorder but more commonly is a sporadic occurrence in some families and demonstrates some degree of familial aggregation without an obvious mendelian inheritance pattern in others (see Table 8-9). One of the predictions of multifactorial inheritance is that the recurrence risk increases the more affected relatives an individual has in the family (see Tables 8-9 and 8-10). Another prediction of multifactorial inheritance is that the risk for CL(P) in relatives of probands that are severely affected will be greater than the risk to relatives of mildly affected probands. Indeed, in families with a proband with an isolated case of CL(P), there is an increase in recurrence risk with increasing severity in the proband, from unilateral to bilateral, and from cleft lip alone to CL(P) (Table 8-11). The explanation for all of these observations is that more severe disease and more affected relatives of the proband indicate a greater load of alleles predisposing to disease in the family.

Progress in identifying genes responsible for multifactorial nonsyndromic CL(P) has come from the study of rare single-gene forms of syndromic CL(P). These include X-linked clefting with ankyloglossia (tethering of tongue by short or anterior frenulum) and two forms of autosomal dominant clefting, one associated with missing teeth and the other with infertility and anosmia (inability to smell). These three mendelian forms of syndromic clefting result from mutations in two transcription factor genes, TBX1 and MSX1, and in the gene FGFR1, which encodes a cell signaling molecule. The most striking finding, however, is that a variety of rare mutations have now been found in all three of these genes in patients from a variety of different ethnic backgrounds who appear to have nonsyndromic CL(P). The frequency of mutation in CL(P) patients is approximately 5% for TBX1, approximately 2% for MSX1, and 1% for FGFR1. In all cases, investigation of additional family members may disclose affected individuals with more typical features of the syndromes associated with mutations in that gene. Another transcription factor gene, IRF6, in which mutations cause the syndromic form of CL(P) known as Van der Woude syndrome, is also involved in nonsyndromic clefting. Van der Woude syndrome has pits in the lower lip in 85% of patients, but 15% may present only with cleft lip or palate. What is very likely, however, is that these genes represent only a fraction of the total genetic contribution to this birth defect and that marked locus and allelic heterogeneity will be the rule. It is unknown to what extent the majority of CL(P) patients will turn out to have the defect because of rare alleles at additional single loci, or because of multifactorial interactions between more common alleles at many loci. Finally, maternal smoking is a well recognized risk factor for CL(P). The degree of risk associated with this environmental factor may itself have a genetic basis due to genetic variation in the mother or the fetus that alters how contaminants produced by tobacco smoke are metabolized.

Sequencing of the genes implicated in CL(P) may provide useful information in families seeking genetic counseling, particularly when there is a family history suggestive of some of the anomalies involving tongue, teeth, ability to smell, or infertility. However, the utility of mutation detection is limited by our lack of knowledge of the penetrance of the spectrum of mutant alleles that may be present at all four of these loci. In the absence of any specific information as to the involvement of a particular locus or mutation, the empirical risk figures (see Tables 8-9 to 8-11) are the only guidelines available for genetic counseling.

**Congenital Heart Defects**

Congenital heart defects (CHDs) are common, with a frequency of about 4 to 8 per 1000 births. They are a heterogeneous group, caused in some cases by single-gene or chromosomal mechanisms and in others by exposure to teratogens, such as rubella infection or maternal diabetes. The cause is usually unknown, and the majority of cases are believed to be multifactorial in origin.

There are many types of CHDs, with different population incidences and empirical risks. It is known that when heart defects recur in a family, however, the affected children do not necessarily have exactly the same anatomical defect but instead show recurrence of lesions that are similar with regard to developmental mechanisms. With use of developmental mechanism as a classification scheme, five main groups of CHDs can be distinguished: flow lesions, defects in cell migration or in cell death, abnormalities in extracellular matrix, and defects in targeted growth. A familial pattern is found primarily in the group with flow lesions, a large category constituting about 50% of all CHDs. Flow
lesions include hypoplastic left heart syndrome, coarctation of the aorta, atrial septal defect of the secundum type, pulmonary valve stenosis, a common type of ventricular septal defect, and other forms (Fig. 8-9). Up to 25% of patients with all flow lesions, particularly tetralogy of Fallot, may have the deletion of chromosome region 22q11 seen in the velocardiofacial syndrome (see Chapter 6).

