Classification of Genetic Disorders
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Key Points
- Single-gene disorders are caused by mutations of specific genes in the human genetic material.
- Polymorphic changes are variations in the genetic material that do not cause disease but may increase an individual's susceptibility to a particular disease.
- X-linked disorders are caused by an inheritance of a mutant gene found in the X chromosome.
- Common diseases of adults, such as coronary artery disease, hypertension, diabetes, and some congenital malformations, are not inherited as a single-gene disorder or a chromosomal abnormality.

Chromosomal Disorders

Genetic material is packaged within the nucleus of the cell in nuclear material termed chromatin. When a cell divides, the genetic material in the nucleus condenses into rod-shaped structures known as chromosomes. The total human DNA material is packaged into 46 chromosomes. The 46 chromosomes include 22 pairs of alike, or homologous, chromosome [homologs] called autosomes and two sex chromosomes, X and Y. Females have two X chromosomes (XX) and males have an X and a Y chromosome (XY). Each chromosome has a characteristic size and shape that allows the numbering and identification of individual chromosomes.

The study of chromosome structure and inheritance is called cytogenetics (Fig. 120.1). Cells for chromosomal analysis must be able to divide in culture, which limits the analysis of human chromosomes to a few cell types. Included in the cells available for study are T lymphocytes collected from the peripheral blood and stimulated to divide with phytohemagglutinin, fibroblasts explanted from skin biopsies and maintained in culture, bone marrow cells, and amniocytes. The chromosomes of a dividing cell are most easily analyzed at the metaphase or the prometaphase-3 stage of mitosis, or cell division. The chromosomes are stained, most typically with Giemsa banding, or G-banding, resulting in a pattern of light and dark bands that is unique for each human chromosome. Approximately 350 to 500 bands are identifiable on the chromosomes using this technique. Morphologically, chromosomes consist of two chromatids joined at the centromere, or central constriction. The centromere divides the chromosome into the long arm, designated q, and the short arm, designated p. Chromosomal morphology and staining allow the identification of the 22 homologous chromosomes and the two sex chromosomes [XX or XY], termed a karyotype (Fig. 120.2).

Chromosomal disorders result from an excess or deficiency of whole chromosomes or portions of chromosomes. There are many documented numeric and structural abnormalities in chromosomes in the human karyotype, and many of these are associated with cardiovascular disease, including Down syndrome [trisomy of chromosome 21] and velocardiofacial syndrome (chromosomal microdeletions in the q11 band of chromosome 22). The major chromosomal disorders associated with cardiovascular disease lead primarily to congenital heart disease.

Aneuploidy is the most common and clinically significant type of chromosomal disorder. Aneuploidy exists when an entire chromosome is missing or when there is an extra chromosome, which means an abnormal number of chromosomes are found on karyotype analysis. Most patients with aneuploidy have trisomy or an extra chromosome (resulting in three homologous chromosomes rather than two). Monosomy, or the loss of an entire chromosome (resulting in only one chromosome of a homologous pair), occurs less often.

Abnormalities of chromosome structure involve chromosomal rearrangement caused by chromosome breakage followed by reconstitution in an abnormal form. Structural rearrangements can involve one or two chromosomes and can retain a complete complement of genetic material (which usually does not result in a clinical phenotype) or can lead to the loss (deletion) or gain (duplication) of chromosomal material. Typically, duplication, or gain, of portions of human chromosomes is less harmful clinically than is the loss of genetic material.

Contiguous-gene syndromes are disorders caused by microduplications or deletions of chromosomal segments...
involving genes linked together on the chromosome. Some contiguous-gene syndromes can be recognized by routine cytogenic techniques. Other syndromes are not visible when such techniques are used, so detection requires high-resolution chromosome analysis or studies using fluorescent in situ hybridization. Typically, these syndromes are sporadic, but some of the disorders can be inherited in an autosomal dominant manner.

Single-Gene Disorders

Single-gene disorders are caused by mutations of specific genes in the human genetic material. Human chromosomes contain an estimated 50,000 to 100,000 genes coding for a variety of proteins and RNAs that serve specific functions in cells and tissues. These disorders follow the patterns of inheritance originally identified by Mendel in his studies of garden peas [mendelian inheritance]. At present, over 10,000 single-gene disorders that are inherited in a mendelian manner have been identified. A genetic locus is a specific location on a chromosome, often used to refer to a certain gene. Alleles are alternative forms of a locus or a gene. An individual with two alike alleles at a given gene is homozygous. If the alleles are different, the individual is heterozygous at the locus.

