

# BASIC HUMAN GENETICS FOR MEDICAL WRITERS

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## ABSTRACT

This paper reviews the application of Mendelian genetics to complex genetic principles, including genetic disease. The discussion includes autosomal recessive disorders, autosomal dominant disorders, X-linked inheritance, abnormalities in chromosome structure, and sex chromosome abnormalities. The concept of cancer as a genetic disease is also reviewed. A glossary of terms is provided for readers new to the study of human genetics.

## INTRODUCTION

**T** HIS review provides basic information about human genetics, especially genetic diseases, and is a follow-up to an earlier paper on basic Mendelian genetics.<sup>1</sup> This review is technical, and although I have tried to simplify important concepts, I have assumed that the reader has a general knowledge of biology, including the components of DNA and the association of DNA and chromosomes. Another previous paper<sup>2</sup> may be helpful in reviewing some basic concepts. Words in the glossary are underlined in the text. Gene names are *italicized*. The terms “male” and “female” are used, rather than “boy” or “girl” or “man” or “woman,” for practical reasons.

Genetics has had an increasingly important role in the practice of clinical medicine; medical genetics is seen as an integral part of our understanding of many diseases. Because most human characteristics, such as eye color, presence of a “widow’s peak,” and skin color, can be said to follow the same principles

of Mendelian genetics as pea plants (e.g., dominant, recessive, incomplete dominance), this paper focuses on medical genetics, particularly the inheritance or causation of genetic diseases, a large proportion of the total human disease burden. Cytogenetics is the term given to the study of chromosomes and their abnormalities, and medical genetics is the application of genetics to medical practice.

## A REVIEW OF THE HUMAN GENOME

All normal humans have 23 pairs of chromosomes, which, like genes, are inherited (one from each parent). Researchers involved with the Human Genome Project have estimated that the 23 pairs of chromosomes contain 30,000 to 40,000 genes, many fewer than the 100,000 genes once thought necessary to explain the complexity of the human body. Each individual probably has several altered genes. Fortunately, most of these altered genes are recessive, and the normal

dominant allele allows the normal trait to be expressed. Chromosomes 1 through 22 are autosomal chromosomes, and they code for all characteristics other than sex. The twenty-third pair of chromosomes is the sex chromosomes: XX for normal females, XY for normal males. Table 1 lists the 23 chromosomes and some genes and diseases attributed to them. Of course, other genes responsible for the production of proteins needed to maintain life are found on chromosomes, but because so many exist and because of this paper’s emphasis on medical genetics, such “housekeeping” genes are not discussed.

All female cells have two X chromosomes, but only one is active. The other becomes genetically inactive early in embryogenesis, forming what is known as a Barr body. The Barr body appears as a dark structure in nucleated cells and can be seen even under the relatively low power of a light microscope. Inactivation of the X chromosome appears to be random; that is, maternally and paternally derived X

**TABLE 1. HUMAN GENES AND ASSOCIATED DISEASES\*<sup>3</sup>**

<b>Chromosome</b>	<b>Genes</b>	<b>Disease or Function</b>
1	<i>GBA</i> <i>HPC1</i> <i>GLC1A</i> <i>PS2 (AD4)</i>	Gaucher's disease Prostate cancer Glaucoma Alzheimer's disease
2	<i>ETM2</i> <i>MSH2</i> <i>MSH6</i> <i>PAX3</i>	Essential tremor Colon cancer Colon cancer Waardenburg's syndrome
3	<i>VHL</i> <i>SCLC1</i> <i>MLH1</i> <i>ETM1</i>	von Hippel-Lindau disease Lung cancer Colon cancer Essential tremor
4	<i>HD</i> <i>EVC</i> <i>Alpha-synuclein</i>	Huntington's disease Ellis-van Creveld syndrome Parkinson's disease
5	<i>SRD51A</i> <i>CSA</i> <i>SMN1</i> <i>DTD</i>	Steroid 5-alpha reductase 1 Cockayne's syndrome Spinal muscular atrophy Diastrophic dysplasia
6	<i>SCA1</i> <i>IDDM1</i> <i>EMP2A</i>	Spinocerebellar atrophy Diabetes Epilepsy
7	<i>GCK</i> <i>ELN</i> <i>Pendrin</i> <i>CFTR</i> <i>OB</i>	Diabetes Williams syndrome Pendred's syndrome Cystic fibrosis Obesity
8	<i>WRN</i> <i>MYC</i>	Werner's syndrome Burkitt's lymphoma
9	<i>CDKN2</i> <i>FRDA</i> <i>ABC1</i> <i>ABL</i> <i>TSC1</i>	Malignant melanoma Friedreich's ataxia Tangier disease Chronic myeloid leukemia Tuberous sclerosis
10	<i>PAHX</i> <i>OAT</i>	Refsum's disease Gyrate atrophy of choroid and retina
11	<i>HRAS</i> <i>LQT1</i> <i>IDDM2</i> <i>HBB</i> <i>VMD2</i> <i>MEN1</i> <i>ATM</i>	Harvey ras oncogene Long Q-T syndrome Diabetes Sickle cell anemia Best's disease Multiple endocrine neoplasia Breast cancer

