TABLE 2-2 Examples of Genetic Diseases Detected by Gene Probes

Disease
Achondroplasia
Alpha1-antitrypsin deficiency
Diabetes mellitus (type 1)
Globin gene cluster (alpha)
Globin gene cluster (beta)
Growth hormone deficiency
Hemophilia A
Hemophilia B
HLA genes
Immunoglobulin genes
Lesch-Nyhan syndrome
Osteogenesis imperfecta (type II)
Phenylketonuria
Prealbumin (amyloidosis)
Sickle cell anemia
Thalassemias
Thrombosis III deficiency

Selected from various sources. For a complete listing, see Cooper and Schmidtke (1986).

which is possible when the amino acid sequence of the gene product is known. The mRNA provides a template for the synthesis of cDNA. The cDNA is used as a probe to locate the gene sequence on a chromosome fragment. A similar method, in situ hybridization, also uses a radioactive DNA strand, but adds the probe to chromosomes in their metaphase of division. The probe hybridizes with the intact chromosome DNA at a specific segment. These methods have permitted many highly imaginative genetic studies and, as investigation of human chromosomes expands at an accelerating rate, the number of useful probes and their applications increase rapidly. Some examples of the locations of genes for specific traits are given in Table 2-3. The location is listed by chromosome number, the area (*p* or *q* arms) and the site on the arm. For example, a collagen gene is located on the long arm (*q*) of chromosome 7 at the 22nd site. Development of these processes has taken place over years of intensive biochemical work, and many are highly sophisticated, so much so that no brief description can do them justice. For more details and elaboration of additional investigation to identify or "map" the human genome, the reader is directed to texts like Hartl (1988), Nichols, (1988), or Vogel and Motulsky (1986).

GENE CLUSTERS AND RESTRICTION FRAGMENT LENGTH POLYMORPHISMS (RFLP)

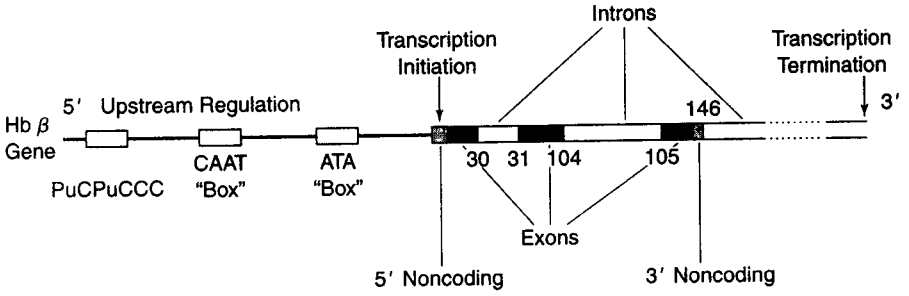
The various means of identifying gene location and the gene's finer structure have revealed some complications. The studies documented many more polymorphisms of DNA than were expected, but, at the same time, there has been some clarification of the excessive amounts of DNA present in the human genome as noted above. Because of the intensive study of human hemoglobin over the last forty years, the genes, gene clusters, and RFLP of this protein may be used to illustrate some recent discoveries.

TABLE 2-3 Sampling of Human Genes Identified by In Situ Hybridization

GENE AND BASE PAIR (BP) LENGTH	LOCALIZATION CHROMOSOME AND REGION
Beta globin (4,400 BP)	11 p
Alpha globin (800 BP)	16 p
Insulin (900 BP)	11 p 15
LGH (550 BP)	17 q 22–24
Interferon	9 p 2.1-pter
IFN alpha + beta	12 q 24.1
Ig (6600 BP)	14 q 32
Ig Kappa (10500 BP)	2 p 12
Alpha-fetoprotein (380 BP)	4 q 11–22
Serum albumin (1600 BP)	4 q 11–22
Ig C lambda (203 BP) (gene family)	22 q 11
Myosin MHC (2200 BP)	17 p 1.2-pter
Collagen-gene	7 q 22

IFN Interferon, gamma or immune type
Ig Immunoglobins
LGH Growth hormone (Lactogenic gene cluster)
Selected from Vogel and Motulsky, 1986.

The genes that regulate synthesis of the alpha and beta globin genes have been located on two different chromosomes: the alpha globin gene of 800 base pair units on the 11th, and the beta gene, 4,400 base pairs, on the 16th. The identification of the beta globin gene offered some unexpected results. In the process of hybridization of beta globin DNA with complementary DNA (cDNA), some loops of unpaired nucleotides were produced on the beta globin strand that were visible under an electron microscope. These were segments of DNA not present as complementary regions on the cDNA. The explanation of the results was straightforward. Since the cDNA was a true copy of the mRNA made by reverse transcription, and since the mRNA represented the amino acid sequences of beta globin, then the unpaired DNA sequences were regions that were not transcribed into the completed mRMA. The unpaired regions were introns, as described above, and three are shown in the beta Hb gene diagramed in Figure 2-13a. The Hb gene actually is a cluster of three groups of nucleotide triplets (the black boxes) separated by noncoding units, the introns (white boxes). The gene is transcribed, and in step one all groups are represented. Then the introns are excised, the three exons are joined, and the mRNA is complete.



(A)

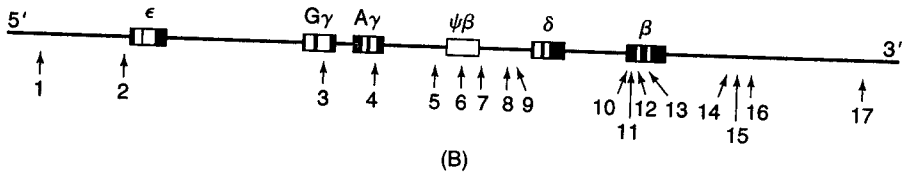
FIGURE 2-13a Diagram of the Beta Globin Gene of Human Hemoglobin.

The *introns* (noncoding) and *exons* (coding) regions of the gene are shown as well as the transcription initiation and termination "boxes." The numbers indicate the location of the codon for a corresponding amino acid position of the beta globin.

These interesting findings opened up a new realm of investigation. First, the search is on for the function, if any, of the introns. The second area of interest is the evidence that a gene exists "in pieces" as a cluster of nucleotides along a portion of the chromosome 11 DNA. There are, in addition to the Hb gene, several other genes (embryonic globin, for example) in this cluster, and a "*pseudogene*," a DNA sequence similar to the functional gene[5] but not transcribed (Figure 2-13b). Additionally, the wide use of several restriction enzymes revealed a great diversity in the size, and triplet sequences in the noncoding regions near the beta globin gene.

RFLP. Because of the attention directed to the study of abnormal hemoglobins, considerable information has been derived about the restriction fragment length polymorphism (*RFLP*). Table 2-4 lists some of the major restriction enzymes used to cut the beta globin gene cluster at different points. These sites, or points of cleavage in the DNA molecule, are illustrated in Figure 2-13b. The considerable variation between individuals is due to single substitutions of nucleotides, or point mutations. Because much of the DNA between gene clusters is noncoding, these substitutions causing sequence variation have no known functional consequences—at least not at this stage of our knowledge. Some of these variations in cleavage sites produce fragments of different nucleotide sequences, and this series or cluster of nucleotides is called a haplotype. They occur in greater frequency in one population compared to another and even among individuals. As shown in Table

[5]After consideration of units of nucleotides called exons, introns, and even pseudogenes, it is necessary to redefine the term *gene*. It may be best defined as that region of the DNA that contains the nucleotide sequence code for the production of a polypeptide chain through the vehicle of an mRNA chain.



(B)

FIGURE 2-13b Diagram of the Beta Globin Gene Cluster.

The coding parts of DNA are frequently linked to other DNA clusters that play no role in the production of the protein—in this case, globin. However, the thousands of base pairs of this cluster may be cut at specific sites by selected enzymes. The resulting fragments can be used to distinguish between populations and sometimes even individuals. The numbers in this diagram represent sites that are cut by the endonucleases corresponding to those listed in Table 2-4.

2-4, the RFLP produced by PVUII (number 5 in the diagram, Figure 2-13b) occurred only in the DNA sample obtained from the Greek population. The Hine II restriction site is recorded at high frequency in Greeks and Asians but is low in African Americans.

