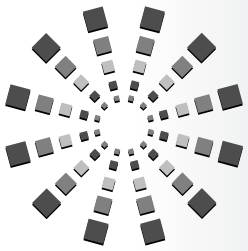

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Genes and Inheritance

KEY WORDS
Genes
Chromosomes
Pedigree
Mutation
Inheritance

The information gained from the Human Genome Project and related genetic research will undoubtedly create significant changes in healthcare practice. It is becoming increasingly clear that nurses in all areas of clinical practice will require a fundamental understanding of basic genetics. This article provides the oncology nurse with an overview of basic genetic concepts, including inheritance patterns of single gene conditions, pedigree construction, chromosome aberrations, and the multifactorial basis underlying the common diseases of adulthood. Normal gene structure and function are be introduced and the biochemistry of genetic errors is described

■ Introduction

We are entering a new age in healthcare Almost weekly, reports are printed in scientific journals, magazines, and local newspapers announcing the discovery of a new gene or genetic predisposition for a disease or physical trait. These reports are exciting, because they provide new insights into and hope for improved methods of diagnosis and treatment modalities for the many children and adults affected with genetic disorders, such as cystic fibrosis, Huntington disease, and muscular dystrophy. These reports also suggest that common diseases, such as colon and breast cancer, which affect many more individuals, are at least partially the result of alterations in an individual's genetic material (genome).

Consequently, it is imperative for oncology nurses to have a basic understanding of genetic concepts, including patterns of inheritance, pedigree construction, chromosome structure and types of aberrations, structure and function of genes, mechanisms for mutation, and methods of genetic testing. A basic understanding of these concepts will allow the oncology nurse to better assess the current and future needs of patients with cancer.

■ Introduction to Chromosomes, Genes, and Deoxyribonucleic Acid

Genes are the instructions that direct the development of the structure of the human body and its organs and direct how our body functions. In the nucleus of each cell, there are 2 copies of each of the 25,000—35,000 different genes (Fig. 1). In the nucleus of each cell, groups of genes are packaged together on microscopic structures called chromosomes. Twenty-two pairs of chromosomes, numbered 1 to 22, are referred to as the "autosomes." The twenty-third pair comprises the sex chromosomes. Deoxyribonucleic acid (DNA) is the chemical substance of which genes are made. As there are 2 copies of each chromosome, there are 2 copies of each gene; 1 from the father and 1 from the mother. Genes are passed from parents to chil-

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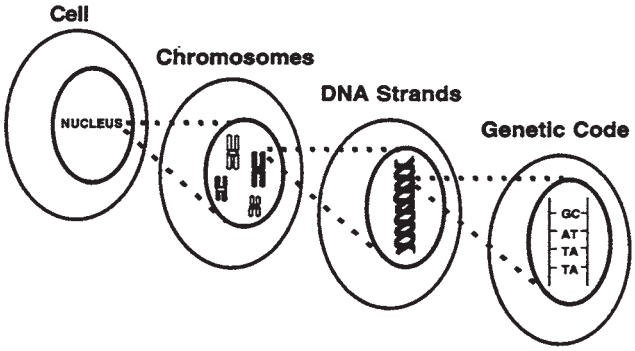

Figure 1 ■ Inside the cell.

dren via the egg and sperm at conception. Each parent contributes half of his or her child's genes.

Historically, mutations in the instructions encoded by a gene were believed to cause specific genetic disorders. However, research has shown that the line between having an altered gene that causes disease and having an altered gene that leads to a susceptibility to disease is becoming increasingly blurred. It is through exploration of the health problems within a patient's extended family that one can identify potential health risks for the patient. Nurses may more readily identify patients at risk for familial cancer syndromes by constructing an expanded family medical history.

■ Expanded Family History

An expanded, three-generation family medical history in a pedigree format is an invaluable tool for an oncology healthcare provider concerned not only about the identification of health risks for his or her patient but also about the health status of the entire family. Nurses already have the advanced clinical assessment skills and family systems approach necessary to complete this task. The pedigree enables the medical history to be easily assessed and synthesized by the nurse and the entire healthcare team. Often, it is not until a pedigree is taken that the underlying basis for cancer in a family comes to light.

> A cerebellar hemangioblastoma was diagnosed in a 28-year-old man, Dan, followed by the development of retinal angiomas 2 years later. Because of the unusual combination of the tumors at Dan's age, his neurologist explored an expanded family history. Dan reported that his brother, Gary, also had been diagnosed with a cerebellar hemangioblastoma 6 months earlier. Further queries revealed that Dan's aunt, Mary, died at 37 years of age from renal cell cancer, and his aunt, Pam, had 2 retinal tumors, and was informed by her doctor that her hypertension was due to excessive adrenaline. Dan's grandfather, Milton, died at age 37 from problems secondary to hypertension and had a history of severe headaches.
>
> By constructing a 3-generation family medical history in pedigree format (Fig. 2), it became evident that multiple family members developed, at young ages, a variety of tumors, some of which were due to malignant processes. This family was referred to a geneticist and was subsequently diagnosed with a cancer syndrome called von Hippel-Lindau syndrome. Each of the affected individuals had been diagnosed and treated at separate institutions. The diagnosis of von Hippel-Lindau syndrome might have been made much earlier had healthcare providers involved in the family's care taken a 3-generation family medical history and documented the pedigree. After the diagnosis of von Hippel-Lindau syndrome, Dan's father, Robert, was determined to have bilateral renal tumors. A rigorous surveillance regimen was initiated for 2 at-risk cousins with hypertension.

In addition to improving the detection of hereditary cancer syndromes and identification of family members who might benefit from a surveillance program, construction of a pedigree provides an opportunity to build or enhance rapport with patients. By carefully listening to how a patient responds to the medical history questions for each family member, a nurse may assess the social relationship of the patient to the nuclear and extended family members. This appraisal often identifies psychosocial issues within the family and offers opportunities for intervention. In summary, the pedigree is a pictorial description of the family structure and provides the family medical history in such a manner that can be quickly accessed by all oncology healthcare providers throughout the care of a patient and his or her family.

■ Basic Construction of the Pedigree

An extended family history usually consists of information about the patient, his or her children, the patient's siblings, parents, aunts/uncles, and grandparents. As shown in Fig. 2, circles in the diagram represent females, squares represent males, and diamonds represent individuals for which the gender is unknown. When a diamond encloses a number, this number represents the number of individuals of that gender. An arrow identifies the patient. Information, such as name, date of birth, cancer history, and other medical problems about the various family members, is noted below each symbol. A diagonal line through a symbol signifies that the represented person is deceased. A single horizontal line between 2 symbols represents a marital or otherwise permanent relationship. A vertical line attached to the marital line at the top and the horizontal sib-ship line at the bottom represents the line of descent. Symbols (circles, squares, and diamonds) attached to the sib-ship line represent the children of the couple. The symbol for each child is attached to the sib-ship line with an individual vertical line. A shaded or solid symbol represents an affected individual. Often to condense a pedigree, nonbiologically related individuals may not be displayed. Pedigrees throughout the rest of this series will introduce you to other common symbols.