*continued on next page*

**TABLE 1. HUMAN GENES AND ASSOCIATED DISEASES\*<sup>3</sup> (CONTINUED)**

Chromosome	Genes	Disease or Function
12	<i>PXR1</i> <i>PAH</i>	Zellweger syndrome Phenylketonuria
13	<i>CX26</i> <i>BRC2</i> <i>RB1</i> <i>ATP7B</i>	Autosomal recessive neurosensory deafness Breast cancer Retinoblastoma Wilson's disease
14	<i>PS1 (AD3)</i>	Alzheimer's disease
15	<i>SNRPN</i> <i>UBE3A</i> <i>FBN1</i> <i>HEXA</i>	Prader-Willi syndrome Angelman's syndrome Marfan syndrome Tay-Sachs disease
16	<i>FMF</i> <i>PKD1</i>	Familial Mediterranean fever Polycystic kidney disease
17	<i>p53</i> <i>CMT1A</i> <i>BRCA1</i>	Tumor suppressor gene Charcot-Marie-Tooth disease Breast cancer
18	<i>NPC1</i> <i>DPC4 (Smad4)</i>	Niemann-Pick disease Pancreatic cancer
19	<i>Jak3</i> <i>APOE</i> <i>DM</i>	Severe combined immunodeficiency Atherosclerosis Myotonic dystrophy
20	<i>ADA1</i>	Severe combined immunodeficiency
21	<i>SOD1</i> <i>APS1</i>	Amyotrophic lateral sclerosis Polyglandular autoimmune syndrome
22	<i>DGS</i> <i>BCR</i> <i>SGLT1</i> <i>NF2</i>	DiGeorge syndrome Chronic myeloid leukemia Glucose-galactose malabsorption Neurofibromatosis
X	<i>PIG-A</i> <i>DMD</i> <i>ATP7A</i> <i>IL2RG</i> <i>TNFSF5</i> <i>FMR1</i> <i>MeCP2</i> <i>ALD</i> <i>HEMA</i>	Paroxysmal nocturnal hemoglobinuria Duchenne's muscular dystrophy Menkes' syndrome X-linked severe combined immunodeficiency Immunodeficiency with hyper-IgM Fragile X syndrome Rett syndrome Adrenoleukodystrophy Hemophilia A

\*Many genetic disorders are the result of one mutation in one gene.

chromosomes have an equal chance of becoming inactivated. The X chromosome codes for such products as factor VIII protein and creatine phosphokinase.

The Y chromosome is small and composed mainly of inactive heterochromatin. A small active portion of the Y chromosome codes for a protein responsible for testis-determining factor. A minor antigen and several housekeeping genes are also found on the Y chromosome.

## **MENDELIAN GENETIC DISORDERS**

Mendelian genetic disorders are caused by a single-gene mutation that leads to an abnormality that is generally confined to a single organ system. These disorders are inherited following classic Mendelian genetics patterns. Hundreds of single-gene disorders have been identified. If the disorder is due to an altered gene on chromosomes 1 through 22, it is inherited as an autosomal recessive or autosomal dominant characteristic. If the altered gene is located on the X chromosome, it is an X-linked characteristic. No Y-linked genetic diseases have been identified.

Examples of single-gene/single-organ system disorders include achondroplasia (skeletal system) and Huntington's disease (central nervous system). If an enzyme (protein) is affected by the genetic abnormality, the disorder may be reflected in more than one organ system. Mucopolysaccharidoses are a group of diseases that involve one gene defect on one chromosome. Only one enzyme is deficient, but it leads to myriad clinical consequences (Table 2).

### ***Autosomal recessive disorders***

Phenylketonuria is an example of an autosomal recessive disorder. Phenylketonuria is caused by a deficiency of the enzyme phenylalanine hydroxylase, which is produced by the liver. Phenylalanine hydroxylase hydrolyzes (breaks down) phenylalanine, an essential amino acid found in many foods, to tyrosine. In phenylalanine hydroxylase deficiency, phenylalanine and its metabolites, such as phenylpyruvic acid, accumulate in the blood and the cerebrospinal fluid. If left untreated, the accumulation of phenylalanine can cause severe brain damage and profound mental retardation. Most pediatricians test for the presence of phenylketonuria within a neonate's first 2 weeks of life. Treatment is usually by dietary restrictions and life-long; patients are relatively healthy and survive into adulthood.