The nucleotide sequences (RFLP) vary in length and are repeated many times throughout the DNA. The larger ones called variable number of tandem repeats, or *VNTR*, are from seven or more nucleotides in length and have a high mutation rate of up to 7 percent. A shorter sequence, the short

TABLE 2-4 Frequency of DNA Polymorphic Sites in the Beta Globin Gene Cluster in Selected Ethnic Groups

POLYMORPHISMS	GREEKS	AMERICAN BLACKS	SOUTHEASTERN ASIANS
Taq I (1)[a]	1.00	0.88	1.00
Hine II (2)	0.46	0.10	0.72
Hind III (3)	0.52	0.41	0.27
Hind III (4)	0.30	0.16	0.04
Pvu II (5)	0.27		
Hinc II (6)	0.17	0.15	0.19
Hinc II (7)	0.48	0.76	0.27
Rsa I (8)	0.37	0.50	
Taq I (9)	0.68	0.53	
Hinf I (10)	0.97	0.70	0.98
Rsa I (11)			
HgiA (12)	0.80	0.96	0.44
Ava II (13)	0.80	0.96	0.44
Hpa I (14)	1.00	0.93	
Hind III (15)	0.72	0.63	
Bam HI (16)	0.70	0.90	
Rsa I (17)	0.37	0.10	

[a]Numbers in parentheses refer to the sites illustrated in Figure 2-13b, which are cut by the restriction enzymes.

Source: Modified from Vogel and Motulsky, 1986.

tandem repeat polymorphism, or *STRP*, has from two to five nucleotides and is more stable with a lower mutation rate (a tenth of a percent or lower). A third type is now identified, the SNP or single nucleotide polymorphism, that has a lower mutation rate still. All three of these forms of nucleotide sequences are interspaced among structural genes as seemingly useless satellites of DNA.

The continued application of different endonucleases has revealed more and more polymorphisms of satellite DNA (VNTR, STRP, and SNP). At this time, there are at least 20,000 DNA markers identified, and the number is growing (Kidd and Kidd, 1996). This work with RFLP sampled in populations from around the world has opened up a whole new frontier in the study of human genetic diversity, as explored in the following chapters. Since much of this polymorphism has no apparent functional significance, the RFLP serve well as population markers suggestive of a common history and of interpopulation relationships. The problems yet to be resolved are twofold; first, the selection of relevant markers, and two, the sampling of populations. These problems and their relevance to studies of human variation and evolution will be taken up in Chapter 4. Finally, the RFLPs are the result of changes in the base sequences or mutations, but these are mutations in the noncoding regions and probably do not influence survival. They may influence applications for certain forensic purposes, such as in paternity cases.

MITOCHONDRIAL DNA

In addition to the DNA in the nucleus, there is a quantity of DNA contained in small subcellular structures, the mitochondria, within the cell's cytoplasm. A typical cell contains about 100 of these mitochondria, whose main function is oxidation of carbohydrate, protein, and fat molecules to provide energy for cellular metabolism. These largely self-sufficient organelles, on average, replicate and divide with each division of the host cell and thereby continue a lineage of coded information contained within this special faction of DNA. This mitochondrial DNA (mtDNA), together with nuclear DNA (nDNA), codes for the production of polypeptide units that regulate the functioning of the oxidative processes of the mitochondria. In a sense, the coding and synthesis proceeds very much like that described above for the transcription, translation and protein synthesis from the nDNA. What sets the mitochondria apart is their number (there are about 100 per cell versus only a single nucleus), their variation in rates of growth and division, and the replication of mtDNA. What is most extraordinary and most useful is the small size of this mtDNA.

Mitochondrial DNA forms a circular single double-stranded helix only 16,569 base pair units long. Most of these 5,523 codons serve a coding function with no intervening sequences, unlike the nDNA coding units that are separated by noncoding units (introns). Each mitochondrion contains several of these circular DNAs and they are easily extracted and examined in the laboratory. A single messenger RNA transcript has been made of the entire mtDNA and cleaved by endonucleases into significant coding regions. As a result, the locations of all of the thirty-seven closely linked genes have been mapped and the nucleotides have been sequenced for each. The functioning of most genes is well established, and certain mutant forms have been related to several disorders of the neurological sensory and neuromuscular systems (see McKusick, 1994).

This cytoplasmic inheritance, as it was once known, offers many opportunities for studies of gene influence on cellular functions. An equally valuable purpose has been suggested for the study of human evolution. Because of mtDNA's high mutation rate (about ten times the mutation rate of nuclear DNA), mtDNA sequences may evolve rapidly. What is most significant is that, since the mitochondria are dispersed in the cytoplasm, it is inherited only through the maternal line; the ova contain hundreds of them while the few clinging to parts of the sperm do not enter the fertilized ova. It is this factor of unilineal inheritance and the high rate of genetic variation of the thousands of mitochondrial DNA that offer an opportunity to compare population relationships and origins by comparing estimates of times of divergence of ancestral groups. However, establishing phylogenetic, or family tree, relationships between contemporary populations by use of DNA polymorphisms (the RFLPs) depends on some broad assumptions about origins and time calibrations that have become a center of controversy over the use of "molecular clocks."

Comparisons of RFLP data taken from 147 people assumed to represent five population groups (African, Asian, Australian, Caucasian, and New Guinean) offered a reconstruction of human ancestry that started a controversy that has continued over the past decade (see Templeton, 1992). Briefly, researchers using RFLPs of mtDNA offered data that traced all geographic populations back to African origins. Their hypothesis was that modern *Homo sapiens* evolved in Africa approximately 200,000 years ago and expanded in numbers, migrating into other parts of the Old World. As these newly evolved populations moved into other geographic areas they replaced the archaic forms of genus Homo (*H. erectus*). Further, since the mtDNA is inherited through the female line, all living humans could trace their mitochondrial DNA back to a female (or females) living 200,000 years ago on the continent of Africa (Cann, 1987, 1988). This phylogenetic reconstruction gave rise to numerous imaginative and sometimes illogical interpretations; descriptions of an "African Eve" appeared in popular science and news magazines that explained that all of humankind could be traced to a single woman. The authors of the original theory of an "out of Africa" origin did little to slow this trend towards ever broader speculation and continued to expand descrip-

tions of origins to include other populations like Native Americans, Australians, New Guineans, Pacific Islanders, et al. (Wilson and Cann, 1992). Wilson, Cann, and their co-workers argued that all of these geographical groups were of recent ancestry, an argument quite contrary to much of the archaeological record (Thorne and Wolpoff, 1992; Frayer et al., 1993). The stage was set for confrontation with paleontologists over theories of human origins when molecular biologists applied their many laboratory skills to anthropological questions.

There are several technical points to consider, however, when population RFLPs are compared. The first is that some regions of the mtDNA are less susceptible to change, while others fix mutations at higher rates (Jeffreys, 1989). This means that changes in base sequences occur at varying rates, contributing to high variability of mtDNA within a population. Second, the fact that all thirty-seven genes are closely linked limits the usefulness of the mitochondria for evolution studies (Spuhler, 1988). Third, and most important, is the difficulty in calibration of this molecular clock. Some calibrations assume a steady mutation rate (i.e., a constant change in base sequences) at 2 percent per million years, while others argue for a slower rate of less than 1 percent. These calibrations are obtained by comparisons of living human and ape mtDNA, mainly chimpanzee. The faster rate assumes that chimps and humans diverged from a common ancestor some five million years ago, a time estimated by an earlier molecular clock application of nuclear DNA data (see Templeton, 1985). The slower rate is obtained because paleontological evidence places the time of chimp and human divergence much earlier, approximately nine million years ago. This slower rate of mutational change pushes the "out of Africa" date back hundreds of thousands of years and is more compatible with the fossil record. Regardless of which date one chooses to accept, or how one may view the "Eve" theory, molecular genetics, with its new and efficient methods, has provided anthropology with an exciting way of measuring human variability. How this variability is to be interpreted and what the results mean have yet to be decided.

FORMAL HUMAN GENETICS

At this point, following a discussion of the finer structure of the gene, the reader might be tempted to conclude that genetic knowledge depended on the discovery of DNA and insight into the effects of mutations, or how changes in the genetic code began, with the availability of restriction enzymes, the endonucleases. No such conclusion is warranted, however, because the study of *formal genetics*, that is, the crossbreeding of experimental animals, insects, and bacteria to produce a particular series of traits in the offspring, laid the foundation for much of our knowledge of genetics before the DNA

structure was defined. Human subjects have played an equally important role in the development of formal genetics. Even though *Homo sapiens* is a complicated organism with a long generation time and between 50,000 and 100,000 genes, a great deal has been learned about trait inheritance from studies of our own species.