■ Categories of Genetic Conditions

Modern genetics traces its roots to 1865, with the publication of a paper by the Austrian monk, Gregor Mendel. Like many

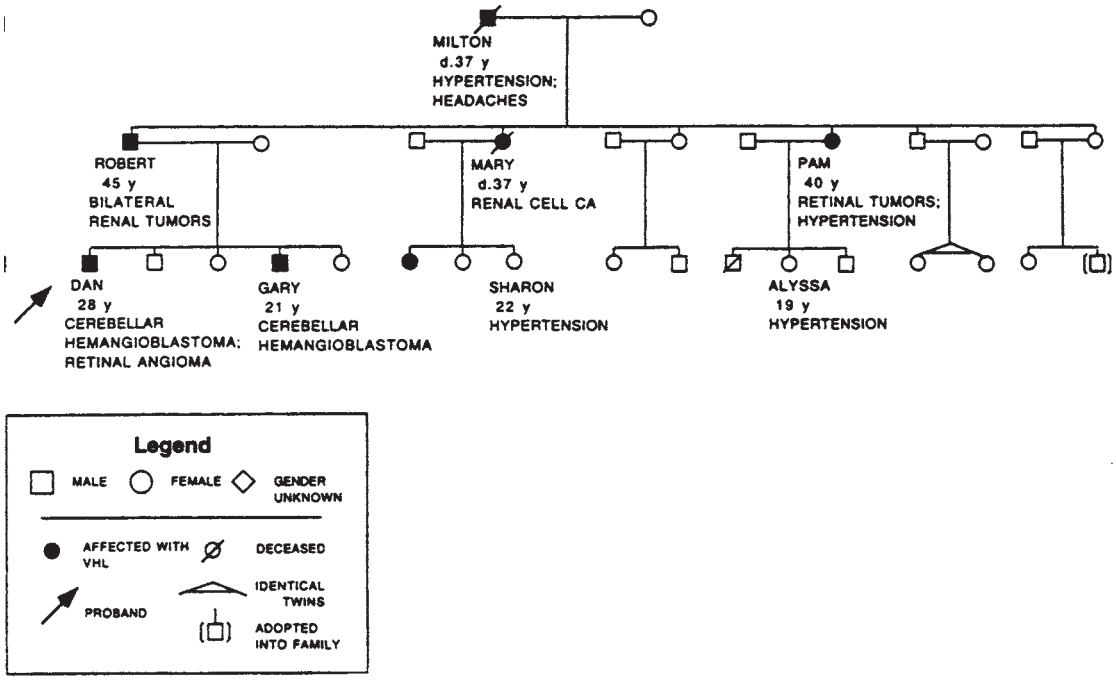

Figure 2 ■ Von Hippel-Lindau family pedigree.

reports of scientific breakthroughs, the paper remained in obscurity for many years, but since its rediscovery decades later, there has been an explosion of information about the inheritance of genetic conditions.

There are 3 primary categories of genetic conditions: single gene (Mendelian), chromosomal, and multifactorial. Conditions that are categorized as "single gene" are conditions caused by a mutation or alteration of a single gene. This category is further delineated as following either an autosomal dominant, autosomal recessive, or X-linked recessive inheritance pattern. Recall the term *autosomal* refers to conditions that are caused by mutated or altered genes carried on one of the chromosome pairs 1 to 22 (autosomes). Genetic conditions that follow an X-linked recessive pattern of inheritance are caused by gene alterations located on the X-chromosome. Conditions categorized as chromosome abnormalities involve an entire or a significant portion of a chromosome, composed of many genes. Finally, conditions categorized as multifactorial are due to the inheritance of 1 or more mutant genes interacting with the environment, other genes, or other factors to produce the trait or disease.

Single-gene Conditions: Autosomal Recessive

Bloom syndrome is an autosomal recessive genetic condition characterized by leukemia, susceptibility to infections, skin cancer, and short stature. It is common for the parents of a child newly diagnosed with Bloom syndrome to respond with the statement, "But, there is no one in our family with it. How can it be genetic?"

Bloom syndrome is "genetic" because it is caused by the inheritance of 2 copies of an altered or nonworking gene located on chromosome 15. An individual must have 2 copies of the altered gene to be affected. Parents of children with Bloom syndrome "carry" 1 copy of the altered gene and 1 normal copy of the gene. Carriers of the altered gene copy are usually asymptomatic, with no known increased risk for cancer or other health problems. With each pregnancy, carriers have a 50% (1 in 2) chance of passing the altered gene copy to their child.

Thus, each child of parents who are carriers of an autosomal recessive condition has:

- a 25% (1 in 4) chance of being affected.
- a 50% (1 in 2) chance of being a carrier and unaffected.
- a 25% (1 in 4) chance of neither having the disorder nor being a carrier.

These recurrence risks are independent of the sex of the child. That is, men and women may be affected by autosomal recessive conditions. Following is a pedigree characteristic of a family with Bloom syndrome (Fig. 3).

When considering if an individual is affected with an autosomal recessive condition, it is often helpful to know the ethnic background of the individual's parents. Although it is estimated that each person, regardless of ethnic background, carries 10 to 15 mutated genes, the frequency of carriers of gene mutations for some disorders is known for a few specific ethnic groups. For example, approximately 1% (1 in 100) of individuals of Ashkenazi Jewish ancestry are carriers of Bloom syndrome.

It is also helpful to know if the parents are biologically related (consanguineous). In general, parents who are biologically related have a higher chance of carrying a copy of the same altered gene than 2 unrelated individuals. For example, first cousins have a 12.5% (1 in 8) chance of carrying the same

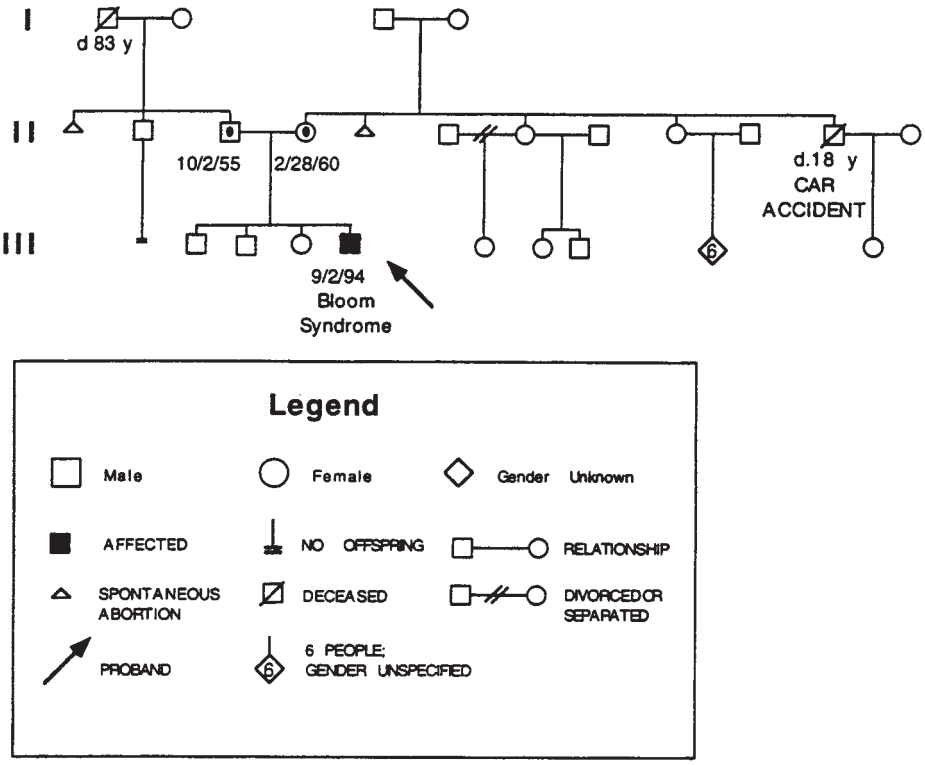

Figure 3 ■ Autosomal recessive pedigree: Bloom syndrome.

mutated gene. Consequently, consanguineous couples have an increased risk for having a child with an autosomal recessive genetic condition. However, it is important to remember that a couple need not be related nor of a certain ethnic background to have a child affected with an autosomal recessive condition. Individuals of all ethnic backgrounds and of unrelated parents may be affected with autosomal recessive conditions. Examples of other autosomal recessive genetic disorders with an increased risk of cancer are xeroderma pigmentosum and Fanconi anemia.

Single-gene Conditions: Autosomal Dominant

It is becoming more and more common to hear from individuals with cancer that there are other members of their families affected with the same type and/or other types of cancer. In many cases, this may be due to chance or to shared environment, but in others, further elucidation of the extended family history will reveal a family affected with a heritable cancer syndrome.