Some patients with phenylketonuria do not respond to dietary restrictions and continue to have high concentrations of blood phenylalanine. This variant of the disease is caused by a second gene mutation. In this situation, the gene for phenylalanine hydroxylase is normal, but the gene responsible for the synthesis of tetrahydrobiopterin, a cofactor of phenylalanine hydroxylase, is mutated. This example is called locus heterogeneity: phenylketonuria can be caused by abnormalities of two genes at two loci.

To express an autosomal recessive characteristic, a child must inherit a copy of the recessive gene from both parents. If a child inherits one recessive gene and one dominant gene, the single copy of the dominant gene is usually sufficient to allow for normal phenotype, albeit often at a reduced production level of the enzyme in question. Most enzyme abnormalities are autosomal recessive, requiring two abnormal genes for clinical expression. Exceptions exist, however, including acute intermittent porphyria, which behaves as an autosomal dominant, single-gene disorder. Individuals who are heterozygous for the recessive gene produce half the amount of the enzyme needed to break down the protein responsible for porphyria, an insufficient amount to prevent clinical presentation of the disease.

### ***Autosomal dominant disorders***

The presence of a single abnormal gene can allow for expression of that gene and its inherent clinical consequences. In such a situation, an individual may have one normal gene and one abnormal gene, but the abnormal gene is dominant and the diseased phenotype is expressed. Huntington's disease is an example of an autosomal dominant disorder. All individuals who have the abnormal gene will invariably develop clinical signs and symptoms of the disease.

Huntington's disease is a progressive neurodegenerative disorder that is initially characterized by bradykinesia and rigidity and finally by choreiform movements. The abnormal gene is on chromosome 4 and is characterized by single trinucleotide sequences containing the bases cytosine, adenine, and guanine (CAG). Normal individuals may have 9 to 34 CAG repeats, whereas individuals with Huntington's disease may have 30 to 100 CAG repeats. The number of CAG repeats tends to increase with succeeding generations, a condition known as genetic anticipation. The Huntington disease gene produces the protein huntingtin that has many glutamine residues near its amino terminus. The expanded glutamine tract leads to a buildup of toxic proteins that kill neurons. Normal huntingtin interacts with enzymes

**TABLE 2. SELECTED MUCOPOLYSACCHARIDOSES<sup>4</sup>**

Disease	Description
Hunter's syndrome	An X-linked recessive disease found only in boys, with onset at age 2 to 4 years. Caused by deficiency of iduronate-2-sulfatase activity. Clinical features of the severe form include mental retardation; short stature; thickening of nostrils, lips, and tongue; respiratory symptoms, including recurrent rhinorrhea; clear corneas; and small nodules over skin of the shoulders, scapulas, and arms. Those with a mild form may have normal intelligence. Clinical features of the mild form also include carpal tunnel syndrome and upper airway obstruction. In both forms, death is usually caused by obstructive airway disease or cardiac failure. Those with the severe form usually die before age 16, but those with the mild form can survive until age 60 years or older.
Hurler's syndrome	An autosomal recessive defect of chromosome 4 with onset at age 6 to 24 months. Caused by deficiency of alpha-L-iduronidase activity. Clinical features include hydrocephalus; limited language skills; profound mental retardation; carpal tunnel syndrome; long face; short stature; noisy breathing; and other cardiovascular, respiratory, and gastrointestinal symptoms. Life expectancy is approximately 10 years.
Maroteaux-Lamy syndrome	An autosomal recessive defect of chromosome 5 with onset at age 2 to 3 years. Caused by deficiency of arylsulfatase B activity. Clinical features include thick nostrils and lips; short trunk and neck; pigeon chest; carpal tunnel syndrome; normal intelligence; restrictive lung disease due to abnormal chest configuration; and other cardiac, respiratory, and gastrointestinal symptoms. Life expectancy is 20 to 30 years, and death is usually due to heart failure.
Morquio's syndrome	Two forms of Morquio's syndrome exist: both are autosomal recessive defects; one form involves chromosome 3 (the other is uncertain). Caused by deficiency of N-acetylgalactosamine-6-sulfatase. Clinical features include normal intelligence; small teeth with frequent caries; depressed nasal bridge; short trunk and neck; short stature; flat feet; flaring of lower ribs; restrictive lung disease due to abnormal chest configuration; and other cardiac and gastrointestinal symptoms. Life expectancy is 30 to 40 years, but death due to cardiac or neurologic complications may occur earlier.
Sanfilippo's syndrome	Autosomal disease with uncertain chromosomal location; disease is frequent in British population and in the Cayman Islands. Caused by deficiency of heparan N-sulfatase activity with age of onset at 2 to 6 years. Clinical features include progressive neurologic disease, including dementia, seizures, and tremor; hyperactivity; poor attention span; temper tantrums; profound mental retardation; recurrent upper respiratory tract infections; and other facial, cardiac, and gastrointestinal symptoms. Life expectancy is 14 to 20 years.
Scheie's syndrome	This syndrome is considered to be a mild form of Hurler's syndrome and is an autosomal recessive defect of chromosome 4. Caused by deficiency of alpha-L-iduronidase activity. Clinical features may include mental retardation, but many affected individuals have normal intelligence; striking prognathism; corneal clouding; aortic valve disease; carpal tunnel syndrome; clawed hands; and deafness. Life expectancy is normal.