Through analysis of traits over several generations, certain human characteristics have been related to simple gene combinations. Studies of human pedigrees and the identification of easily perceived phenotypes, even centuries ago, have added to our understanding of *dominant* and *recessive* inheritance. For example, Maupertius, a French astronomer and philosopher of the eighteenth century, began to satisfy a growing interest in biology by the study of a rare human condition called *polydactyly*, extra fingers or toes. He learned of a Berlin family with a number of individuals with extra digits. The father of the family had six fingers and toes like one of his parents; the other parent had the normal number. With the father's cooperation and interest, Maupertius traced the appearance of polydactyly through four generations of the family. Since the condition could appear in some of the children even if one of their parents were normal, he described the condition as a dominant trait. What was of special interest was that the polydactyly trait could be expressed differently. One of the two sons in the fourth generation had six toes on his left foot but the normal five on his right, while his right hand had six fingers and the left hand had only a poorly developed stump for the sixth digit.

Maupertius expanded his interest in family traits by studies of abnormalities of skin color. Reports of the occasional appearance of nonpigmented skin in children of dark-skinned parents in Africa and among Native Americans of Panama attracted Maupertius's attention. He also considered this abnormal trait a hereditary condition but somewhat different in its transmission between generations compared to polydactyly (Glass, 1955). Other scholars of the period and even of previous centuries made many observations on frequencies of rare characteristics occurring in some families. One such trait that attracted attention, even in biblical times, was the tendency for certain males to bleed profusely when cut. If a male infant showed this tendency, usually identified during the circumcision rite, then his brothers were excused from undergoing the rite. This inherited trait, appearing in the male line and now known as hemophilia, was later identified in the royal families of Europe. Genealogists have traced it back to Queen Victoria of England, who passed it on to several of her children and their descendants. One of the most famous of the recipients was the last Russian czar's son, Alexei.

Such keen observations of easily perceived traits distributed through family pedigrees prepared the way for the genetics studies to come. What is surprising was that it took so long (two centuries) for the potential to be fully realized. With the rediscovery of Mendel's work and the recognition of his two

principles of particulate inheritance at the beginning of the twentieth century, the search was on for more evidence of human genes. Many new discoveries were made, but the rush to embrace particulate inheritance led down many blind alleys, especially in the realm of human behavior and developmental variability.

Dominant Inheritance

Some traits are inherited as dominants; that is, the presence of a single dominant gene will cause the traits to be expressed. *Achondroplasia,* a type of human dwarfism caused by arrested growth of the long bones due to a defect in cartilage development, is an example of a phenotype determined by a dominant allele. This dominant allele may appear in a family lineage with no previous history through a mutation that has been reported at a high rate in some northwestern European populations (see Table 2-5). A person who possesses the mutant allele for this condition will be significantly shorter than normal because of a failure of growth of the arms and legs; the body trunk is usually of normal size. Another well-known but unrelated affliction, the so-called *Hapsburg lip,* made famous by numerous individuals of this royal family of central Europe, is also determined by a dominant allele at another locus. Individuals with this condition have a protruding lower jaw and enlarged lower lip, and chances are that half of their children will show the same abnormality. The peculiar trait of a white streak or forelock in the hair is another example of the influence of the action of a dominant allele. These simple, easily perceived dominant traits fully express their characteristics in each generation, and a simple ratio or proportion exists: If one parent has the trait, there is a 50 percent chance that each child conceived will also possess it. However, if both parents have the trait, then the probability that their children will have it increases to 75 percent (Figure 2-14).

TABLE 2-5 Estimated Human Mutation Rates for Selected Traits

AUTOSOMAL DOMINANTS	MUTATION PER MILLION
Gametes	
Achondroplasia (dwarfism)	10–14
Retinoblastoma (eye tumor)	6–18
Huntington's disease (progressive degeneration of central nervous system)	1
Neurofibromatosis (tumors of nervous system)	13–25
Marfan's syndrome (disorder of connective tissue)	4–5
X-Linked Recessives	
Hemophilia A (bleeder's disease)	20–30
Duchenne's muscular dystrophy	30–100

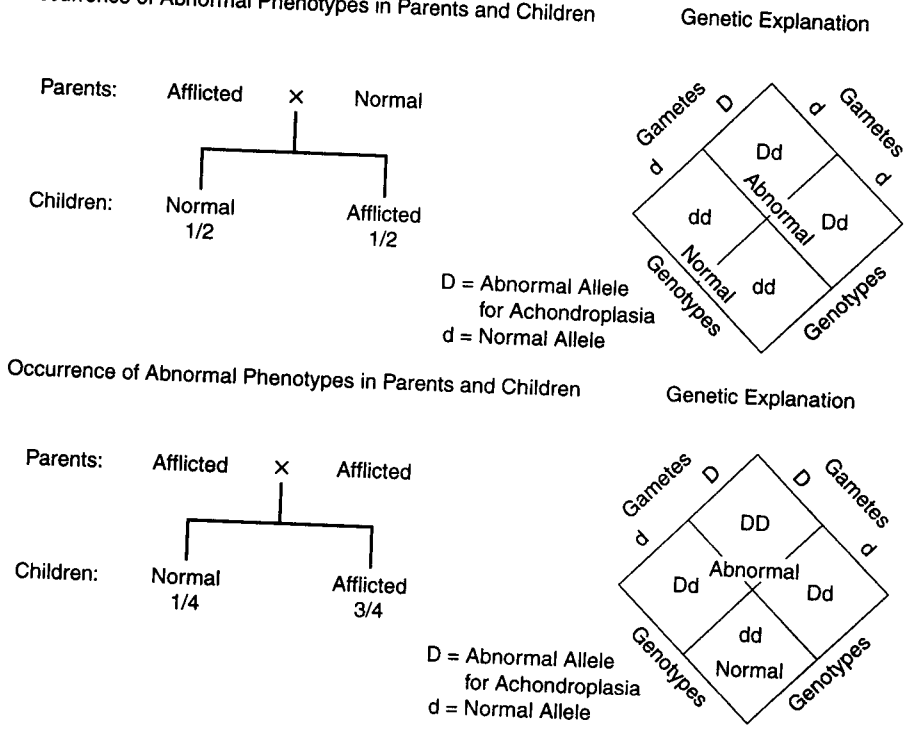


FIGURE 2-14 Dominant Inheritance: Examples of Abnormal Traits.

Recessive Inheritance

Unlike simple dominant alleles, the presence of recessive alleles cannot always be detected and sometimes causes characteristics to appear in children of unafflicted parents, often to their dismay. Rather than blame one's bloodlines or one's grandparents, or argue that devilish forces are at work, it is best to recognize that humans possess many sets of genes whose actions or potential actions are masked by the expression of the more dominant allelic form. Such genes, called *recessives,* can cause a characteristic to appear in an individual only when they combine as a pair (homozygous combination). A large number of human traits are determined in this way, from conditions of the skin to enzymes, or growth processes to blood types.

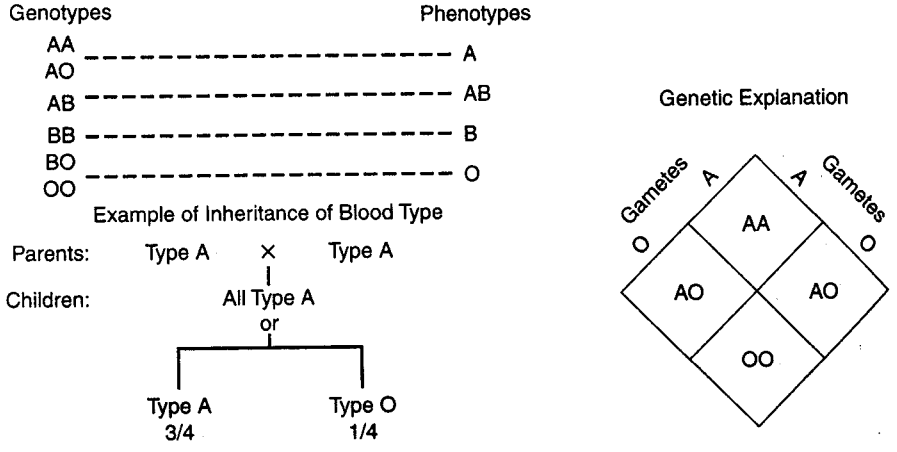
One example is a well-known condition that interrupts the synthesis of melanin pigment and causes the individual to be without color in the hair and skin; such an individual is known as an *albino.* This condition occurs in European populations only about once in 20,000 births, but once in 3,000 births in several Nigerian populations and once in 200 among the Cuna Indians of Panama. In a majority of these cases the parents are normal but each is a carrier of a recessive allele that affects the synthesis of an enzyme essential for the

production of melanin; these genes may combine upon conception to produce an offspring who has the recessive pair. There are at least five other albinism types under the control of genes at other chromosome loci but they are much rarer than this albino type I. There is even a record of two albino parents producing a normal offspring; this led to the conclusion that the parents carried albino genes at different loci (see McKusick, 1994). The explanation for the varying frequencies in different populations will be discussed in Chapter 6.