Are isolated CHDs inherited as multifactorial traits? For flow lesions, the relative risk ratios for sibs, \( \lambda_{sib} \), support familial aggregation for this class of CHD (Table 8-12). Until more is known, the figures given can be used as estimates of the recurrence risk for flow lesions in first-degree relatives. There is, however, a rapid fall-off in risk (to levels not much higher than the population risk) in second- and third-degree relatives of index patients with flow lesions. Similarly, relatives of index patients with types of CHDs other than flow lesions can be offered reassurance that their risk is no greater than that of the general population. For further reassurance, many CHDs can now be assessed prenatally by ultrasonography (see Chapter 15).

### Mental Illness

Mental illnesses are some of the most common and perplexing of human diseases, affecting 4% of the human population worldwide. The annual cost in medical care and social services exceeds $150 billion in the United States alone. Among the most severe of the mental illnesses are schizophrenia and bipolar disease (manic-depressive illness).

Schizophrenia affects 1% of the world’s population. It is a devastating psychiatric illness, with onset commonly in late adolescence or young adulthood, and is characterized by abnormalities in thought, emotion, and social relationships, often associated with delusional thinking and disordered mood. A genetic contribution to schizophrenia is supported by both twin and...
family aggregation studies. MZ concordance in schizophrenia is estimated to be 40% to 60%; DZ concordance is 10% to 16%. The recurrence risk ratio is elevated in first- and second-degree relatives of schizophrenic patients (Table 8-13).

Although there is considerable evidence of a genetic contribution to schizophrenia, little certainty exists as to the genes and alleles that predispose to the disease. Counseling, therefore, relies on empirical risk figures (see Table 8-13). One exception is the high prevalence of schizophrenia in carriers of the 22q11 deletion responsible for the velocardiofacial syndrome (also referred to as the DiGeorge syndrome) (see Chapter 6). It is estimated that 25% of patients with 22q11 deletions develop schizophrenia, even in the absence of many or most of the other physical signs of the syndrome. The mechanism by which a deletion of 3 Mb of DNA on 22q11 causes mental illness in patients with the velocardiofacial syndrome is unknown.

Bipolar disease is predominantly a mood disorder in which episodes of mood elevation, grandiosity, high-risk dangerous behavior, and inflated self-esteem (mania) alternate with periods of depression, decreased interest in what are normally pleasurable activities, feelings of worthlessness, and suicidal thinking. The prevalence of bipolar disease is 0.8%, approximately equal to that of schizophrenia, with a similar age at onset. The seriousness of this condition is underscored by the high (10% to 15%) rate of suicide in affected patients.

A genetic contribution to bipolar disease is strongly supported by twin and family aggregation studies. MZ twin concordance is 62%; DZ twin concordance is 8%. Disease risk is also elevated in relatives of affected individuals (Table 8-14). One striking aspect of bipolar disease in families is that the condition has variable expressivity; some members of the same family demonstrate classic bipolar illness, others have depression alone (unipolar disorder), and others carry a diagnosis of a psychiatric syndrome that involves both thought and mood (schizoaffective disorder). As with schizophrenia, the genes and alleles that predispose to bipolar disease are largely unknown. Counseling, therefore, relies on empirical risk figures (see Table 8-14).

**Coronary Artery Disease**

Coronary artery disease (CAD) kills about 450,000 individuals in the United States yearly and is the number one cause of morbidity and mortality in the developed world. CAD due to atherosclerosis is the major cause of the nearly 1,500,000 cases of myocardial infarction (MI) and the more than 200,000 deaths from acute MI occurring annually. In the aggregate, CAD costs more than $100 billion in health care expenses and lost productivity each year in the United States. For unknown reasons, males are at higher risk for CAD both in the population and within affected families.