Examples of genetic conditions with a predisposition to cancer that follow an autosomal dominant pattern of inheritance are neurofibromatosis, tuberous sclerosis, von Hippel-Lindau, and hereditary nonpolyposis colorectal cancer. Not all individuals with these autosomal dominant genetic disorders develop cancer, but all have a predisposition to and an increased risk of cancer. Unlike autosomal recessive conditions, an individual with an autosomal dominant genetic condition needs only to have one mutated gene to be affected. Each child of an individual who has an autosomal dominant genetic condition has:

- a 50% (1 in 2) chance of inheriting the altered (nonworking) gene and being affected.
- a 50% (1 in 2) chance of inheriting the unaltered (working) gene and not being affected.

Gender has no bearing on whether a child will be affected by an autosomal dominant condition. That is, men and women may be affected. Fig. 4 shows the pedigree of a family with neurofibromatosis, type 1.

Some types of breast and ovarian cancer appear to have an autosomal dominant pattern of inheritance, but because breast cancer is common, it can be difficult to distinguish between an individual who is affected due to the inheritance of an altered gene and an individual who is sporadically affected.

Single-gene Conditions: X-linked

In some cases, the gender of an individual does have relevance to whether he or she will be affected with a specific genetic condition. For example, Wiskott-Aldrich syndrome is a genetic condition characterized by small abnormal platelets, thrombocytopenia, and abnormal immunoglobulin levels. This condition preferentially affects males, because it is caused by an alteration of a gene carried on the X-chromosome and follows the X-linked recessive pattern of inheritance.

Recall, men and women have 2 copies of autosomes (chromosomes 1 to 22). However, men and women differ in their sex chromosomes. Females have 2 X-chromosomes, whereas males have 1 X-chromosome and 1 Y-chromosome. For the most part, the genes on the X-chromosome differ from those on the Y-chromosome. Thus, men have only 1 copy of each of the genes car-

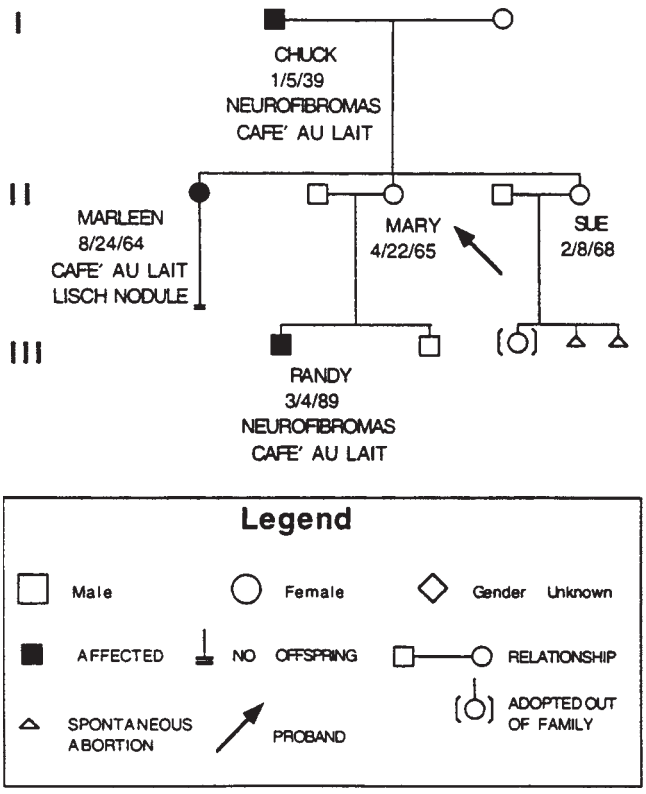

Figure 4 ■ Autosomal dominant pedigree: neurofibromatosis.

ried on the X-chromosome, whereas women have 2 copies. A deleterious mutation in a gene on the X-chromosome will always be expressed in men, because they only have one copy of each of those genes. They do not have a working copy of the gene on a second X-chromosome. An alteration in a gene on 1 of the 2 X-chromosomes in a female generally produces no symptoms, because the unaltered, or working, gene on the second X - chromosome compensates for the mutated gene's effects.

The mother of a boy affected with Wiskott-Aldrich syndrome or any other X-linked recessive genetic condition may be a carrier of the condition or the child may be affected as a result of a new mutation. A male child inherits his X chromosome only from his mother and his Y chromosome only from his father. With each pregnancy, women who are carriers of a deleterious mutation on one of their two X chromosomes face the following possible outcomes:

With each pregnancy, women who are carriers of a deleterious mutation on one of their two X chromosomes face the following possible outcomes:

- 50% (1 in 2) chance that a son will inherit the X chromosome with the altered (nonworking) gene and be affected.
- 50% (1 in 2) that a son will inherit the X chromosome with the unaltered (working) gene and not be affected.
- 50% (1 in 2) chance that a daughter will inherit the X chromosome with the altered (nonworking) gene and be a carrier, but unaffected.
- 50% (1 in 2) chance that a daughter will inherit the X chromosome with the unaltered (working) gene and be neither a carrier, affected, nor at risk for having an affected son.

All the daughters of a man affected with an X-linked genetic condition will be carriers of the condition, but generally will be unaffected. His sons will not be carriers of, nor affected by the condition. An affected father can never pass the X-linked recessive condition to his son. Thus, one feature that distinguishes the X-linked recessive pattern of inheritance from the other patterns of inheritance is the absence of male to male transmission. Fig. 5 demonstrates a pedigree characteristic of a family with Wiskott-Aldrich syndrome.

■ Chromosomal Disorders

The second category of genetic conditions involves chromosomal aberrations–associated disorders. The field of cytogenetics is the study of chromosomes and how they are transmitted from parents to their offspring. A single chromosome consists of a tightly coiled and compacted strand of DNA, which is made up of hundreds to thousands of functional genes. A large percentage of chromosomal DNA does not encode genes; its role is not completely understood. In other words, a strand of DNA is not comprised of genes lying next to one another but more like beads on a string with spacer material between the functional genes.

Recall, individuals typically have 23 pairs of chromosomes; 1 of each pair is inherited from the mother's egg and the other pair is inherited from the father's sperm. Chromosomes are designated by number according to their size and shape. Chromosome 1 is the largest, and chromosome 22 is one of the smallest. As stated, chromosome pairs 1 to 22 are called autosomes and the 23rd pair consists of the sex chromosomes. Men have an X and a Y chromosome, and women have two X chromosomes (Fig. 6).

Human chromosomes consist of a short and long arm separated by an area of constriction known as the centromere. The short arm of the chromosome is referred to as the p-arm, and the long arm of the chromosome is referred to as the q-arm. Therefore, the designation 8q refers to the long arm of chromosome 8. In the laboratory, chromosomes can be stained to reveal alternating light and dark horizontal bands. These bands assist in the identification of individual chromosomes, because the banding pattern is unique to each chromosome. The bands also can serve as geographic landmarks for localization of genetic markers and genes. In the cytogenetic laboratory, the chromosomes are stained and analyzed for number, structure, and missing (deleted) or additional (duplicated) genetic material. A karyotype is a picture of the chromosomes produced by taking a photograph and cutting out each of the 46 chromosomes and lining the pairs together. By convention, the chromosomes are arranged so that the short arm is on top and the long arm is the on the bottom and in descending order of size.