Another example of recessive inheritance is provided by the ABO blood-group system. We all have an inherited blood type in this system, and within this century, the medical importance of blood type has been recognized. Accordingly, the mechanisms of inheritance have been well established. The allele that determines type O blood is recessive to both the A and the B alleles. Hence, it often happens that parents, neither of whom is type O, have an offspring with type O blood. There should be no question of paternity. The type O child simply demonstrates that the parents were carrying the type O allele, a recessive whose presence is masked by the action of either the A or the B allele (see Figure 2-15). If the genotype is AB, however, both alleles will influence the phenotype. This codominance of the A and B will give a blood type AB, as indicated in Figure 2-15. *Codominance,* where both alleles contribute to the phenotype, is found to be a condition at numerous genetic loci.

The ratio of recessive trait occurrence in each generation depends on the gene combinations of the parents and is somewhat more difficult to determine than the simple dominant ratio. If neither parent has the trait but both are carriers of the recessive gene, there is a 25 percent chance that a child they produce will have the trait. But if one parent is the carrier and the other parent has the trait, then there is a 50 percent chance that their child will have the combination (see Figure 2-16).

FIGURE 2-15 Inheritance of ABO Blood Types.



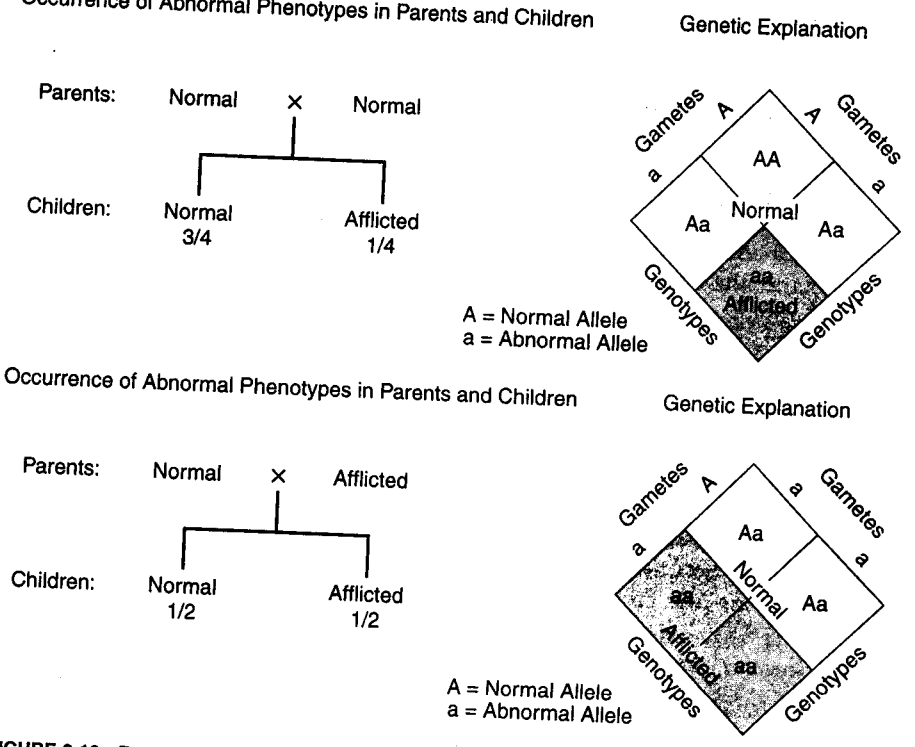


FIGURE 2-16 Recessive Inheritance: Examples of Abnormal Traits.

Gene Combinations and Interactions

The preceding examples shown in Figures 2-15 and 2-16 illustrate the relationship between genotype and phenotype; a certain allele or pair of alleles will determine a particular trait. Many human traits, however, are of complex inheritance, and several genes may determine the phenotype through their combined action. Such traits are called *polygenic* or multifactorial since the products of two or more genes at different loci interact to contribute to the development of a phenotype. Growth processes and body form are under the control of many genes exerting influence during critical stages of the life cycle, for example. Human skin color, another example, varies over a wide range throughout our species because the synthesis of the melanin pigment proceeds through a series of stages of biochemical processes under the control of several genes to produce the final product. The hue of the skin—that is, as the color appears to the eye—covers a broad and continuous range from very dark to light. The human eye is a poor measure of this range, so other means have had to be devised to evaluate "color." Measures made of the light-reflectance characteristics of untanned skin surfaces have been used instead. The skin reflectance properties of offspring of one dark-skinned and one fair-

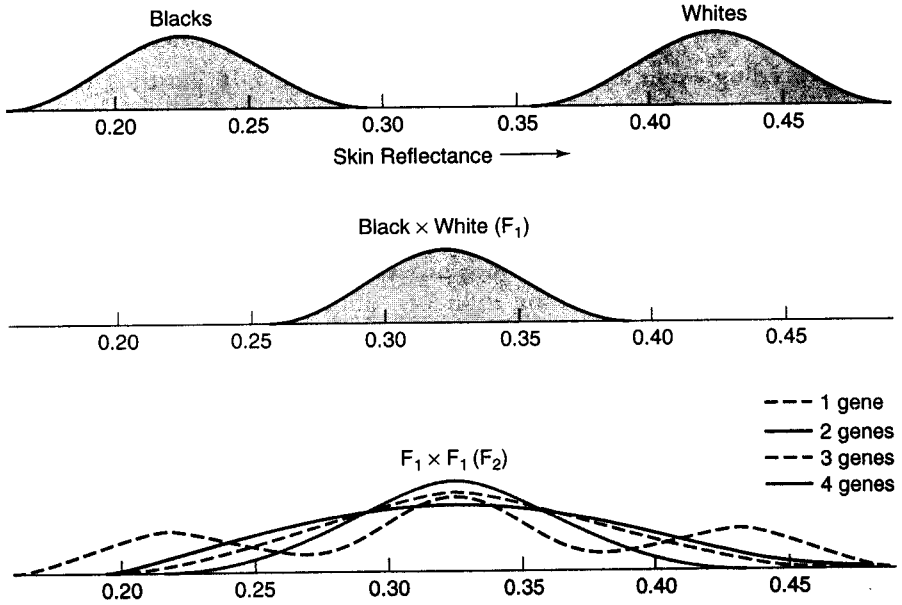
skinned parent measured between the ranges of their parents (Figure 2-17). This measure matches closely that suggested by the hypothesis that genes at three or four loci are responsible for the inheritance of skin color.

These measurements of skin reflectance are made on skin from an unexposed area of the body to avoid the tanning influence of the ultraviolet rays of the sun. If exposed, then skin pigment in most people will increase; even those with naturally dark skin will increase pigmentation. This illustrates environmental influence (sunlight) on a genetically complex phenotype (skin color), and the outcome of this interaction is a highly variable reflectance property. This property is measurable as a quantitative trait, or described as a multifactorial trait because of several genes and environmental interactions.

There are numerous other human multifactorial traits that demonstrate a range of environmental and genetic influence. Several *congenital* diseases (present at birth) and diseases of mature adults seemingly "run" in families; there is a history of appearing in one spouse's pedigree because some genetic or environmental factors influence the development of the fetus. Birth defects like neural tube anomalies (e.g., spina bifida), cleft palate, club foot, and heart defects are examples. The midlife diseases such as hypertension,

FIGURE 2-17 Skin-Color Distributions in Blacks and Whites. (From Bodmer, W. F., and L. L. Cavalli-Sforza, *Genetics, Evolution, and Man.* Copyright © 1976. San Francisco: W. H. Freeman and Company.)

Skin color is measured by the skin reflectance for light of 685 mμ wave length. For the F_2 generation, distributions shown are those expected under various hypotheses about the number of genes involved. Observations on F_2 and backcrosses tend to resemble those expected if the trait is determined by three of four genes.



adult onset diabetes (type II), and coronary heart disease are other multifactorial conditions frequently studied in reference to combinations of familial and environmental influence. The blood pressure of close relatives of a hypertensive person is higher, on average, than for that age group in the general population. Likewise, the relatives of diabetics often show a lessened ability to regulate blood sugar levels and are at risk for developing the disease in later life if excess carbohydrates are consumed.