\*All are lysosomal storage disorders characterized by the accumulation of acid mucopolysaccharides. These genetic disorders usually involve a single gene, but the mutated protein influences several organ systems.

that allow normal neuronal metabolism. It may be possible to use knowledge of the working of normal huntingtin to find a way to treat Huntington's disease.

Huntington's disease has many interesting aspects. It is inherited from the father in more than 80% of cases. Estimates are that only 10% of patients with Huntington's disease experience the onset of symptoms before age 20, meaning that many people are well into their reproductive years before they are diagnosed with the disease. Another interesting aspect is a strong inverse correlation between the length of the CAG repeats and the age of onset of the disease. Thus, unless one is very sure of his or her genotype and family history of the disease or lack thereof, it is possible to pass the gene on to the next generation.

Another autosomal dominant disorder is retinoblastoma, a malignant tumor of the retina. Most cases (75%) of retinoblastoma are unilateral (i.e., involve one eye), and the rest (25%) are bilateral (i.e., involve both eyes). Most patients with retinoblastoma have no family history of the disease. The gene responsible for retinoblastoma is *Rb*, which is located on chromosome 13. *Rb* codes for a tumor suppression protein and the resultant protein, which has DNA-binding properties and regulates transcription. The loss of *Rb* leads to neoplastic growth. One abnormal *Rb* is not sufficient to cause retinoblastoma. The normal *Rb* must also be eliminated to produce a retinal cell with no functional Rb protein (pRb) (i.e., no regulatory control). Not all persons who inherit *Rb* coding for retinoblastoma will develop the disease: a second "hit" is required. Thus, susceptibility to retinoblastoma is inherited as a dominant trait, but the expression of *Rb* in the eye requires two abnormal genes and is technically a recessive trait.

### **X-linked inheritance**

Diseases caused by genes carried on the X chromosome are called X-linked diseases, and most X-linked diseases are recessive. Because normal males have only one X chromosome, the presence of an abnormal gene on their one X chromosome is always expressed (i.e., no dominant normal gene is present to suppress the genotype and express the normal phenotype). For this reason, X-linked disorders such as hemophilia, red-green color blindness, and muscular dystrophy are expressed in sons and transmitted by physically normal carrier mothers.

Women who carry X-linked recessive disorders have a 50% chance with each pregnancy of passing on the abnormal recessive gene. If this defective X chromosome pairs with a Y chromosome, the offspring will be a male

with the disease. If this defective X chromosome pairs with another X chromosome (from the woman's partner, not from the woman herself), the offspring will be physically normal but will be a carrier (Figure).

Panel A

	(X)	(X <sup>c</sup> )
(X)	XX	XX <sup>c</sup>
(Y)	XY	X <sup>c</sup> Y

Panel B

	(X)	(X)
(X <sup>c</sup> )	XX <sup>c</sup>	XX <sup>c</sup>
(Y)	XY	XY

**FIGURE.** Punnett square of inheritance of X-linked disorder. The example of red-green color blindness is used, and the disorder is noted as a superscripted "c". In panel A, a normal male and a carrier female are crossed; the results are a 25% chance of a normal female (XX), a 25% chance of a carrier female (XXc), a 25% chance of a normal male (XY), and a 25% chance of a color blind male (XcY). In panel B, an affected male and a normal female are crossed; the results are a 50% chance of a carrier female (XXc) and a 50% chance of a normal male (XY).

Some diseases are not linked to a sex chromosome, but have different outcomes, however, if the gene is inherited from the father rather than from the mother. These diseases are not X-linked or Y-linked, are associated with chromosomes 1 through 22, and are caused by deletions (discussed later).

### **ABNORMALITIES IN CHROMOSOME STRUCTURE**

Abnormal genes cause many genetic mutations and their subsequent diseases. However, abnormalities in chromosome structure can also occur, often with

deleterious effects. Chromosomes can break and can be repaired improperly. Sometimes after a repair, chromosomal material is lost or gained. If the loss or gain is unbalanced (termed an unbalanced rearrangement), significant clinical consequences can occur. If no loss or gain of chromosomal material occurs, but material is rearranged (termed a balanced rearrangement), the resultant individual may be physically and mentally normal; however, the risk increases that such individuals will have abnormal offspring because of their production of chromosomally unbalanced gametes. Human chromosomes vary in size and placement of the centromere. A Robertsonian translocation involves the reciprocal transfer of the long arms of two of the acrocentric chromosomes (13, 14, 15, 21, or 22). A relatively common Robertsonian translocation is between chromosome 14 and chromosome 21, forming a trivalent during meiosis. By the end of meiosis, gametes are formed, which can be normal (a chromosome 14 and a chromosome 21), a balanced translocation, such as t(14;21); a disomy, such as either 14 and t(14;21) or 21 and t(14;21); or a nullisomy (a chromosome 14 or a chromosome 21, but not both). The best-known outcome of a t(14;21) balanced translocation is Down syndrome.