Changes at a given locus or gene may be benign. Polymorphic changes are variations in the genetic material that do not cause disease but may increase an individual's susceptibility to a particular disease. In contrast, changes in DNA that do produce disease are termed mutations. Mutations in specific genes are the underlying causes of single-gene disorders. Disorders are said to be either autosomal or X-linked, based on the chromosomal location of the mutant gene. Autosomal single-gene disorders are caused by mutations in genes on one of the 22 pairs of nonsex chromosomes. X-linked disorders are those caused by mutations on the X chromosome. Dominant conditions are disorders in which a clinical phenotype is expressed in the heterozygous state (that is, the individual has one copy of a mutant gene and one copy of a normal gene). Recessive conditions are disorders that manifest a clinical phenotype in the homozygous state [that is, an individual must have two mutated genes to have the disease]. Table 120.1 provides examples of single-gene disorder with cardiovascular manifestations.

Autosomal dominant inheritance is expression of a clinical phenotype caused by a heterozygous mutant gene on an autosomal chromosome. As shown in Figure 120.3, the inheritance pattern is vertical [the disorder is passed from one generation to the next generation]. Both males and females are affected, although the severity of the disorder can be influenced by the sex of the affected individual. Male-to-male transmission occurs and helps to distinguish autosomal dominant inheritance from X-linked dominant inheritance. An affected individual has a 50% chance of passing the condition to any of his or her children. Unaffected family members do not pass the trait on to their children. Of the identified single-gene disorders diseases with mendelian inheritance, the majority are inherited in an autosomal dominant fashion.7

A number of special characteristics are associated with autosomal dominant inheritance. With classic autosomal dominant inheritance, the affected individual usually has an affected parent, but this is not true in all cases. Sporadic cases [without a family history of the disorder] can arise in dominant disorders through new mutations in the gene, which causes the disorder. The term variable expression of
a dominant disorder refers to different levels of the clinical expression of a mutated gene. This variability can include the type and severity of symptoms or the variation in the age of onset of a disorder. Decreased penetrance of an autosomal dominant condition is the lack of phenotypic expression of a disease in an individual who has inherited the mutated gene that causes the disease. The penetrance of dominant disorders is determined by family or population studies of different disorders and is influenced by the ability of clinical or laboratory studies to detect the phenotype.

In autosomal recessive inheritance, the expression of a clinical phenotype occurs only when an individual has inherited, at a single locus, two genes that are mutated; the affected individual has inherited a mutant gene from both parents (Fig. 120.3). The parents are heterozygous for the mutant gene and do not have the disease. They are called carriers. The inheritance is horizontal rather than vertical and tends to be limited to siblings within a family. If both parents are carriers of a recessive disorder, they have a 25% chance of passing on the disorder to their children. Males and females are equally affected. Consanguinity, or mating between people who are related, can be an underlying cause of the presence of autosomal recessive diseases. Autosomal recessive disorders are often caused by mutations in the genes that encode for enzymes or that transport proteins.

X-linked disorders are caused by inheritance of a mutant gene found on the X chromosome. Because males have only one X chromosome, X-linked disorders are fully expressed in males. Females have two X chromosomes, and therefore expression of the disease is dependent on whether the mutated gene is dominant or recessive. Diseases that are rarely expressed in females are called X-linked recessive. X-linked recessive disorders are restricted to males, and there is no male-to-male transmission (Fig. 120.3). Females who carry the mutant gene on one of their X chromosomes rarely express the disease and are therefore carriers.

X-linked dominant disorders are expressed in both males and females who inherit the X chromosomes with the mutant gene. The pattern of inheritance is vertical, as in autosomal dominant disorders. The distinguishing feature of X-linked dominant disorders is that there is no male-to-male transmission of the condition (Fig. 120.3).

Multifactorial Inheritance

Common diseases of adults, such as coronary artery disease, hypertension, diabetes, and schizophrenia, and some congenital malformations, such as clubfoot, cleft lip, neural tube defects, and pyloric stenosis, demonstrate familial aggregation but are not inherited as a single-gene disorder or a chromosomal abnormality. Instead, these disorders are multifactorial genetic diseases, indicating that they are caused by the interplay of multiple genes with multiple

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**TABLE 120.1. Single-gene disorders with major cardiovascular features**

<table>
<thead>
<tr>
<th>Name of disorder</th>
<th>Defective gene</th>
<th>Prevalence</th>
<th>Inheritance</th>
<th>Cardiovascular manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immotile cilia syndrome</td>
<td>DNAI1&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1:40,000</td>
<td>AR</td>
<td>Situs inversus visceral</td>
</tr>
<tr>
<td>[Kartagener's syndrome]</td>
<td>DNAH5&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen syndrome</td>
<td>KVLQT1&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Rare</td>
<td>AR</td>
<td>Prolonged QT interval, arrhythmias</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1&lt;sup&gt;14&lt;/sup&gt;</td>
<td>1:10,000</td>
<td>AD</td>
<td>Cardiac rhabdomyomata</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC2&lt;sup&gt;15&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia</td>
<td>ENG&lt;sup&gt;16&lt;/sup&gt;</td>
<td>—</td>
<td>AD</td>
<td>Telangiectasias, arteriovenous fistulas, vascular malformations</td>
</tr>
<tr>
<td>(Osler-Weber-Rendu disease)</td>
<td>ALK1&lt;sup&gt;17&lt;/sup&gt;</td>
<td>1:10,000</td>
<td>AD</td>
<td>Thoracic aortic aneurysms, aortic dissections, valvular disease</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>FBN1&lt;sup&gt;19&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriohepatic dysplasia (Alagille’s syndrome)</td>
<td>JAG1&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Rare</td>
<td>AR</td>
<td>Peripheral pulmonary artery stenosis</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; MVP, mitral valve prolapse.