Further, complexity of the genetic system may cause a trait to vary in frequency or in expression. There are genes that are known to influence more than one trait, and these genes are said to be *pleiotropic.* Because the primary products of gene action are polypeptides (chains of amino acids, shown in Figure 2-10), they may be part of a biochemical pathway leading to the production of several other products. For example, a recessive allele that prevents the production of an enzyme needed in the metabolism of an essential amino acid, phenylalanine, can indirectly cause severe damage to the central nervous system through the accumulation of toxic levels of this amino acid. This condition, resulting from the inheritance of the pair of recessive genes controlling phenylalanine metabolism, is known as *phenylketonuria* (PKU). In addition, persons homozygous for this gene will have paler skin and a reduced thyroid activity because phenylalanine is not converted into a necessary ingredient for the synthesis of another amino acid, tyrosine. This amino acid is the precursor from which melanin, the skin pigment, is made. It also is the basic compound from which thyroxine (the active iodine compound of the thyroid gland) is formed.

Another contributor to phenotypic diversity is the fact that genes do not always cause a character to be expressed in the same way, and sometimes the phenotype does not appear at all, even though the genotype for it is known to be present. For example, the pedigree of a family that possessed a muscle defect of the small finger that causes the digit to be permanently bent showed a distribution of the autosomal dominant gene through four generations. One of the males in the third generation lacked this inherited defect, though he passed along the gene to both of his daughters in the fourth generation. This skipping of generations is an event that occurs when a gene is partly or incompletely penetrant. In some individuals autosomal dominant traits may be more severe than in other persons. This condition, known as *variable expressivity,* is illustrated by the presence of extra fingers or toes (*polydactyly*). As discussed above, a dominant allele causes the presence of extra fingers or toes, but the trait is not always expressed in the same way. Sometimes an extra digit will appear on both hands and feet, or sometimes only a hand or foot will have an extra digit. These and other traits recorded in family pedigrees illustrate some of the variety of expressions of complex traits. To understand them and their intergenerational transmission, it is necessary to consider the organization and clustering of human populations as they influence future generations.

BIOLOGICAL UNITS

The discussion of the mechanisms of inheritance and of the effects of genes on individuals now must be considered in the context of those groups or units within which individuals interact. These are the populations or species whose numbers and genetic composition will alter through time in response to environmental forces. Normally, a certain range of individual variability for many characteristics is encompassed, but the most favorable traits are present at the highest frequency, with some exceptions. Such frequencies are typically represented down through the generations. One of the major concerns, though, is how these traits may vary between generations. Equally important is the geographic distribution or spatial clustering of traits in population groups.

Species

The venerable idea of species is based on the observation of the striking discontinuity of life forms in nature. The study of this discontinuity among groups of living organisms developed into a discipline that recognized a species as something "different" and used these differences to classify plants and animals in the natural world. The earlier classifications, based on simple morphological traits, did not take into account the range of variability, and there was often misunderstanding, as illustrated by descriptions of polytypic species that emphasized an idealized form. This old typological approach has been replaced in biology by the recognition of the biological diversity in many species and the difficulty encountered when attempts are made to differentiate between groups of organisms solely on the basis of a few select morphological features.

The species concept has undergone a long history of development and change, especially in this century. As more has been learned about variation and its genetic basis, the definition of species has focused more on genetic variability, isolating mechanisms, and ecology. For example, many authors today stress reproductive isolation, natural habitat, and ecological niche in their attempts to define species. This follows Mayr's observations described in his extensive and important review of animal species (see Mayr, 1963). Mayr referred to *species* as the largest and most inclusive reproductive community and noted that a species is also an ecological unit. But even this perspective underwent further development, as illustrated by the definition that he offered years later: ". . . a species is a community of populations (reproductively isolated from others) that occupies a specific niche in nature" (Mayr, 1982:273).

Populations

The nature of species, especially of wide-ranging, complex organisms, encompasses a concept of gene pool today. The species' gene pool is composed of divisions or groups of interbreeding organisms called populations.

Within each of these populations are collections of individuals who bear a part or a small sample of the total species gene pool for the term of their life span. These individuals form what is described as a breeding population or *deme* and collectively represent a portion of the species. Within each population the gene combinations are reassorted each generation through the mechanisms involved in the reproduction process. The total number of combinations of all genes creates a *gene pool* whose composition will depend on the degree of interbreeding between populations; also, natural forces may alter the gene pool each generation. The distribution of characteristics among the individuals of a population may be described by a normal curve, as in the case of stature or skin color discussed above. This concept of gene pool contrasts with the idea of type or average, which emphasizes the central tendency (arithmetic mean). Typological comparisons between groupings of individuals or populations throughout the species rely on arithmetic means, stressing differences between one type and another, whereas in reality there is often a great deal of similarity between widely dispersed populations within our species. The populationist view considers the distribution of traits throughout the gene pool and attempts to show the similarity or dissimilarity between adjacent populations, which could be illustrated by the wide range of overlap of these normal curves of a population. Geographical distributions of many gene frequencies form a continuum over a wide area, and the gene frequencies of each population overlap those of its neighbors. The effect can be a smooth clinal distribution of gene frequencies.

FACTORS OF VARIATION AND EVOLUTION

Evolution has been described as "descent with modification," a definition that refers to a gradual change of populations of organisms throughout tens of thousands of generations, changes that accumulate and lead to the formation of new species. Such a definition is applicable to studies of paleontological species in comparisons with their modern living descendants who may be diverse in form, as in the examples of the variety of primate species living today. Many of these primate species can be traced through the fossil record to a few common ancestors tens of millions of years ago. This is an abbreviated way of describing an aspect of Darwin's theories of evolution. He emphasized that the world is not constant and that the diverse living forms were connected by descent to common ancestors. The similarities of certain characteristics among groups of species have been demonstrated through comparisons of morphology; hence, humans are grouped with the great apes of Africa rather than with baboons because there is greater anatomical similarity. The development of techniques that compare blood proteins and DNA have validated these earlier observations.

Since Darwin's theory was developed, the knowledge of genetics, and now the clearer understanding of the nature of the gene, has contributed to a new form of the definition of evolution. Geneticists and many anthropologists describe evolution as change in gene frequencies in a population from one generation to the next. This cannot be considered evolution unless these changes persist as a new pattern over time. The accumulation of these changes, often under the influence of natural selection, is described as *microevolution*. There is an abundance of examples in simpler organisms but it is more difficult to demonstrate microevolution among living humans, as we shall describe in the following chapters. Considering the new knowledge of genetics and the recognition of the significance of a species' environment, about mid-century *evolution* was understood as a change in the adaptation and in the diversity of populations of organisms. According to Mayr (1982, 1988), this emphasized the dual nature of evolution as a vertical phenomenon of adaptive change and a horizontal phenomenon of diversity among populations. The degree of change and its rate over time were subject to a variety of forces that affected population composition throughout the generations.

Stability or change within a biological unit (the breeding population or gene pool) depend on a great many factors. If these factors balance out so that a net change takes place and persists over generations, the result is evolution. If the elements that cause change are counteracted by those that tend to maintain stability, then there will be no net change in gene-pool composition. Such stability is, of course, an ideal situation. The actual condition of a population may be small gene-frequency variation among several generations, partly because each generation varies somewhat in number of individuals and in age distribution and sex ratio, more so in former times with high mortality rates than today with a longer life expectancy at birth. Treating population equilibrium or disequilibrium has always presented a problem because demographic as well as genetic factors must be considered. An important step was taken with the recognition of Mendelian genetics followed by the development of the foundation of population genetics.

Hardy-Weinberg Equilibrium

Early in this century, even after particulate inheritance was recognized, there still was considerable confusion over the relationship between dominant and recessive alleles. The question frequently raised was: If one allele was dominant to another, would not the dominant one eventually, after a period of time, come to be the most frequent allele in the population? The answer is no, of course not. In 1908, an English mathematician, G. H. Hardy, and a German physician, W. Weinberg, independently of each other, offered a mathematical formula $(p + q)^2$, which described in simple terms the proportion of a pair of alleles in a randomly mating population living under stable

conditions. This formula explained why the dominant allele would not increase.