Unlike translocations, inversions involve only one chromosome. In an inversion, a chromosome breaks and, in the subsequent repair, the segment is rejoined in an inverted or opposite manner (i.e., "upside down"). No gain or loss of chromosomal material occurs, and the carriers are phenotypically normal. During meiosis, the normal chromosome and the inverted chromosome will form a loop. A loop must be formed because chromosomes must line up in perfect order during prophase I of meiosis. When crossing over occurs during meiosis, however, gametes are formed that have both deletions and duplications that often are not compatible with life, resulting in a high incidence of miscarriage (spontaneous abortion). The consequence is that most carriers of inversions do not have abnormal offspring. Carriers are usually discovered only if a child is born with a chromosomal abnormality or if a chromosome study is done to determine the cause of the miscarriage. As noted earlier, not all deletions are equal. Deletion of a segment of the long arms of chromosome 15 produces two diseases. If the deletion is inherited paternally, the child has Prader-Willi syndrome, and when the deletion is inherited maternally, the child has Angelman syndrome. The reason for these different manifestations is that the deletion occurs in a region that is only active in the maternal chromosome and a maternally inherited deletion removes the only active copy of the gene, causing Angelman syndrome. Several genes appear to be involved in Prader-Willi syndrome and they are active only in the chromosome inherited paternally.

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**TABLE 3. PHENOTYPES OF VIABLE TRISOMIES<sup>4-7</sup>**

Trisomy/Syndrome Name	Description
13/Patau's syndrome	Occurs in 1 per 4,000 to 10,000 live births. Patau's syndrome is caused by trisomy 13 (75%), translocations (20%), or mosaicisms (5%). A single defect during the first 3 weeks of development of the prechordal mesoderm can lead to defects of midface, eyes, and forebrain. The syndrome has a very poor prognosis, with 45% dying by age 1 month and 75% dying by age 12 months. Clinical features are microcephaly with sloping forehead; colobomas of iris; low-set ears; deafness; simian crease; thin or missing ribs; seizures; severe mental retardation; bicornate uterus in females; polycystic kidneys; and hernias.
18/Edwards' syndrome	Occurs in 1 per 8,000 live births and is more common in females than males (4:1). It is the second most common autosomal aberration. Some (10%) individuals with Edwards' syndrome do not have trisomy 18 but have mosaicism (i.e., only some cells have trisomy); the latter form is associated with longer survival. The syndrome has a very poor prognosis (30% die by age 1 month, 90% die by age 12 months). Clinical features are major facial and skeletal abnormalities, including microcephaly, cleft lip and cleft palate, short sternum, small pelvis, rocker-bottom feet, simian crease, hypoplasia of fingernails, and fixed flexion deformity of the fingers (i.e., overlapping of the second and fifth fingers over the third and fourth fingers). All individuals are severely retarded, have poor suckling ability, a weak cry, and failure to thrive. More than 95% have cardiovascular malformations.
21/Down syndrome	Occurs in 1 per 8,000 live births. More babies with Down syndrome are born to women <35 years old than to older women because >90% of babies are borne by women in this age group. An estimated 75% of embryos with Down syndrome spontaneously abort. Most (75%) individuals with Down syndrome have trisomy 21, 3% to 4% have unbalanced translocation, and 1% to 2% have mosaicism. The syndrome has a good prognosis (80% survive to age 30 years or older). Clinical features include epicanthal folds; a flat facial profile; hyperflexibility of joints; excessive skin on the neck; seizures; poor muscle tone; borderline to moderate mental retardation; simian crease; and cardiac, respiratory, gastrointestinal, and urogenital problems. Alzheimer's disease and leukemia occur quite frequently in individuals with Down syndrome.
X/Triple X syndrome	Occurs in 0.3 to 1 per 1,000 female neonates. Triple X syndrome is the most common X chromosomal anomaly in females. Clinical features are quite varied but almost always include tall stature. Intelligence can range from moderate to severe mental retardation to superior. Some affected girls have coordination problems and awkwardness due to their stature. All have normal life spans.
XYY/Supermale syndrome	Occurs in 1 per 1,000 male neonates. Appears to be common without particular medical or social implications. Many males with XYY are tall (approximately 7 cm taller than the average height for age) and may be more physically active than other males. Other clinical features may include delayed mental maturation with associated learning problems, speech development, and aggressiveness.
XXY/Klinefelter's syndrome	Occurs in 1 per 500 to 1000 male neonates. Appears to be common without particular medical or social implications. The four most common clinical features are sterility, breast development, incomplete masculine body formation, and social and school learning problems. Most males with Klinefelter's syndrome are tall. Testosterone therapy may be helpful in increasing the size of the penis and scrotum (but not the testes), increasing beard growth, deepening the voice, and increasing muscle bulk and strength, but it cannot cure the sterility.