There are 2 main classes of chromosome anomalies: abnormal chromosome number (aneuploidy) and structural rearrangements. The usual process by which an individual possesses an abnormal chromosome number in every cell is due to an error occurring during meiosis. Meiotic cell division is the process by which the sperm and egg receive one half of the genetic material, or 23 chromosomes. At conception, the

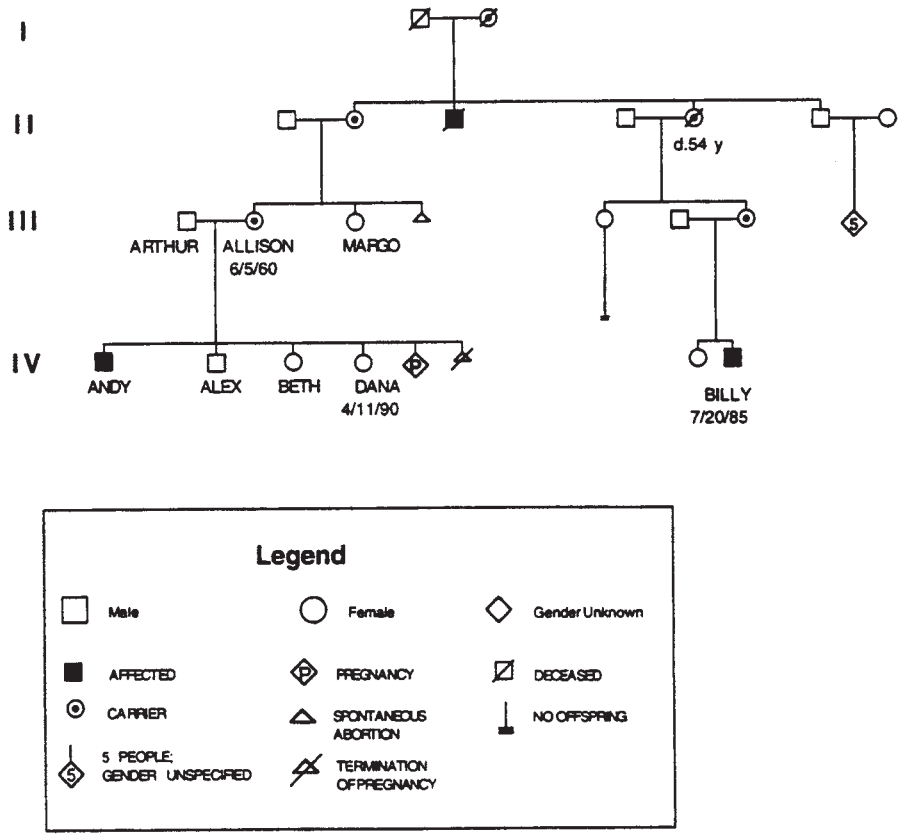

Figure 5 ■ X-linked recessive pedigree: Wiskott-Aldrich.

sperm and egg fuse to produce a fertilized egg with the restored number of 46 chromosomes.

■ Aneuploidy

Aneuploidy is generally the result of errors in meiotic cell division before the time of conception, creating a sperm or egg with too many or too few chromosomes. This abnormal chromosome number is passed on to the child at conception. The most common chromosome disorder in live born infants is Down Syndrome, also referred to as Trisomy 21. As the genetic name implies, the majority of the individuals with Down Syndrome have 3 copies of chromosome 21 (Fig. 7). This syndrome is characterized by typical physical features, mild to severe mental retardation, and an increased risk for other health problems, including congenital heart disease, thyroid dysfunction, and leukemia.

Other examples of aneuploid chromosomes include Trisomy 13 and Trisomy 18, often-lethal disorders of neonatal life. However, some children with these 2 types of trisomies survive with significant physical disabilities and mental impairment. Individuals who have 1 too many or 1 too few chromosomes either have an extra set of every gene on that chromosome or lack an entire set of genes from the missing chromosome. Because of this large number of additional or missing genes, there are few aneuploid situations that are consistent with a normal lifespan or without major health problems.

The risk of having a child with chromosomal aneuploidy increases with maternal age. Women older than the age of 35 years are offered prenatal diagnosis by amniocentesis or chorionic villus sampling to detect changes in chromosome number. For couples that have a child with chromosomal aneuploidy, the chance of having another child with an abnormal number of chromosomes is slightly (0.5% to 1.0%) higher than would be expected based on the mother's age. This recurrence risk is based on empiric data rather than on a specific mode of inheritance. Aneuploidy does not transmit in Mendelian patterns of inheritance observed in single-gene disorders.

Chromosome instability is another mechanism in which individual cells acquire or lose chromosomes. Chromosomal instability in tumors leading to the gain or loss of whole chromosomes, or portions thereof, will be addressed in the next module.

■ Structural Rearrangements

Another class of chromosomal errors is the structural rearrangement of one or more chromosomes. Several types of structural abnormalities are observed, but the most common abnormality involves the breaking and rearrangement of 2 or more chromosomes. In these situations, usually 2 chromosomes break somewhere along their length and the free chromosome pieces exchange places. This is referred to as a reciprocal translocation (Fig. 8). If the chromosomal break occurs in a section of the DNA that does not contain a structural gene and there is no gain or loss of chromosomal material (balanced translocation), there most likely will be no impact on the health of the individual. However, such a rearrangement does

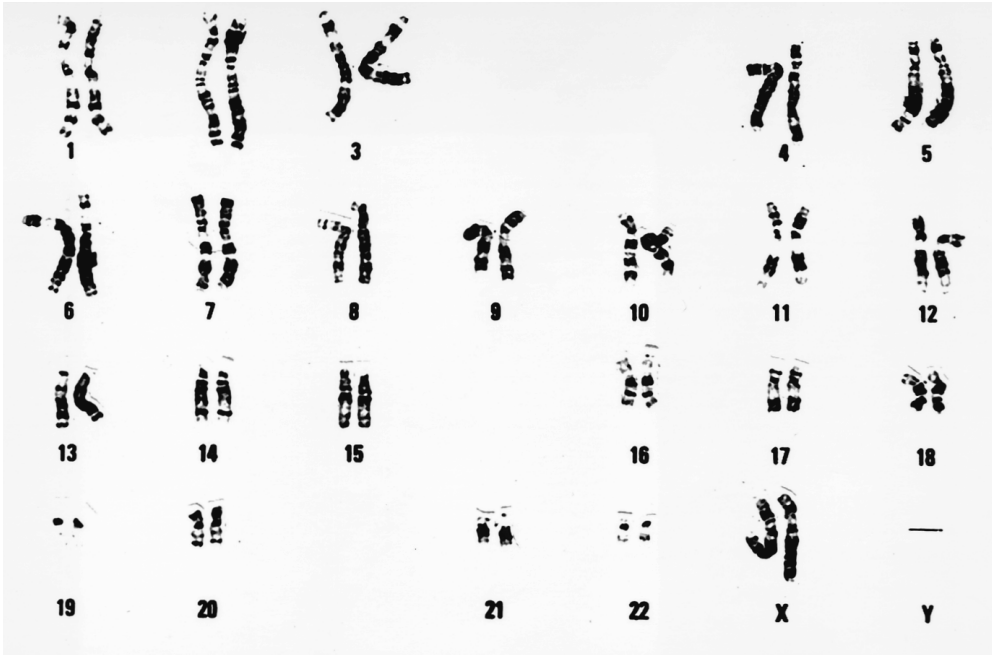

Figure 6 ■ Normal female karyotype (courtesy of Cytogenetics Laboratory, Department of Obstetrics and Gynecology, Georgetown University Medical Center, Washington, DC).

result in an increased risk of pregnancy loss. Approximately 1 in 500 to 1,500 persons carry a balanced translocation. When carriers of balanced translocations conceive, the child may receive an unbalanced amount of chromosomal material, resulting in an increased risk of miscarriage or a child with physical and/or mental abnormalities.

Chromosomal breaks can occur in critical regions of a chromosome with disruption of gene function due to loss (deletion) or gain of critical genetic material. Translocations also can cause problems by placing one critical gene next to or within another critical gene. In these situations, the location or combination of the 2 gene sequences may promote oncogenesis. One of the earliest known relationships between a chromosomal translocation and cancer was the reciprocal translocation between chromosomes 22q and 9q found in the bone marrow of 95% of adults with chronic myelogenous leukemia (Fig. 9). This translocation places the *c-abl* oncogene from chromosome 9q next to the breakpoint cluster region (bcr) on chromosome 22q. The juxtaposition of these 2 genes enhances the growth-promoting properties of *c-abl* oncogene, which predisposes the cells to undergo malignant transformation.