If the symbols of A and a are used to indicate the alleles, then the gametes (sperm and ova) will carry one or the other allele, and recombination through reproduction will occur at a constant frequency. The following combinations are expected:

		SPERM	
		A	a
OVA	A	AA	Aa
	a	Aa	aa

This simple table shows that one AA genotype is reproduced for every two Aa combinations and every one aa genotype—the *Mendelian ratio*. In the hypothetical situation in which the alleles A and a are present in equal numbers in a population, one-half of the gametes carry the A allele and one-half carry the a. Let p equal the frequency of A and q equal the frequency of a; then the allele frequencies of all combinations can be derived from the table:

FREQUENCY OF *OVA* CARRYING ALLELES A AND a	FREQUENCY OF *SPERM* CARRYING ALLELES A AND a: p (.5)	q (.5)
p (.5)	p^2 (.25)	pq (.25)
q (.5)	pq (.25)	q^2 (.25)

Adding up the frequencies of all combinations to derive a total for the population we get

$$p^2 + 2pq + q^2$$
$$(.25) + 2\,(.25) + (.25)$$
$$p^2 + 2\,pq + q^2 = 1,$$

and then $(p + q)^2 = 1$ because it is the binomial expression of the quadratic equation. Taking the square root of the equation we get

$$p + q = 1$$

which is a mathematical way of saying that, in a sexually reproducing population, the total number of alleles at any locus is equal to unity. Therefore, if we know the frequency of one, then the other can be determined

(expressed as $p = 1 - q$, or $q = 1 - p$). This should be easy to comprehend if one recalls that only a single allele is present at a locus on a chromosome (though the other chromosome of the pair may carry another allelic form of the gene). In our example of two allelic forms, it is an either–or situation; the A or a is present. Given the random mating conditions, each type of sperm has equal opportunity to fertilize each type of egg, so the 1:2:1 Mendelian ratio of the genotypes AA, Aa, and aa will be maintained throughout the generations and there will be no change in gene frequency. The *Hardy-Weinberg Law* states that the frequencies of p and q will remain the same throughout any number of generations given a stable, random-breeding population isolated from other populations.

An example can be made of the number of individuals who are taste-sensitive to a chemical, *phenylthiocarbamide* (PTC), a substance that is bitter tasting to a majority of persons but tasteless to about 25 percent of Europeans tested. It was found some years ago that this tasting ability was inherited as a dominant allele (T). So a person either TT or Tt was a taster whereas the homozygous recessive tt was a nontaster. If a random sample of a population shows that there are 250 nontasters out of 1,000, then 25 percent of the population have the genotype tt. The gene frequency of the recessive allele (q) in this example can be calculated: $q^2 = .25$ and $q = \sqrt{.25}$, which is equal to .5, or one-half of the alleles for the PTC locus are the recessive form. The frequency of the dominant allele (T) would then be .5 or (1 – q). Nevertheless, even though the alleles are of equal frequency in the population, three-quarters or 75 percent of the individuals have the taster phenotype. This is simply explained by reference to the ratio of the genotypes previously shown. One-half of the recessive alleles (t) are combined with the dominant alleles to form the heterozygote who is a taster (Tt). Throughout future generations, assuming random mating with respect to taste sensitivity, the gene frequencies of these alleles will remain the same and there will be the same number of individuals who are tasters (see Table 2-6).

The Hardy-Weinberg formula assumes, in addition to random mating, that certain conditions exist that contribute to population stability, and if these conditions are maintained, gene frequencies will remain invariable throughout any number of generations. Few natural populations fit this model situation exactly, but the basic formula established a reference against which change can be measured, and it provides a useful tool in studies of variation and evolution. The forces for change in a population's gene frequencies are *mutation, natural selection, genetic drift* (a sampling error), and *gene flow.*

Mutation

As noted earlier, the change in a genetic code results in an alteration in its action and introduces a new variety of allele. This adds different genotypes within a population. Mutation, then, is the ultimate source of all genetic variation in a population and may provide a species with an ability to respond to a variety of environmental conditions. Some mutations, however, cause such a radical metabolic disturbance that an organism cannot survive; many more are detrimental but are not lethal. Still other mutations may affect changes in the way organisms metabolize certain substances, resist parasites, or produce antibodies against infectious diseases. A question frequently raised in the past was whether or not all point mutations are "bad." All are seen now as an error in DNA coding with a greater or lesser effect on protein synthesis, depending on the amino acid substituted. If the substitution occurs in a polypeptide position that reduces or eliminates the protein's function to a level that places the individual's survival at risk, then it may be considered bad. In certain environments, however, the mutant allele, though depressing some metabolic processes, may convey a survival advantage to the carrier of the allele. The influence on survival of such an error, or change in code, will be taken up in the following chapters. Here, mutations, without evaluating effect (lethal mutations excepted) may be considered one of the sources of disturbance of genetic equilibrium between generations as measured by the Hardy-Weinberg Equilibrium.

In *Homo sapiens,* mutations apparently occur at a low rate, though this rate may be influenced by certain forces (for instance, ionizing radiation) from natural or human-caused sources. The results from exposure to radiation cannot be predicted—that is, which genes will mutate is not known. Some human mutation rates that occur due to unknown causes have been measured in family lineages and are listed in Table 2-5. As shown, the rates are

TABLE 2-6 Frequencies of Offspring from All Types of Matings

GENOTYPES OF PARENTS	FREQUENCY OF MATINGS	FREQUENCY OF OFFSPRING			NUMBER OF INDIVIDUALS		
		TT	Tt	tt	TT	Tt	tt
TT x TT	p^4	p^4	—	—	625	0	0
TT x 2 Tt 2 Tt x TT	$4p^3q$	$2p^3q$	$2p^3q$	—	1,250	1,250	0
TT x tt tt x TT	$2p^2q^2$	0	$2p^2q^2$	—	0	1,250	0
2 Tt x 2 Tt	$4p^2q^2$	p^2q^2	$2p^2q^2$	p^2q^2	625	1.250	625
2 Tt x tt tt x 2 Tt	$4pq^3$	—	$2pq^3$	$2pq^3$	0	1,250	1,250
tt x tt	q^4	—	—	q^4	0	0	625
All Types	1	p^2	2pq	q^2	2,500	5,000	2,500

Adding up each column gives a total of $p^2 + 2pq + q^2$ = (all types of matings) and the numerical example adds up to a total of 10,000. This table shows, in a randomly mating population of this size with p of .5, that the numbers of individuals with the three genotypes will be distributed 1/4TT (2,500), 1/2Tt (5,000), and 1/4tt (2,500) each generation. Under conditions of stability, as described earlier, this distribution will remain unchanged throughout any number of generations.

very low, and population gene frequencies will be disturbed only slightly, but a mutant gene may convey an advantage and contribute to increased fitness in certain environments where selective forces favor the carrier of the mutant. This may cause the frequency of the mutant allele to increase rapidly in just a few generations.

Natural Selection

Though chance plays a role in the production of variation within a population of sexually reproducing organisms, the range of variability and composition of a breeding population is limited. All possible genotypes are not represented in each generation with equal frequency. There are factors that limit the extent of population diversity and determine the gene frequencies from generation to generation. A major factor that acts to limit and stabilize genetic diversity is called *natural selection.*

Some individuals, because of one or several combinations of genotypes, have characteristics that are adaptive in certain environments and enable them to survive at a higher rate, with an extended reproductive period. They reproduce at a higher rate than other individuals and, thus, contribute more offspring to the next generation. Such persons, by definition, are the fittest in the sense of *Darwinian fitness* (those who produce the most offspring). Even small inherited differences among individuals, over time, may lead to differences in the gene pool composition. Those genotypes that confer some reproductive advantage no matter how small will increase within a population throughout generations.

There are several mechanisms that determine reproductive success; the sum total of all those processes that determine survival and reproduction are lumped under the term *natural selection.* The word *natural* indicates that there are certain conditions that exist in the environment within which the organism lives that are relatively advantageous to some individuals. These natural conditions are in contrast to those created by the animal breeder who selects chickens or cattle and breeds only those animals that possess the economically desirable traits—rapid weight gain, for example. Selective breeding of farm animals, dogs, or race horses is a good example of the practice of artificial selection for desirable characteristics. Darwin, offering an explanation of how evolution occurred, noted that what humans have done in a limited way in an effort to domesticate plants and animals, nature has achieved on a grand scale through natural selection.

The effect of natural selection is the maintenance of certain desirable characteristics throughout the generations. Mutations, which occur spontaneously, may convey an advantage under certain environmental conditions, and the number of individuals possessing the mutant allele will increase each generation, perhaps slowly or rapidly, depending on the life span of the organisms and the intensity of selection. It has been difficult to demonstrate natural

selection in human populations because of our long life span and because of the impossibility of exerting laboratory controls, but insects and certain mammals are another story and have provided some excellent examples.