Chromosome number also can be abnormal. Gametes are haploid (N), and normal individuals are diploid (2N). Triploid (3N) or tetraploid (4N) cases are rare and usually incompatible with survival. Only six trisomy fetuses come to term: trisomy 13 (Patau's syndrome), trisomy 18 (Edward's syndrome), trisomy 21 (Down syndrome), trisomy of the X chromosome (XXX), trisomy XYY (Supermale syndrome), and trisomy XXY (Klinefelter's syndrome) (Table 3).

## SEX CHROMOSOME ABNORMALITIES

The sex chromosomes are inherited in the same manner as the autosomal chromosomes and are subject to any of the problems associated with autosomal chromosomes, including inversions, nondisjunctions, and deletions.

Normal females are XX, and normal males are XY. The Y chromosome determines maleness, and maleness is inherited from the paternal lineage (i.e., women do not determine the sex of their offspring). Only one Y chromosome is necessary to determine maleness; theoretically, individuals who are XXY, XXXY, XYY, XYYY, etc., are male, although individuals with multiple copies of either the X or Y chromosome are not common and probably abort spontaneously as embryos.

Some genetic disorders of the sex chromosomes have been discussed as triploid disorders. Another genetic disorder is Turner's syndrome, in which individuals have only one sex chromosome, an X. These females are designated as XO, although some females with Turner's syndrome are designated XX even though one X chromosome is nonfunctional owing to deletion or duplication of parts of the chromosome. A very small percentage of females with Turner's syndrome are mosaics, and some are XY (2% to 5%). Turner's syndrome occurs in 1 per 2,000 to 5,000 female neonates. The clinical characteristics of Turner's syndrome include short stature; excessive skin at the nape of the neck; a short, webbed neck; epicanthal folds, as in Down syndrome; congenital cardiac malformations; abnormal kidney structure; and urogenital defects. Females who have the genotype 45,X/46,XY usually undergo surgery at a very young age to remove the remnants of male genitalia. These females are rarely fertile, but some do go through spontaneous puberty.

## CANCER AND GENETICS

More than 200 genes have been described as directly or indirectly linked to cancer.<sup>8</sup> Cancer occurs because of somatic cell-gene deregulation or because of genetic susceptibility. Although the outcome is the same (i.e.,

cancer), the disease may not be inevitable in children of patients with cancer. More than 90% of cancers are estimated to arise in epithelial cells, and most of these cancers occur in surface epithelial cells (e.g., skin, respiratory tract, or digestive tract) or in secondary sexual organs (e.g., prostate or breast). This relationship suggests a possible interaction between cells and carcinogenic materials; only 10% of primary cancers are in supportive tissues (e.g., blood or other connective tissues); this finding is important because most known carcinogens cannot penetrate deep into the body. Supporting this theory are the links between cigarette smoking and lung cancer, viruses and cervical cancer, and sun exposure and malignant melanoma.

Aging is a major factor in the development of cancer: almost 60% of all cancers occur in people 65 years or older; specifically, prostate (80%), colon (74%), and pancreatic (72%) cancers are more common in the elderly.<sup>8</sup> The cell has inherent mechanisms for dealing with inaccurate DNA replication that allows for normal cell division to continue for 50 to 60 divisions. With each successive division, however, the chance of replication error, base-pairing error, or nondisjunction of chromosomes increases. Any one of several errors can set the mechanism for cancer in motion.

Michael Bishop, a Nobel laureate, describes the etiology of cancer as "a malady of the genes,"<sup>9</sup> but this description does not mean that most cancers are of genetic origin. DNA can be mutated by errors introduced during replication, physical or chemical modifications of the nucleotides, or changes in chromosomes. The body has several pathways for repairing modifications in DNA caused by replication errors or DNA damage, including dozens of enzymes that can recognize damage. When these enzymes note an altered base, they excise it by cutting the DNA strand and replacing it with the correct base. However, if DNA is not repaired correctly (i.e., the repair enzymes themselves introduce another error), several diseases can occur, including xeroderma pigmentosum, Fanconi's anemia, and hereditary nonpolyposis colorectal cancer. Besides these pathways, human chromosomes contain specialized structures, called telomeres, at the ends of chromosomes.<sup>10</sup> Telomeres are sequences of the bases thymine (T), adenine, and guanine (e.g., TTAGGG) repeated in arrays of 100 to 10,000. Telomeric length is thought to determine the life span of a cell. As cells divide and chromosomes duplicate, bits of the telomeres are lost. Eventually, the cell can no longer divide, and it dies. Human cells in culture have a limited life span, which is dictated by the number of cell divisions, or the Hayflick number.<sup>11</sup> Cancer cells appear to be immortal (i.e., they can replicate indefinitely in cell cultures), leading to the hypothesis that tumor cells have