■ Multifactorial Inheritance

The third category of genetic conditions is one in which disorders are attributed to an interaction between one or more genes (polygenic) or between one or more genes and environmental influences. Genes do not function in isolation but in concert with other genes and are influenced by the surrounding environment. Most human traits are determined by the interaction of many genes and environmental influences rather than the function of a single gene. When environmental factors are known to influence the expression of a genetic trait or disease, the term *multifactorial inheritance* is used.

Multifactorial inheritance is believed to be the basis for most, if not all, of the common chronic diseases of adulthood such as diabetes, essential hypertension, multiple sclerosis, coronary artery disease, and cancer, as well as some of the common isolated birth defects of childhood including cleft lip/palate, congenital heart disease, and neural tube defects. It has long been observed that these conditions can occur in more than one member of an extended pedigree but do not follow clear Mendelian inheritance patterns.

Figure 7 ■ Trisomy 21 karyotype (courtesy of Cytogenetics Laboratory, Department of Obstetrics and Gynecology, Georgetown University Medical Center, Washington, DC).

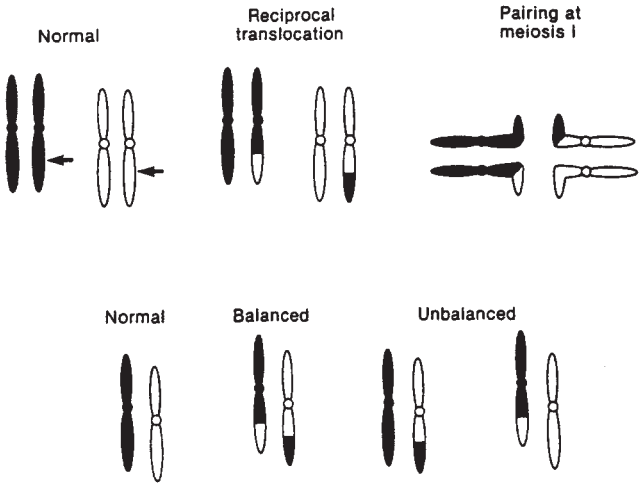

Figure 8 ■ Reciprocal translocation and its consequences. From Thompson JS, Thompson MW. *Genetics in Medicine.* 4th ed. Philadelphia: WB Saunders; 1986. Used with permssion of W.B. Saunders Company.

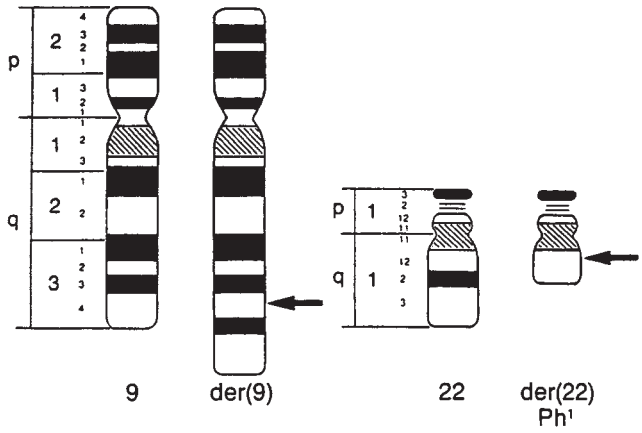

Figure 9 ■ Schematic model of the Philadelphia chromosome. From Thompson JS, Thompson MW. *Genetics in Medicine.* 4th ed. Philadelphia: WB Saunders; 1986. Used with permssion of W.B. Saunders Company.

Every individual has genes that predispose or increase susceptibility to particular traits or disease. The presence of a predisposing gene, alone, does not result in the trait or disease but confers susceptibility to that particular characteristic. The likelihood of developing a disease or having a trait increases when a person who possesses a predisposing gene also carries other genes that influence the function of that gene or provides added predisposition to that particular trait or disease. This risk is further amplified when specific environmental influences are present.

An example of the interplay between genes and environment is presented in Fig. 10, which illustrates factors involved in coronary artery disease. An individual who carries the polygenic traits of hypertension, obesity, or elevated cholesterol as individual conditions may not be destined to develop coronary artery disease. However, if that person possesses a major gene for defective Apolipoprotein E metabolism and leads an unhealthy lifestyle, the risk of coronary artery disease would be substantially increased because of this combination of factors. An understanding of the genetic and environmental contributions to the pathophysiology of a particular disease may lead to more effective prevention, earlier detection, and specific, more effective treatment modalities of these diseases. Many common sporadic cancers follow a similar model of inheritance as coronary artery disease.

Risks to other family members can often be provided with confidence in single-gene inheritance; however, it is more difficult to assess the risk in multifactorial conditions. Identifying the specific roles of multiple genes involved in a given condition and to elucidate the effects of a variety of environmental influences is a daunting task. For most multifactorial diseases, empiric risks are provided. Empiric risks are based on a collection of large population studies and may or may not reflect the risks for a specific individual. Reliable empiric data are available for a few of the more common cancers such as breast and colon, but not all cancers with a multifactorial etiology.

Variation in Gene Expression

As stated above, genes do not act alone, but are influenced by the genetic background of an individual and by the external or internal environment. A person's genetic constitution, or genome, is referred to as his or her genotype. How these genes express themselves in height, hair color, body chemistry, etc., is referred to as his or her phenotype. There are several factors that play a role in how a gene is expressed.

Variable expressivity and incomplete penetrance are features observed frequently in heritable conditions and may also play a role in genetic predisposition or susceptibility to common diseases. An altered or mutated gene may not always be expressed (incomplete penetrance) or, if expressed, may vary widely in different individuals (variable expressivity).

Fig. 4 demonstrates a neurofibromatosis type 1 (NF1) pedigree. NF type 1 is an autosomal dominant disorder characterized by neurofibromas (soft cutaneous nodules), café'au lait spots (light brown, flat skin lesions), Lisch nodules (benign, small tumors of the iris), and an increased risk of malignancy.

From analysis of this pedigree, it can be postulated that Mary must carry the NF gene, because her father and son are affected. However, she does not demonstrate clinical features of the syndrome. Therefore, neurofibromatosis is considered to be nonpenetrant in Mary. Some genetic disorders are highly penetrant, meaning that if an individual has the gene in question, he or she is highly likely to have clinical features of that disorder. Conversely, there are some genetic disorders that have decreased or low penetrance. In these conditions, if an individual inherits the mutated gene in question, he or she may not experience clinical features of the disorder. Penetrance of genetic disorders varies from disorder to disorder and from one family to another, and nonpenetrance is actually quite unusual in NF, type 1.

This family also demonstrates the phenomenon of variability of expression, which is different from the phenomenon of penetrance. The clinically affected members of this family all have NF, but their clinical features vary in both their severity

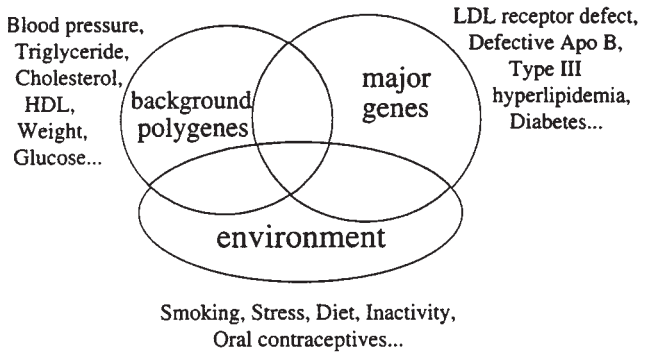

Figure 10 ■ Schematic for model of gene–environment interactions. From McCante, Heuther, eds. *Pathophysiology: the biological basis for disease in adults and children.* Copyright 1994 by Roger R. Williams. Used with permission of Mosby-Year Book, Inc.

and organ(s) of involvement. Mary's father, Chuck, has multiple café au lait spots, has multiple disfiguring cutaneous neurofibromas, and had abdominal surgery becuase of invasion of a large neurofibroma within the peritoneal cavity. Marleen's only clinical features of neurofibromatosis are 15 café'au lait spots and 1 Lisch nodule. Randy, Mary's son, has clinical symptoms consisting of multiple café'au lait spots and an enlarging neurofibroma along the vertebral column. This pedigree demonstrates reduced penetrance and variable expressivity. Variability of expression and penetrance are features more commonly observed in autosomal dominant genetic disorders.