Family and twin studies have repeatedly supported a role for heredity in CAD, particularly when it occurs in relatively young individuals. The recurrence risk in male first-degree relatives is greater than that in the general population when the proband is female (7-fold increased) compared with the 2.5-fold increased risk in female relatives of a male index case. When the proband is young (<35 years), the risk for CAD is 11.4-fold that of the general population. Twin studies show similar trends. A study of 21,004 twins in Sweden revealed that after controlling for risk factors such as diabetes, smoking, and hypertension, if one male twin experienced an MI before the age of 65 years, the other twin’s risk for MI was increased 6-fold to 8-fold if he was an MZ twin and 3-fold if a DZ twin. Among female twins, the increase in risk for MI in MZ twins was even greater: 15-fold for an MZ twin and only 2.6-fold for a DZ twin when one twin experienced an MI before the age of 65 years. The older the first twin was at time of MI, the less increased was the risk to the other twin. This pattern of increased risk suggests that when the index case is female or young, there is likely to be a greater genetic contribution to MI in the family, thereby increasing the risk for disease in the proband’s relatives.

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**Table 8-13**

<table>
<thead>
<tr>
<th>Relation to Individual Affected by Schizophrenia</th>
<th>Recurrence Risk (%)</th>
<th>λr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child of two schizophrenic parents</td>
<td>46</td>
<td>23</td>
</tr>
<tr>
<td>Child</td>
<td>9-16</td>
<td>11.5</td>
</tr>
<tr>
<td>Sibling</td>
<td>8-14</td>
<td>11</td>
</tr>
<tr>
<td>Nephew or niece</td>
<td>1-4</td>
<td>2.5</td>
</tr>
<tr>
<td>Uncle or aunt</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>First cousin</td>
<td>2-6</td>
<td>4</td>
</tr>
<tr>
<td>Grandchild</td>
<td>2-8</td>
<td>5</td>
</tr>
</tbody>
</table>

*From [www.nchpeg.org/cdrom/empiric.html](http://www.nchpeg.org/cdrom/empiric.html).*

**Table 8-14**

<table>
<thead>
<tr>
<th>Relation to Individual Affected with Bipolar Disease</th>
<th>Recurrence Risk (%)</th>
<th>λr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child of two parents with bipolar disease</td>
<td>50-70</td>
<td>75</td>
</tr>
<tr>
<td>Child</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>Sibling</td>
<td>20-30</td>
<td>31</td>
</tr>
<tr>
<td>Second-degree relative</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

*Recurrence of bipolar, unipolar, or schizoaffective disorder. From [www.nchpeg.org/cdrom/empiric.html](http://www.nchpeg.org/cdrom/empiric.html).*

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There are many stages in the evolution of atherosclerotic lesions in the coronary artery at which genetic differences may predispose or protect from CAD (Fig. 8-10; also see Box). What begins as a fatty streak in the intima of the artery evolves into a fibrous plaque containing smooth muscle, lipid, and fibrous tissue. These intimal plaques become vascular and may bleed, ulcerate, and calcify, thereby causing severe vessel narrowing as well as providing fertile ground for thrombosis resulting in sudden, complete occlusion and MI.

A few mendelian disorders with CAD are known. Familial hypercholesterolemia ([Case 14]), an autosomal dominant defect of the LDL receptor discussed in Chapter 12, is the most common of these but accounts for only about 5% of survivors of MI. Most cases of CAD show multifactorial inheritance, with both non-genetic and genetic predisposing factors. The risk factors for CAD include several other multifactorial disorders with genetic components: hypertension, obesity, and diabetes mellitus. In this context, the metabolic and physiological derangements represented by these disorders also contribute to enhancing the risk of CAD. Diet, physical activity, and smoking are environmental factors that also play a major role in influencing the risk for CAD. Given all the different proteins and environmental factors that contribute to the development of CAD, it is easy to imagine that genetic susceptibility to CAD could be a complex multifactorial condition (see Box).

CAD is often an incidental finding in family histories of patients with other genetic diseases. In view of the high recurrence risk, physicians and genetic counselors may need to consider whether first-degree relatives of patients with CAD should be evaluated further and offered counseling and therapy, even when CAD is not the primary genetic problem for which the patient or relative has been referred. Such an evaluation is clearly indicated when the proband is young.