a mechanism for overcoming telomeric loss. This hypothesis was proven when telomerase (i.e., an enzyme able to repair or prevent loss of the telomere) was measured with a sensitive assay.<sup>12</sup> Telomeric activity has been measured in 90% of human tumor samples, but it is absent from most normal human tissues, except for germ cells, which must be long-lived. Germ cells express high levels of telomeric activity and, consequently, can maintain long telomeres.

Although cancer is a disease of the genes, it would be wrong to assume that all cancers are inherited in a clear Mendelian fashion. For example, only a fraction of human colorectal cancers (hereditary nonpolyposis colorectal cancers) have strong familial associations. Some families have a very high incidence of particular forms of cancer and a very high incidence of mutated specific genes that may increase the risk of cancer. Although genetic makeup can increase the risk of developing certain cancers, usually a combination of several genetic defects and environmental factors, including diet, must be met before an individual develops cancer.

## SUMMARY AND DISCUSSION

Chromosomes are composed of thousands of genes, each of which comprises segments of DNA that code for a specific protein. Changes in the makeup of a gene (i.e., alteration, repetition, addition, or subtraction of base pairs) have the potential to change the gene's ability to produce the needed protein. Chromosomes, too, are subject to modification (i.e., inversions or deletions) or

may fail to navigate cell division, allowing for unequal partition of chromatids. Any of these circumstances can lead to zygotes or embryos that spontaneously abort or to the birth of infants that range from severely impaired to seemingly normal. Sometimes neonates with genetic disorders are born to normal parents. This can occur if spontaneous new mutations occur within the egg or sperm before fertilization, if the egg or sperm itself has a genetic defect, or if a parent is a phenotypically normal carrier.

Genetic defects can result from damage to either autosomal or sex chromosomes. An X-linked disorder is usually inherited by males from their mothers. For a female to inherit such a disorder, she would need both a carrier mother and an affected father. Even then, the chance would be 50% affected, 50% carrier. With a normal partner, a man with an X-linked disorder will have only normal sons, but all his daughters will be carriers.

The most common cause of genetic disorders is multifactorial inheritance. The traits of many genes must be combined, along with environmental factors, for the disorder to be expressed. Multifactorial conditions (e.g., cleft lip, cleft palate, schizophrenia, and diabetes) often are said to "run" in families. However, the expression of these disorders is not as predictable as the expression of single-gene defects. It is possible for one of a set of identical twins, who have the same genotype, to have a disorder while the other does not. Many genetic factors are solely risk factors: individuals with alpha-1-antitrypsin deficiency have a risk of coronary disease, and this risk is multiplied if the individual smokes or is obese.

Mendelian genetics is quite good, although not perfect, for predicting the genetic behavior of peas, but it is less accurately predictive of human genetics, which is more complicated and includes nontraditional patterns of inheritance such as mosaicism, imprinting, uniparental disomy, triplet repeats, mitochondrial inheritance, and contiguous gene syndromes (Table 4).

With the publication of the human genome,<sup>13,14</sup> the interactions of genes, disease, and the environment possibly will be more fully elucidated rather quickly. One can only wonder what Gregor Mendel would think if he knew that his simple garden experiment, done with only good record keeping and great patience, had led not only to the discovery of the elements responsible for inheritance but also to the manipulation of those elements.



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**TABLE 4. NONTRADITIONAL INHERITANCE**

Process	Definition	Examples of Resulting Disease
Contiguous gene syndrome	These occur secondary to microdeletions or microduplications and involve several genes next to each other.	DiGeorge syndrome, Miller-Dieker syndrome, Alagille syndrome
Imprinting	This is modification of a gene as transmitted paternally or maternally, usually through meiosis.	If part of the paternal chromosome 15 is deleted, the offspring has Prader-Willi syndrome; if the identical part of the maternal chromosome 15 is deleted, the offspring has Angelman's syndrome
Mitochondrial inheritance	Only maternal mitochondria are inherited, but this can affect males or females. The extent of inheritance depends on the number of mitochondria inherited.	Leber's hereditary optic neuropathy, myoclonic epilepsy with ragged red fibers
Mosaicism	This is the presence of two or more distinct cell lines, one of which is abnormal; it can be a chromosomal or genetic abnormality.	Turner's syndrome, osteogenesis imperfecta, segmental neurofibromatosis
Triplet repeats	Three bases, such as CAG or CGG, are repeated sequentially and at varying lengths, more so than in normal individuals.	Fragile X syndrome, Huntington's disease, myotonic dystrophy
Uniparental disomy	Both chromosomes are inherited from one parent.	Cystic fibrosis