There is a clear record of an increase in the number of insect species resistant, or even immune, to the effects of insecticides. Resistant strains of the common housefly began to appear throughout the world within two years after the insecticide DDT was introduced in an effort to control this and other insect pests. It appears that fly larvae of the resistant strains develop faster and survive better in a crowded environment than the DDT-susceptible strains. Studies of the DDT-resistant insect strains showed that the presence of a certain enzyme (dehydrocholorinase) aided in the metabolism of the insecticide. This enzyme was also present, but in lower quantities, among those flies most susceptible to DDT. It is not difficult, then, to reconstruct an evolutionary history for the flies that depicts a population heterogeneous for this trait (a mix of flies with high and low quantities of the enzyme). When their environment shifted drastically with the introduction of DDT, the resistant strain of flies survived longer and reproduced in greater numbers, until a majority in future generations were of the resistant type. The varieties were already present, probably due to past mutations, and if the rapid reproduction of flies is considered, then even a slight advantage of one genotype over another would cause major changes in the populations' response to their environment. More of a danger to humans has been the proliferation of resistant strains of malaria-carrying mosquitos.

Other examples of environmental change and natural selection are seen in the rise of bacteria strains resistant to certain antibiotics, a resistance that has made them more and more difficult to control. Each of these examples shows environmental changes caused by human intervention and is an excellent demonstration of the operation of natural selection on simpler organisms. Many populations of complex organisms also provide evidence for the action of natural selection, as in the case of the spread of rabbits in Australia and the attempts to control their population boom.

The European wild rabbit was introduced into Australia in 1859 when a colony of twenty-four were turned loose on an estate in Victoria in the southeastern part of Australia. By 1928 the fast-breeding rabbits, without any natural predators in their new homeland, had multiplied to an estimated 500 million, spread over much of Australia. The rabbits became a major pest, destroying grazing land and crops and causing millions of dollars' worth of damage each year. All attempts to control the rabbits with traps and poisons proved futile until 1950, when a virus (myxoma) lethal to rabbits was introduced into the population. From the first infection induced among rabbits in South Australia, the virus spread into most areas, killing 95 percent of the rabbits by 1953. After this drastic decline, however, the population recovered and began to increase due to the survival and reproduction of a few individuals whose genetic complement provided them with some

degree of immunity. In addition, the virus itself underwent a transformation, and new strains appeared that were less lethal. Selection favored the disease-resistant rabbit, and there was a co-adaptation of the virus and host (rabbit). In order for a virus to survive long enough to multiply and to be transmitted to another host it must not be too lethal. If the rabbit dies before the virus can be transmitted to a new host (usually by mosquito), then the virus strain also dies. Selection, therefore, favored a less deadly virus and a rabbit with a degree of resistance to the infection. These results have been verified many times in laboratory tests and thus provide an illustration of the action of selection.

Reproductive success is the mark of fitness and ensures the survival of the species and the successful adaptation to environmental fluctuations. However, the mere success of a population may lead to a wide range of increases and decreases in population size. A case in point is the rapid-breeding field mouse (*Microtus awalis*). The female is fertile at 13 days and if bred will produce a litter (4 to 6) 20 days later. Fertilization can occur again immediately after the female gives birth, and a second litter can follow within 20 days. These mice have been bred in captivity and can produce 24 litters within 20 months. Such frequent reproduction increases the population to a point where it far exceeds the carrying capacity of the environment (usually measured in terms of available food), and widespread destruction of the resources occurs followed by a rapid population decline or "crash." Within months, the cycle can be repeated. Selection exerted by disease and the limitation of food resources tend to check population size, but in the case of rapid breeders, insects and even some mammals, the extremes in maximum and minimum population sizes can be enormous.

Slow-breeding animals have a different sort of problem. The elephant, the slowest of the mammals with a gestation period of 22 months, may, under favorable conditions, reproduce 6 offspring during its reproductive span. Even slight environmental variations can have profound effects. Drought and disease work a heavy toll and may have been responsible (probably aided by human predators—the Paleolithic hunters of the New World) for the extinction of the mammoths (prehistoric elephants) in the Western Hemisphere 8,000 years ago. In the case of the human species, with a shorter gestation period of 9 months, we, too, have a limited reproductive potential due to the lengthened dependency period of the young and the relatively short reproductive period of the female (compared with life span). Human reproductive potential is further restricted by numerous regulations imposed by society that forbid sexual intercourse between certain individuals. The net result is a reduction in the absolute numbers of offspring produced, which often is below the biological potential. In sum, natural selection refers to all those features of a population's environment that influence reproduction and survival contributing to a steady production of individuals over the generations who, as Darwin described, have a reproductive advantage.

In the case of human populations, natural selection is much more complicated, as will be explained in the following chapters. Throughout our history some populations have increased while others have declined. Diseases once a deadly menace have now declined to be replaced by others; in this decade, mortality from a previously unknown disease, acquired immune deficiency syndrome (AIDS), has risen dramatically. Until the last few centuries human existence had always been precarious. Frequently, high fertility was exceeded by an even higher mortality until human adaptation underwent a dramatic improvement. First, the Neolithic revolution, when plant and animal domestication began about 10,000 years ago, was a very successful adaptation with high fertility that contributed to major population increases. Then again during the Industrial Revolution of 200 years ago, Western Europe underwent a population "explosion"; fertility rates went up while death rates declined dramatically. A short time later, the rest of Europe and certain other parts of the world followed in this new pattern. Today, many national groups are undergoing a similar experience of population increase but at much higher rates. Those countries that had major growth throughout the period of the Industrial Revolution are now experiencing a lowering of birth rates together with a reduction of mortality rates that has brought the annual increase of population down to a lower level. There has been, throughout human history, disproportionate growth among human populations. No one regional group has predominated for very long, and there have been tendencies for fluctuations in population growth, as I will describe in Chapter 8.

Gene Flow

In addition to growth, there has been considerable population movement throughout human history, and much of this migration has occurred in the last few centuries. The migration and mixing of peoples increase genetic exchange, and populations that were isolated in past centuries have undergone a considerable change in gene frequencies. Interpopulation contact through migration, trade, or warfare has had a major influence on the genetic variability of many populations of *Homo sapiens.*

This *gene flow,* as it is often called, refers to exchanges between different population gene pools so that the next generation is a result of admixture of the parental population. This has been an important factor that has reduced the influences of isolation and reduces development of unique gene combinations within a breeding population. It has the potential for introducing new gene combinations, causing the population to be more heterogeneous. The relative influence of gene exchange between breeding populations depends, of course, on the size and length of time in contact. Invading armies, colonists, travelers, and traders have all had an effect on genetic distribution throughout our species. The distribution of gene frequencies today and in the recent past is quite different from what it was prior to the major colonial

expansion of western Europe beginning in the fifteenth century, and it is continuing to undergo changes.

Genetic Drift

A critical factor influencing gene frequencies from generation to generation is the total number of individuals who make up the effective breeding population (males and females in their reproductive years). When this number is very small there is the possibility that not all gene combinations will be represented in the next generation. This may be described as a sampling error or genetic drift. The chance distribution of the genotypes of offspring from the mating of heterozygotes can serve to illustrate the influences of population size on sampling error. When there is a mating of heterozygotes (Aa × Aa), there is a probability of 25 percent that the offspring will be AA. If the couple produce five children in all, then the probability is less than .1 percent that they all will be genotype AA, while there is 1.5 percent chance that three children will have this genotype (see Table 2-7). Should either of these unlikely events occur and more AA genotypes be produced than either Aa or aa, the frequency of the recessive allele, a, would decrease through chance alone in a population with only a few matings in each generation. The larger the number of matings, the greater the probability that all genetic combinations will be reproduced, so the gene frequencies will remain stable from one generation to the next. By contrast, the fewer the matings each generation, the smaller the sample of the total gene pool. Under this condition there will be a greater chance that certain genes will not be passed on because of the small size of the sample.

There are a number of examples where genes have become fixed at high frequencies in human populations within just a few generations. Island populations throughout the Pacific and other regions, as well as religious colonists whose beliefs have resulted in self-imposed breeding isolation, document the influence of population size on gene frequencies. The smaller the size of the effective breeding population (ratio of males and females of reproductive age to total population), the greater the chance of gene frequency change between the generations.