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**FIGURE 120.3. Mendelian patterns on inheritance.**

Pedigree patterns for autosomal dominant, autosomal recessive, X-linked recessive, and X-linked dominant inheritance are shown.
attributable to genetic factors. Multifactorial inheritance is due not to changes in a single gene but to a combination of genetic changes that predispose to or produce the disease. In the most common disorders seen in adults, genetic factors predispose an individual to the disorder, but environmental factors also influence its expression. Although these disorders tend to be familial, no distinct pattern of inheritance can be determined. The risk that family members will develop these disorders cannot be calculated as easily as it can for single-gene disorders, but certain characteristics of multifactorial inheritance help to predict the risk. Recurrence risks represent empiric risk figures and vary among different families, but in general, affect only 5% to 10% of first-degree relatives. The risk for first-degree relatives is greater than the risk for second-degree relatives. The greater the number of family members affected with the disorder, the greater the risk that other family members will have the disorder. The risk for relatives of an affected patient increases as the frequency of occurrence of the disease in the more general population decreases. The more premature the onset of the disease or the more severe the malformation, the greater the recurrence risk for family members. Finally, if the disease is more common in one sex, the risk is higher for relatives of patients of the less susceptible sex. A number of common diseases with cardiovascular manifestations demonstrate multifactorial inheritance.

Coronary artery disease (CAD) is a well-studied adult disorder caused by genetic factors in combination with a strong environmental component, and it serves as a model for the manner in which genetic factors influence complex diseases. At one end of the genetic spectrum leading to this disease is familial hypercholesterolemia (FH), an autosomal dominant disease resulting from mutation in low-density lipoprotein (LDL) receptor gene (LDLR). Familial hypercholesterolemia is an example of a single-gene disorder that results in atherosclerosis. Coronary artery disease is due to elevations in plasma LDL levels, thereby contributing to the genetic basis of this common disease. Individuals heterozygous for the LDL receptor mutations are common in the general population, with an estimated prevalence of 1 in 500. In addition to genes that alter plasma lipoprotein levels leading to CAD, one gene has been identified that causes familial CAD inherited in an autosomal dominant manner in the absence of alterations in plasma lipoproteins; mutations in MEF2A have been identified as a cause of mendelian inheritance of CAD in families. MEF2A is a member of the MEF2 family of nuclear transcription factors, and mutations in this gene are found in up to 2% of patients with CAD.

In addition to CAD rarely being inherited in families as a mendelian trait, studies have demonstrated familial aggregation of CAD in families that had premature CAD without a clear mode of inheritance.8 Studies among graduates of Johns Hopkins Medical School demonstrated that CAD was almost four times as common among siblings of individuals with CAD as among siblings of persons without heart disease.9 Familial aggregations of ischemic heart disease were noted, especially in the families of the female patients, the sex less commonly affected by CAD. Therefore, CAD demonstrates many of the features associated with multifactorial inheritance, including familial aggregation without a clear mode of inheritance and a higher risk for relatives of individuals with premature CAD and relatives of affected females.

The genes that lead to familial aggregation in families are genes that increase the risk for CAD and may or may not cause disease based on other genes and environmental factors. In contrast to mendelian inheritance of risk for CAD due to mutations in genes, polymorphisms in genes, most commonly single nucleotide polymorphisms (SNPs), are the alterations that lead to this increased susceptibility to disease. Case control association studies are the most frequently used method to identify SNPs that increase an individual’s susceptibility to CAD. In these studies, the frequencies of SNPs are determined in both the cases (individuals with CAD) and the controls (individuals of the same ethnic background as the cases who do not have CAD). A SNP is considered associated with this disease if the frequency of the SNP differs significantly between cases and controls. These methods have been used to study a large number of SNPs in genes hypothesized to cause CAD and have identified a large number of possible susceptibility genes for CAD. Many of these studies need further validation or replication in other patient populations to verify the association. Recently, the technology for detection of SNPs associated with disease has become more rapid and cost-effective, and the development of a high-density SNP map covering the entire human genome has allowed case control association studies to scan SNPs throughout the human genome.

References