■ Molecular Biology: Normal Structure of the Gene

A prerequisite for understanding the complexities of cancer genetics and the nuances of genetic testing is a fundamental knowledge of the anatomy and biochemistry of genes and DNA. DNA must undergo replication, transcription, and translation before producing protein as a final gene product. The next few sections provide an overview of the basics of gene structure and function. Genes are composed of DNA and serve as instructions for cellular assembly of proteins. In 1953, Watson and Crick identified the 3-dimensional double helix structure of DNA, which provided an explanation of how DNA replicates, or copies itself.

DNA is made up of 2 long, twisted strands. Each strand is composed of smaller chemical units called nucleotides. Each nucleotide is made up of 3 components: a sugar, a phosphate, and a nitrogenous base. The sugar and phosphate molecules bond tightly into 2 strands, providing the structural backbone of DNA. The third component of the nucleotide is 1 of 4 nitrogenous bases: A (adenine), T (thymine), G (guanine), and C (cytosine). The 2 DNA strands line up next to one another like 2 sides of a zipper with the bases acting like interlocking teeth. The 2 sides of the zipper fit together in only 1 way: A always pairs with T, and G always pairs with C (Fig. 11). The only shape that will accommodate this exact matching of bases is the DNA helix.

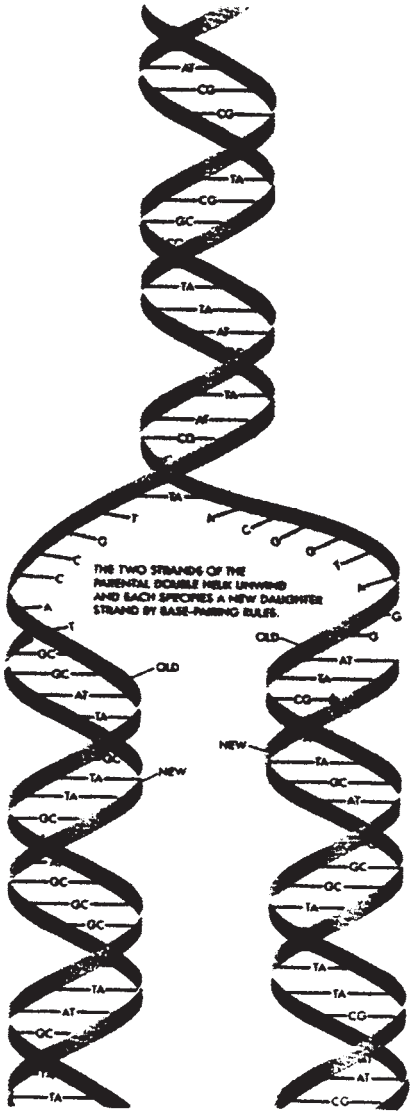

Figure 11 ■ DNA helix demonstrating replication of a new DNA strand. From Watson, Tooze, and Kurtz. *Recombinant DNA: A Short Course.* Copyright 1983 by James Watson, John Tooze, and David T. Kurtz. Used with permission of W.H. Freeman and Company.

■ Deoxyribonucleic Acid Replication and Transcription

Before cell division, a new DNA strand must be synthesized. To do this, the 2 strands separate and unwind, with each strand becoming a template for a new strand (Fig. 11). The new DNA strand is produced by a protein celled DNA polymerase, which travels up the template strand, adding each complementary nitrogenous base according to the template. DNA polymerase also plays a role in maintenance and repair of DNA, proofreading as it travels up the DNA template strand. Human cells have a number of mechanisms for identification and repair of copy errors to improve the accuracy of DNA replication. This way, each gene is faithfully replicated in preparation for cell division.

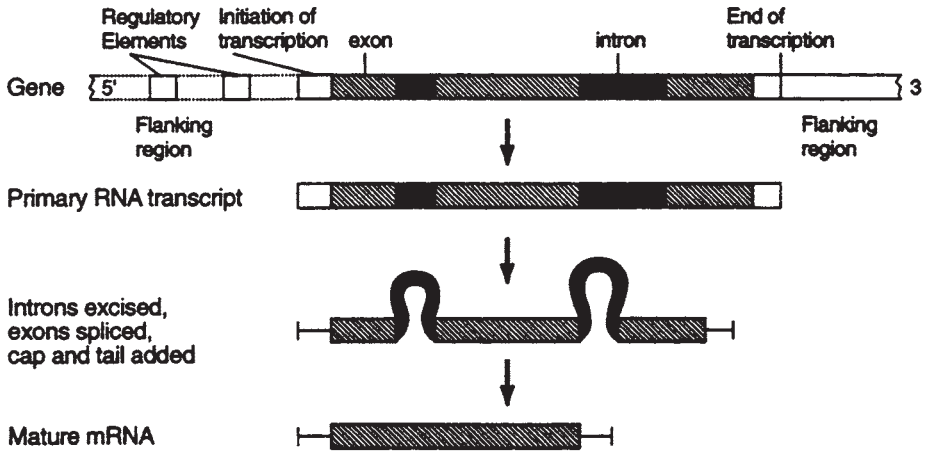

Figure 12 ■ Transcription and processing of a beta-globin gene to form a mature messenger RNA. From Thompson JS, Thompson MW. *Genetics in Medicine*. 4th ed. Copyright 1986 by James S. Thompson and Margaret W. Thompson. Used with permission of W.B. Saunders.

DNA is formed and replicated in the cell nucleus, whereas protein synthesis takes place in the cytoplasm of the cell. The transportation of the genetic code from the nucleus to the cytoplasm and the interpretation of the code involves 2 basic processes: transcription followed by translation. Ribonucleic acid (RNA) is the nucleic acid involved in these 2 processes. Similar in structure to DNA, RNA differs because it comprises only 1 strand, and the nitrogenous base thymine (T) is replaced by uracil (U). Transcription (Fig. 12) is the process by which RNA is synthesized from the DNA template. Genes comprise both coding (exons) and noncoding (introns) regions. Introns are noncoding regions interspersed throughout most genes, which are spliced out (removed) after transcription. This process results in a mRNA (messenger RNA) transcript, which is free to move out of the nucleus and into the cytoplasm.

■ Genetic Code

Genes direct the synthesis of all the body's proteins. The body contains 20 essential amino acids that assemble together in an infinite number of ways to create the larger, more complex proteins. In general, 3 nucleotides make up a triplet, called a codon. Thus, an example of a codon is "CCG." In general, each codon specifies the production of one amino acid. Proteins, or polypeptides, are then formed, made up of sequences of many amino acids. Thus, each gene that codes for a complex protein is composed of a series of codons, which act as instructions for the building of a protein. The 4 letters of this code (A, T, G, and C) are used to write an infinite combination of instructions for thousands of proteins, which is called the genetic code (Fig. 13). The codons are read sequentially from left to right in sequences of triplets, thereby specifying the sequence of amino acids. The division of bases into triplets that specify the amino acid sequence of the protein is called the reading frame.

■ Translation

Translation is the process in which the codon sequence of the RNA transcript is converted into a sequence of amino acids. This is accomplished by a cytoplasmic particle called the ribosome, which reads the code and assembles the prescribed amino acids, thereby constructing a complete polypeptide (Fig. 14). Thus, each complex protein produced in our body is a product; the production of which is directed, or coded, by a gene.

Gene function and expression are influenced by regulatory elements located either in vicinity to the gene or at some distance from the gene. Examples of regulatory elements are enhancers, which upregulate or enhance gene expression, and repressors, which down regulate or slow gene expression. With this background of genetics, it is possible to consider molecular pathology and how these errors relate to human disease.