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### Genes and Gene Products Involved in the Stepwise Process of Coronary Artery Disease

A large number of genes and gene products have been suggested and, in some cases, implicated in promoting one or more of the developmental stages of coronary artery disease. These include genes encoding proteins involved in the following:

- Serum lipid transport and metabolism—cholesterol, apolipoprotein E, C-III, the LDL receptor, and lipoprotein(a)—as well as total cholesterol level. Elevated low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol, both of which elevate the risk for coronary artery disease, are themselves quantitative traits with significant heritabilities of 40% to 60% and 45% to 75% respectively.
- Vasoactivity, such as angiotensin-converting enzyme
- Blood coagulation, platelet adhesion, and fibrinolysis, such as plasminogen activator inhibitor 1, and the platelet surface glycoproteins Iib and IIIa
- Inflammatory and immune pathways
- Arterial wall components

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**Figure 8-10**  -- Sections of coronary artery demonstrating the steps leading to coronary artery disease. Genetic and environmental factors operating at any or all of the steps in this pathway can contribute to the development of this complex, common disease. (Modified from an original figure by Larry Almonte, with permission.)
Genetic Counseling of Families of Patients with Multifactorial Traits

The underlying mechanisms by which genes and environment interact to cause diseases with complex inheritance are largely unknown. For genetic counseling, we are dependent on measuring actual recurrence risks in collections of families to generate average empirical estimates of the recurrence risks. Of course, the actual risk for an individual family may be larger or smaller than the average. For now, these population-based empirical risks, although often inadequate, are the only source available for genetic prediction. Certain general principles must be considered, however, in providing genetic counseling for multifactorial disorders:

- The recurrence risk is much higher for first-degree relatives of affected family members than for more distant relatives.
- The best estimate of the recurrence risk is the empirical risk, which is simply the recurrence risk, observed in similar families, for a relative with the same degree of relationship. It is often useful to state the empirical risk as a multiple of the population risk of the defect. The empirical risk is based entirely on past experience and does not imply that the genetic and environmental factors in the pathogenesis of the malformation are understood. An empirical risk is an average for the population and is not necessarily accurate for a specific family.
- In general, the recurrence risk is increased by the presence of more than one affected relative; a severe form or an early onset of the disorder; an affected person of the sex less likely to be affected; and consanguineous parentage.

Two common errors in risk calculation should be avoided:

- If the parent of a child with a multifactorial birth defect has another child by a different partner, the children are second-degree, not first-degree, relatives, and the empirical risk for the second child is much lower than if the children had both parents in common (usually, the risk is approximately 1% instead of approximately 5%).

- When an unaffected uncle or aunt of a child with a multifactorial defect inquires about the risk of the same defect in his or her offspring, the relevant risk is not the risk to the aunt or uncle (a second-degree relative to the proband) but the risk to the offspring of the aunt or uncle (a third-degree relative).

For many common disorders with familial aggregation, a minority of cases will be due to single-gene disorders with mendelian inheritance that is masked by small family sizes and incomplete penetrance. Because the recurrence risk is much higher in mendelian forms, the geneticist needs to maintain a high index of suspicion that there may be a single-gene disorder when there is anything unusual about the disease presentation, particularly if there is an unusually early age of onset or if there are associated clinical features not typically found in the disorder. Mendelian forms of the disorder may have characteristic clinical or laboratory features that need to be specifically investigated.

GENERAL REFERENCES


REFERENCES FOR SPECIFIC TOPICS


**USEFUL WEBSITE**

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**PROBLEMS**

1. For a certain malformation, the recurrence risk in sibs and offspring of affected persons is 10%, the risk in nieces and nephews is 5%, and the risk in first cousins is 2.5%.
   a. Is this more likely to be an autosomal dominant trait with reduced penetrance or a multifactorial trait? Explain.
   b. What other information might support your conclusion?

2. A large sex difference in affected persons is often a clue to X-linked inheritance. How would you establish that pyloric stenosis is multifactorial rather than X-linked?

3. A series of children with a particular congenital malformation includes both boys and girls. In all cases, the parents are normal. How would you determine whether the malformation is more likely to be multifactorial than autosomal recessive?