TABLE 2-7 Distribution of Offspring of Two Heterozygous Parents (Aa × Aa)

GENOTYPE OF FIRST OFFSPRING	PROBABILITY OF FIRST OFFSPRING	GENOTYPE OF SECOND OFFSPRING	PROBABILITY OF SECOND OFFSPRING	TOTAL PROBABILITY
AA	1/4	AA	1/4	Both offspring AA, 1/16
AA	1/4	Aa	2/4	AA followed by Aa, 2/16
AA	1/4	aa	1/4	AA followed aa, 1/16
Aa	2/4	AA	1/4	Aa followed AA, 2/16
Aa	2/4	Aa	2/4	Both offspring Aa, 4/16
Aa	2/4	aa	1/4	Aa followed by aa, 2/16
aa	1/4	AA	1/4	aa followed by AA, 1/16
aa	1/4	Aa	2/4	aa followed by Aa, 2/16
aa	1/4	aa	1/4	Both offspring aa, 1/16

The influence of the founders' gene combinations is another form of sampling error and is referred to as *founders' effect*, described by Mayr (1963). Because of the improbability of a small group of colonists representing all of the variety of the parent population, this initial error in sampling will have a major influence on future generations of descendants from the founding population. This restricted sampling, or "bottleneck" effect, may be repeated in future generations if, through natural catastrophe or disease, the population loses large numbers of its people over a short period. Consider the example of the small South Atlantic island of Tristan da Cunha, midway between South America and Africa. The 270 persons occupying the island in 1961 could trace their ancestry back to the original 15 colonists consisting of soldiers, shipwrecked sailors, and a few women who arrived in 1816.

The lonely, isolated island has no natural harbor to shelter ships from the rough seas and its environment is harsh, so, except for an occasional individual, there has been no immigration. Despite these restrictions the population had grown to 103 by 1855, when it suffered a setback with the departure of all but 33 persons. A second bottleneck occurred when a small boat, with 15 males aboard, capsized leaving no survivors. Following this disaster many of the widows and their offspring emigrated, reducing the island population from 106 to 54. The population recovered to reach 270 by 1961. The events that caused this small founding population to undergo an expansion, followed by severe reduction, and then expansion again have caused some rare genetic recessive traits and unique gene frequencies to exist among the modern-day descendants.

Even larger populations, descendants of a few founders, will often contain a high frequency of rare genetic defects. An example of such detrimental genes reaching high frequencies is the inherited defect *porphyria*. This metabolic disorder prevents chemical conversion of the porphyrin compound, the iron-bearing pigment of hemoglobin, and results in the excretion of excessive amounts in the urine. Persons with the South African type of *porphyria*, inherited as an autosomal dominant, are ultrasensitive to sunlight, which produces severe skin lesions. The accumulation of porphyrin in the blood leads to a number of symptoms of the digestive tract and to nervous system disorders, and persons with the affliction are sensitive, as well, to certain types of drugs like barbiturates. This metabolic defect is rare throughout the world, with most cases reported in the Afrikaans population. The gene responsible for this affliction has been traced through genealogies back to 1688 to a young girl from Rotterdam and her spouse, another immigrant from the Netherlands. The 8,000 carriers of this autosomal dominant allele

today are descendants of this marriage. These findings are not surprising, considering that an estimated one million of three million Afrikaans are descendants of 40 original couples settling in the Cape area (see Dean, 1963).

Random Mating

The Hardy-Weinberg Equilibrium assumes that matings take place without regard to genotype; that is, they are random. Persons marry without considering the blood group genotypes; for example, persons do not select a mate of type A blood and reject one of type B. Therefore, calculations for many of the human gene frequencies will not be disturbed by a nonrandomness of breeding. However, random breeding in another sense does not usually apply in the choice of mates because a number of social as well as biological criteria are considered. In human populations all males and females do not have an equal chance of mating, and there are a number of barriers that reduce random mating. One is *positive* assortative mating, which describes a tendency for "like" to marry "like." Tall people tend to marry tall people and short people tend to marry short people. Also, there is a high positive correlation between the I.Q.s of husband and wife. Persons frequently marry those within their social circle and, until just a few generations ago, geographic distance played a major role in mate selection; marriages took place most often between individuals who lived near each other. Though the distances between prenuptial households is steadily increasing, marriage to "the boy or girl next door" was more fact than fiction until quite recently. Another factor that has effected random matings is society's rules that prohibit matings between close relatives, but these rules might be suspended when small community size limited mate choice, as described in Chapter 6.

Society's rules governing marriage have influenced a degree of outbreeding, or population *exogamy*, where mates are selected from outside of one's family or village, reducing homozygosity while increasing heterozygosity. Population *endogamy*, or inbreeding, causes the reverse—an increase in homozygosity. The consequences of the relative degree of inbreeding may be in evidence in health, growth, and genetics. Children of *consanguineous* matings (marriages of relatives of some degree) are smaller in size, have a higher frequency of congenital abnormalities, and exhibit greater mortality during the first six years of life (Morton, 1958, 1961; Schull and Neel, 1965). The degree of genetic relationship of the parents increases the chance of pairing deleterious recessives in the offspring because of a higher probability that the parents may be carriers of the same recessive alleles, due to their sharing of a close common ancestor. This increased homozygosity of recessives is shown by higher incidence of genetic diseases in certain populations. There is a greater frequency of consanguinity among parents of affected offspring than among the general population (see Table 2-8).

TABLE 2-8 Percentages of Affected Offspring of Cousin Marriages

TRAIT	% CONSANGUINITY*
Albinism	19–24
Alkaptonuria	30–42
PKU	5–15
Tay-Sachs	27–53
Xeroderma pigmentosum	20–36
Ichthyosis congenita	30–40
Congenital total blindnes	11–21

*This indicates the frequency of consanguinity of those parents who produced affected offspring. This should be weighed against the average for the general population, which is less than 1 percent.

Source: Data adapted from: Stern, 1973; Vogel and Motulsky, 1986.

GENES AND POPULATIONS: A SUMMARY

Mendel's experiments laid the foundation for modern genetics. The significance of these experiments was that they clearly demonstrated, for the first time, particulate inheritance, and the concept of inheritance by a blending of traits was at last put to rest. There are several points that should be emphasized. The first is that genes are transmitted in groups because they are a part of the chromosomes that exist as paired structures except when separated at meiosis to form the gamete. At this point in cell division, each chromosome goes its own way; there is an independent assortment that takes place, as Mendel showed with his experiments with dihybrid plants. Another way of describing this chromosome assortment is to consider that in humans, who have forty-six, one-half of the chromosomes are provided by each of the parents. However, this is not necessarily the same order in which they, in turn, will be passed to the next generation. As our gametes develop they will contain some mixture of chromosomes from each of our parents so it is highly improbable that any person will possess one-fourth of his or her genome from each grandparent. Recall Mendel's second law; the Law of Independent Assortment, which contributes to a large number of gamete types, over eight million.

A second point to consider is that a crossing of heterozygotes produces results that will usually differ somewhat by chance alone from the Mendelian ratio (1:2:1). This is to be anticipated, though, and simple statistical tests can show whether this deviation significantly differs from the expected or if it differs simply due to a chance variation. If the difference is statistically significant then one of the factors of the Hardy-Weinberg Equilibrium may be involved.

In considering a Mendelian population (breeding population), those sources of variation and the forces for stability will have to be identified and

compared in order to understand any change in gene frequency throughout the generations. Sources of new genetic material (mutations) cause small, minor changes in gene frequency in contrast to migration, which can disturb equilibrium in a single generation. If the mutation is one that conveys an advantage, then natural selection can cause a rapid rise in the frequency of the new allele. Mutations, as discussed, play the role of supplying new genetic material and, considering the complexity in the copying of the genes at meiosis, it is surprising that mutation rates are so low. It is likely that many more mutations occur than have been measured, and that these mutations are responsible for the wide range of biochemical variability that we are beginning to recognize in the human species. Most of these deleterious mutations are, fortunately, masked by the normal allele except in those rare cases when they are combined in the homozygote. We now know of the many variations in DNA fragment lengths, recently described, that frequently occur from either crossovers or from base pair changes.

Population size is a critical consideration in any study of human variation because of the possibility of loss of alleles through chance alone. The *effective breeding population* consists of those in their reproductive years (generally considered to be between fifteen and forty-four) and is, on the average, roughly one-third of the total population. Add to this the restrictions imposed by society's rules dictating the matings allowed, and chance can be seen as a major factor in gene frequency change. Also, chance plays a role in reproduction (the variety of gametes is an example) but human behavior channels a good bit of genetic variability along a certain course, as we describe later.

This chapter has provided an overview of the biological basis of human inheritance and variability. These basic concepts are developed throughout the balance of this book, and appropriate examples are given. The examples offer evidence that *Homo sapiens* is subject to basic biological laws. Though human behavior may alter the direct effect of the forces acting on a species, our total gene combinations are still related to certain environmental variables that exert selective forces. The appreciation of the importance of these forces enables us to understand the development of biological diversity.