■ Molecular Biology: Mutations

Genes are generally stable and are passed through generations without change. However, genes occasionally change, and this process is referred to as a mutation. The term *mutation* suggests a negative consequence; however, mutations frequently occur without health consequences. Genetic mutations are most likely the explanation for evolutionary changes in our species. Between the structural genes are long segments of noncoding DNA with as yet unknown function. Within this DNA are mutations or variations in nucleotide sequence, which have no apparent phenotypic effects. These normal variations are relatively frequent in the population and are referred to as benign polymorphisms.

Mutations can occur in the germ line (sperm and egg) cells or may occur in the somatic (body) cells after fertilization. Much of the DNA is composed of sequences that do not code for specific proteins, so that a change or alteration in these noncoding regions often may not be detected. However, if a mutation occurs in the coding sequence of a structural gene, the final gene product, a protein, may not be formed correctly. The protein may not be produced at all or the quantity/quality and function may be significantly altered. There are several categories of mutations, the most frequent are point mutations and frameshift mutations.

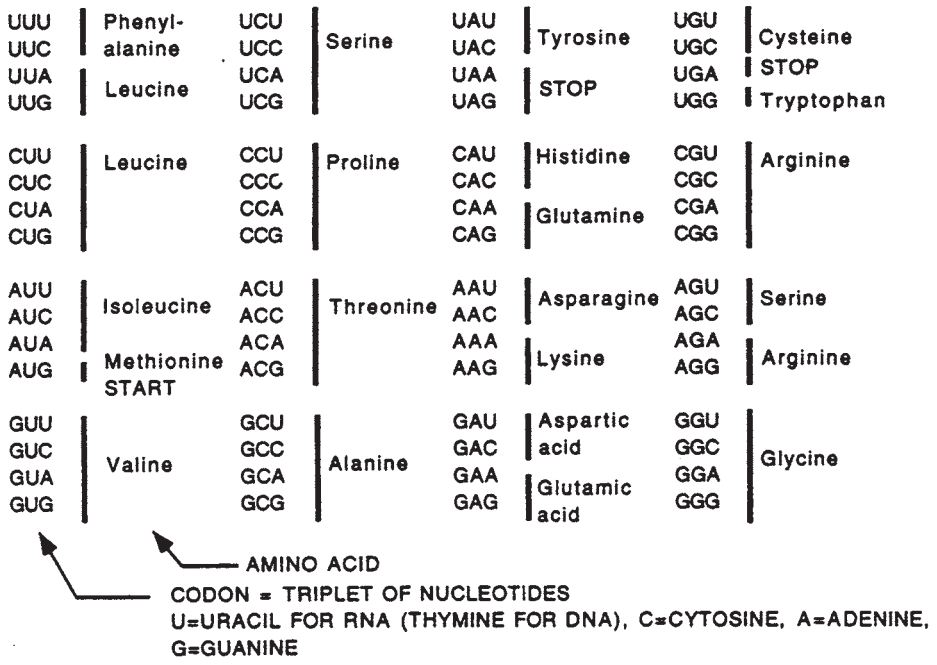

Figure 13 ■ The Genetic Code.

Point Mutations and Frameshift Mutations

Point mutations involve the substitute of 1 nitrogenous base (A,T,G,C) for another. One can make an analogy to spelling errors. Imagine a spelling error in which a simple typographical error occurs. GTT may be "misspelled" ATT. This type of error is a point mutation in which the nitrogenous base (G) is substituted by the nitrogenous base (A). In this example, the amino acid, isoleucine, would be produced instead of valine. A base substitution may have either no detectable effect on the biologic activity of a protein or may result in a protein product that has no activity, reduced activity, or increased activity. This is why some mutations are benign whereas others lead to disease. Point mutations do not interrupt the reading frame of a gene. The codons following the one in which a point mutation occurred are not disturbed.

Codons can be interrupted by the insertion or deletion of a single or multiple bases. In these situations, often a significant change results in the amino acid sequence of the final protein product. This is due to a change in the reading frame for all the subsequent codons (frameshift mutation). In the example shown in Fig. 15, a deletion of 1 base pair has occurred, switching the reading of the codons from GCU to CUG. Recall that uracil (U) replaces thymine (T) in the RNA transcript. In this example, the amino acid leucine replaces alanine in the assembly of the final gene product, which is repeated in subsequent codons. The function of the final protein product is likely to have changed significantly.

Both point mutations and frameshift mutations may result in a premature message to stop production of the polypeptide. A polypeptide chain is assembled according to the codons along the RNA transcript until a STOP codon is reached. If a mutation in a codon for an amino acid results in a codon that provides a premature message to stop translation, the assembled protein is shortened. This is generally a useless protein that is often degraded resulting in absence of the normal gene product, which can lead to disease.

Occasionally entire codons are eliminated. Cystic fibrosis provides an example. The first mutation discovered to cause cystic fibrosis was the deletion of 1 three-letter codon. Therefore, the final protein produced is missing a single amino acid. The absence of this single amino acid accounts for the spectrum of clinical problems faced by many CF individuals. Since then, more than several hundred different mutations in the cystic fibrosis gene have been identified, many unique to a single family. Molecular laboratories today are not testing for all known CF mutations, only the most common ones. Therefore, a negative cystic fibrosis mutation test eliminates the presence of the most common mutations, but cannot guarantee that a person does not carry any of the hundreds of other mutations that can cause cystic fibrosis. Similar problems have been found in cancer susceptibility genes. More than 300 mutations have been identified in the BRCA1 gene.

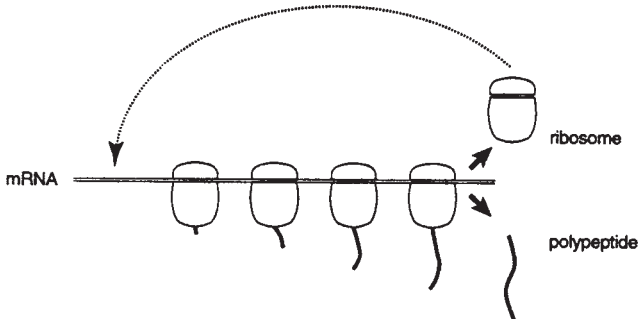

Figure 14 ■ Translation of mRNA into a polypeptide chain. From Thompson JS, Thompson MW. *Genetics in Medicine.* 4th ed. Copyright 1986 by James S. Thompson and Margaret W. Thompson. Used with permission of W.B. Saunders.

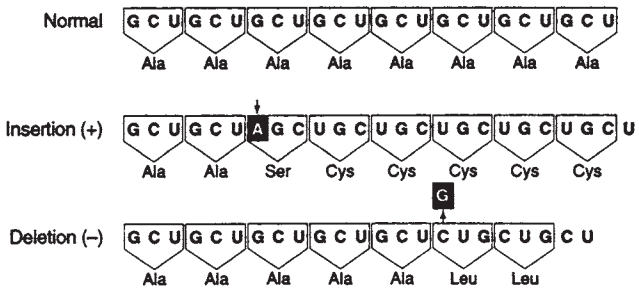

Figure 15 ■ Frameshift mutation schematic demonstrating a normal sequence, an insertion of a single base, and a deletion of a single base. The two frameshift mutations after the reading frame and thus the amino acid composition of the final protein.

■ Molecular Genetic Testing

As genetic testing becomes increasingly used in the oncology field, appropriate interpretation of genetic test results is essential, because people may base important life-altering decisions on the information. To accomplish this, it is imperative that healthcare providers have a basic understanding about the structure and function of genes, mechanisms for genetic errors, and genetic testing methods. Molecular genetic testing is accomplished either by direct mutational analysis or by indirect methods, each having different levels of sensitivity and complexity. Direct testing can be done in situations in which the precise gene mutation has been identified in an affected individual. Finding an affected person's mutation is generally done by gene sequencing. When the precise mutation is identified in a family, at-risk family members may be tested specifically for the presence or absence of that mutation. Direct testing for the deleterious gene in these situations has a high degree of accuracy when performed by an experienced molecular laboratory. With the exception of one class of mutations, most mutations are stable and will not change within and among family members.