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**SUGGESTED RESOURCES**

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## GLOSSARY

- acrocentric:** a chromosome with centromere near one end
- allele:** one of several alternative forms of a gene occupying a particular locus on a chromosome
- Angelman syndrome:** condition caused by deletion of a segment of maternally inherited chromosome 15; disease is characterized by severe mental retardation, seizures, and uneven gait
- autosomal:** pertaining to chromosomes other than sex chromosomes
- Barr body:** sex chromatin visible as a dark area in nucleus; represents condensed second X chromosome in normal women
- base pair:** units of complementary DNA bases in a double-stranded DNA molecule (A-T, C-G)
- bradykinesia:** abnormally slow movements
- centromere:** constricted part of a chromosome
- choreiform movements:** continuous rapid, highly complex jerky movements that are involuntary
- chromatid:** one arm of a chromosome
- chromosome:** a structure in the nucleus of a cell, composed of DNA and protein, that contains genetic information for the cell
- Fanconi's anemia:** disease characterized by anemia and susceptibility to leukemia; may be due to instability in chromosome 8
- deletion:** usually a chromosomal aberration in which part of a chromosome is lost
- diploid:** having two sets of chromosomes
- disomy:** a translocation that occurs during meiosis, leading to unequal division of chromosomes
- dominant:** the allele that determines the phenotype in a heterozygote with another (recessive) allele
- gene:** the segment of DNA involved in producing a polypeptide chain; the unit of heredity passed from parent to offspring
- genetic anticipation:** apparent occurrence of a hereditary disease at a progressively earlier age in successive generations
- genotype:** the genetic constitution of an organism
- haploid:** having a single set of chromosomes
- hereditary nonpolyposis colorectal cancer:** disease caused by a mutation in any of four DNA mismatch repair genes; disease characterized by bowel tumors and increased susceptibility to other cancers
- heterochromatin:** a state of chromosomes in which they appear tightly coiled with dark staining
- heterogeneity:** the state of being heterogeneous (ie, mixed genetic alleles)
- heterozygous:** having different alleles at a given locus
- housekeeping genes:** genes whose proteins are required for maintenance of a cell and, ultimately, maintenance of the organism
- inversion:** a chromosomal aberration caused by the inverted reunion of a chromosomal segment at two points, resulting in a reordered sequence of base pairs
- locus (plural, loci):** the position on a chromosome at which the gene for a given trait is found
- meiosis:** the type of cell division used in the formation of gametes, resulting in haploid cells
- mosaic:** an individual that has two or more genetically distinct cell lines that are derived from a single zygote
- multifactorial:** describes traits or diseases that are produced by the interaction of multiple genes and environmental factors
- nondisjunction:** the failure of two homologous chromosomes to pass to separate cells
- nucleotide:** the building block of nucleic acids, composed of a base, a sugar, and a phosphate group
- nullisomy:** the state of lacking one pair of chromosomes
- phenotype:** the appearance or expression of characteristics in an organism; it results from interaction of the genetic constitution with the environment
- Prader-Willi syndrome:** condition caused by deletion of a segment of paternally inherited chromosome 15; disease is characterized by short stature, poor muscle tone, obesity, mild mental retardation, and hypogonadism
- recessive:** an allele obscured in the phenotype of a heterozygous organism because of the existence of a dominant allele

## GLOSSARY CONTINUED

**Robertsonian translocation:** occurs when the short arms of two nonhomologous chromosomes are lost and the long arms fuse at the centromere; a single chromosome with two long arms, each from a different chromosome, is formed; carriers of a Robertsonian translocation appear normal because no essential genetic material is lost (i.e., short arms rarely have important genes), but the carriers have only 45 chromosomes per cell (normal is 46)

**telomere:** the extremity of a chromosome

**tetraploid:** having four sets of chromosomes

**translocation:** a structural chromosomal aberration in which one segment of a chromosome is transferred to a nonhomologous chromosome, the result of breakage of both chromosomes with repair resulting in an abnormal arrangement

**transcription:** the process by which RNA is used to synthesize DNA

**triploid:** having three sets of chromosomes

**trivalent:** a three-armed chromosome structure

**variant:** something that is different from other members of the class to which it belongs

**xeroderma pigmentosum:** condition characterized by dry scaly skin prone to excessive freckling and abnormal pigmentation; individuals with xeroderma pigmentosum have a greatly increased risk of skin tumors

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