Indirect methods of genetic testing are less precise and involve more complex interpretive analyses. Indirect testing relies on identifying whether an individual has inherited a region of a specific chromosome that contains a gene, rather than looking for the precise gene mutation. During meiosis, maternal and paternal chromosomes normally line up next to one another, exchanging portions or segments. It is this normal process of meiotic recombination that accounts for the unlimited variation observed in humans, such that each individual is entirely unique. It is also the basis for understanding linkage analysis, an indirect method of genetic testing.

■ Linkage Analysis

In many instances, before the discovery of a disease-causing gene, testing involves localization of the gene to a particular chromosome and then to a specific segment of that chromosome. This is accomplished through an indirect process known as linkage analysis. Known sequences of DNA (polymorphisms) near the gene of interest act as biologic markers that can be tracked or followed from generation to generation. The closer the known gene sequence (marker) is to the disease gene, the higher the likelihood the person inherited the marker and disease gene together. The farther the distance from the marker, the greater the possibility that a meiotic crossing-over event occurred. This possibility leads to a statement of probability that a member of a family might also have the disease gene but not a definitive determination.

Linkage analysis generally involves the testing of multiple members of a family, offering the benefit of possible gene discovery, but with the limitation of imprecise interpretation: linkage analysis is most often used in the research setting, but is an example of an indirect testing method, which should be familiar to the oncology healthcare professional. There are many nuances and complexities to genetic testing that will be addressed in greater detail in a later series article. These complexities must be understood by healthcare professionals because increasing numbers of genetic tests are becoming available resulting from the Human Genome Project and genome-related research overall. As we are continually faced with daily headlines reporting new gene discoveries, we will face increasing interest from the public in understanding potential uses of new gene tests.

■ Human Genome Project

The information gained from the Human Genome Project (refer to the first article in this series) will undoubtedly create significant changes in healthcare practice. All human genes will eventually be found, and accurate diagnoses will be developed for most inherited diseases. In addition, animal models for human disease research will be more easily developed, facilitating the understanding of gene function in health and disease.

Researchers have identified single genes associated with a number of diseases such as neurofibromatosis, Duchenne muscular dystrophy, retinoblastoma, inherited forms of breast and colon cancer, and cystic fibrosis. As research progresses, investigators will also uncover the mechanisms for diseases caused by several genes or by a gene interacting with environmental factors. Genetic susceptibilities have been implicated in many major disabling and fatal diseases, including heart disease, stroke, diabetes, and cancer. The identification of these genes and their proteins will pave the way for more effective therapies and preventive measures. Investigators determining the underlying biology of genome organization and gene regulation will also begin to understand how humans develop from single cells to adults, why this process sometimes goes awry, and what changes take place as people age.

Suggested Reading

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CE TEST: Genes and Inheritance

Lindsay A. Middelton, RN, CGC; Kathryn F. Peters, MS

General Purpose: To present registered professional nurses with an overview of basic genetic concepts, including inheritance patterns, pedigree constructions, chromosome aberrations, and the multifactorial basis underlying the common diseases of adulthood.

Objectives: After reading this article and taking this test, you will be able to:

1. Outline factors helpful in understanding, identifying, and distinguishing autosomal recessive, autosomal dominant, and X-linked genetic disorders.
2. Describe the symbols and notations used to construct a genetic pedigree.
3. Explain features of chromosomal and other genetic disorders.

CE Test

1. A child of parents who are both carriers of an autosomal recessive genetic disorder has a 50% chance of
a. having the disorder.
b. not having the disorder and not being a carrier.
c. not having the disorder and being a carrier.
d. having the disorder, but only if he is male.

2. An example of an autosomal recessive disorder is
a. neurofibromatosis.
b. xeroderma pigmentosum.
c. von Hippel-Landau syndrome.
d. nonpolyposis colorectal cancer.

3. A child of a person who has an autosomal dominant condition
a. can only get the condition if both parents have it.
b. has a 25% chance of getting the condition.
c. can only get the condition if he is male.
d. has a 50% chance of getting the condition.

A CONTINUING EDUCATION ENROLLMENT FORM: GENES AND INHERITANCE

Credit: 3.0 contact hours Fee: $19.95 Registration deadline: October 31, 2003

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Clinical Specialty — Where You Work Most Often _____

B **Test Responses:** Darken one for your answer to each question.

	A	B	C	D		A	B	C	D		A	B	C	D
1.	❍	❍	❍	❍	7.	❍	❍	❍	❍	13.	❍	❍	❍	❍
2.	❍	❍	❍	❍	8.	❍	❍	❍	❍	14.	❍	❍	❍	❍
3.	❍	❍	❍	❍	9.	❍	❍	❍	❍	15.	❍	❍	❍	❍
4.	❍	❍	❍	❍	10.	❍	❍	❍	❍	16.	❍	❍	❍	❍
5.	❍	❍	❍	❍	11.	❍	❍	❍	❍	17.	❍	❍	❍	❍
6.	❍	❍	❍	❍	12.	❍	❍	❍	❍					

C

1. Did this CE activity's learning objectives relate to its general purpose? ___ Y ___ N
2. Was the journal home study format an effective way to present the material?___ Y ___ N
3. Was the content current to nursing practice? ___ Y ___ N
4. How long did it take you to complete this CE activity? _____ hours
5. Suggestions for future topics _____
   _____

4. An example of an autosomal dominant disorder is
a. tuberous sclerosis.
b. Wiskott-Aldrich syndrome.
c. Fancomi anemia.
d. Bloom syndrome.

5. A man who has an X-linked condition will pass the
a. condition to all of his daughters.
b. carrier state to all of his daughters.
c. condition to all of his sons.
d. carrier state to all of his sons.

6. In a family history constructed in a pedigree format, a shaded circle connected by a horizontal line to an unshaded square indicates
a. a married couple in which the wife has the indicated disorder and the husband does not.
b. a mother whose son has the indicated disorder.
c. a married couple in which the husband is deceased and the wife is alive.
d. a father whose daughter has the indicated disorder.

7. In a family history constructed in a pedigree format, a diagonal line through a circle indicates
a. unknown paternity.
b. a deceased female.
c. a male with the indicated condition.
d. an unmarried female.

8. In a family history constructed in a pedigree format, a symbol with the number 2 inside it indicates
a. a married couple.
b. two people who have the indicated condition.
c. two individuals of the same gender, whether male, female, or unknown.
d. the second generation represented in the pedigree.

9. The designation 17p refers to
a. the long arm of autosome 17.
b. the short arm of autosome 17.
c. the long arm of sex chromosome 17.
d. the short arm of sex chromosome 17.

10. Down syndrome is an example of
a. having an extra chromosome.
b. structurally rearranged chromosomes.
c. having a missing chromosome.
d. multifactorial inheritance.

11. The way a person's inherited characteristics are demonstrated in features like height and hair color is called that person's
a. genotype.
b. genome.
c. phenotype.
d. phenome.

12. Low penetrance of a genetic disorder means that
a. a person is unlikely to inherit the gene for the disorder.
b. a person who has the gene that causes a particular condition might not have the clinical features of the condition.
c. clinically affected people in a family may have variations in the severity of the disease.
d. the genetic disorder cannot be passed to subsequent generations.

13. The nitrogenous base guanine is always paired with which of the following nitrogenous bases?
a. adenine
b. thymine
c. guanine
d. cytosine

14. The function of a codon is to specify the production of a single
a. protein.
b. DNA strand.
c. amino acid.
d. chromosome.

15. One nitrogenous base substituted for another creates an error called a
a. point mutation.
b. splice-site mutation.
c. frameshift mutation.
d. silent mutation.

16. When all the codons following the insertion or deletion of single or multiple bases are affected, the mutation is called a
a. point mutation.
b. splice-site mutation.
c. frameshift mutation.
d. silent mutation.

17. Linkage analysis
a. is a direct process that identifies a precise gene mutation.
b. is rarely used in the research setting.
c. usually involves testing a single family member.
d. tracks known sequences of DNA near the gene of interest from generation to generation.