Chapter 1 : Genetics 101

Almost every human trait and disease has a genetic component, whether inherited or influenced by behavioral factors such as exercise. Genetic components can also modify the body's response to environmental factors such as toxins. Understanding the underlying concepts of human genetics and the role of genes, behavior, and the environment is important for appropriately collecting and applying genetic and genomic information and technologies during clinical care. It is important in improving disease diagnosis and treatment as well. This chapter provides fundamental information about basic genetics concepts, including cell structure, the molecular and biochemical basis of disease, major types of genetic disease, laws of inheritance, and the impact of genetic variation.

1.1 Cells, Genomes, DNA, and Genes

Cells are the fundamental structural and functional units of every known living organism. Instructions needed to direct activities are contained within a DNA (deoxyribonucleic acid) sequence. DNA from all organisms is made up of the same chemical units (bases) called adenine, thymine, guanine, and cytosine, abbreviated as A, T, G, and C. In complementary DNA strands, A matches with T, and C with G, to form base pairs. The human genome (total composition of genetic material within a cell) is packaged into larger units known as chromosomes—physically separate molecules that range in length from about 50 to 250 million base pairs. Human cells contain two sets of chromosomes, one set inherited from each parent. Each cell normally contains 23 pairs of chromosomes, which consist of 22 autosomes (numbered 1 through 22) and one pair of sex chromosomes (XX or XY). However, sperm and ova normally contain half as much genetic material: only one copy of each chromosome.

Each chromosome contains many genes, the basic physical and functional units of heredity. Genes are specific sequences of bases that encode instructions for how to make proteins. The DNA sequence is the particular side-by-side arrangement of bases along the DNA strand (e.g., ATTCCGGA). Each gene has a unique DNA sequence. Genes comprise only about 29 percent of the human genome; the remainder consists of non-coding regions, whose functions may include providing chromosomal structural integrity and regulating where, when, and in what quantity proteins are made. The human genome is estimated to contain 20,000 to 25,000 genes.

Although each cell contains a full complement of DNA, cells use genes selectively. For example, the genes active in a liver cell differ from the genes active in a brain cell because each cell performs different functions and, therefore, requires different proteins. Different genes can also be activated during development or in response to environmental stimuli such as an infection or stress.

1.2 Types of Genetic Disease

Many, if not most, diseases are caused or influenced by genetics. Genes, through the proteins they encode, determine how efficiently foods and chemicals are metabolized, how effectively toxins are detoxified, and how vigorously infections are targeted. Genetic diseases can be categorized into three major groups: single-gene, chromosomal, and multifactorial.

Changes in the DNA sequence of single genes, also known as mutations, cause thousands of diseases. A gene can mutate in many ways, resulting in an altered protein product that is unable to perform its normal function. The most common gene mutation involves a change or "misspelling" in a single base in the DNA. Other mutations include the loss (deletion) or gain (duplication or insertion) of a single or multiple base(s). The altered protein product may still retain some normal function, but at a reduced capacity. In other cases, the protein may be totally disabled by the mutation or gain an entirely new, but damaging, function. The outcome of a particular mutation depends not only on how it alters a protein's function, but also on how vital that particular protein is to survival. Other mutations, called polymorphisms, are natural variations in DNA sequence that have no adverse effects and are simply differences among individuals.

In addition to mutations in single genes, genetic diseases can be caused by larger mutations in chromosomes. Chromosomal abnormalities may result from either the total number of chromosomes differing from the usual amount or the physical structure of a chromosome differing from the usual structure. The most common type of chromosomal abnormality is

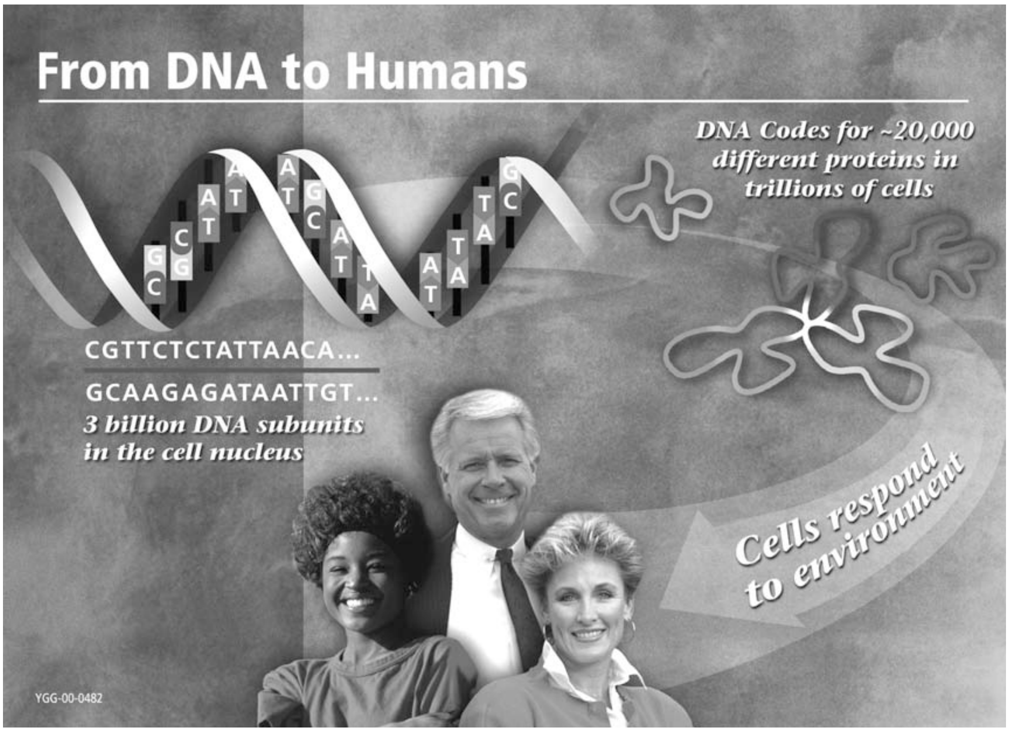


Image Credit: U.S. Department of Energy Human Genome Program, *http://www.ornl.gov/hgmis.*

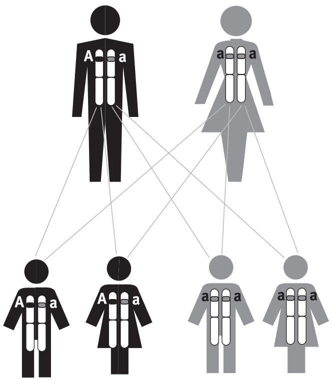
known as aneuploidy, an abnormal number of chromosomes due to an extra or missing chromosome. A usual karyotype (complete chromosome set) contains 46 chromosomes including an XX (female) or an XY (male) sex chromosome pair. Structural chromosomal abnormalities include deletions, duplications, insertions, inversions, or translocations of a chromosome segment. (See *Appendix F* for more information about chromosomal abnormalities.)

Multifactorial diseases are caused by a complex combination of genetic, behavioral, and environmental factors. Examples of these conditions include spina bifida, diabetes, and heart disease. Although multifactorial diseases can recur in families, some mutations such as cancer can be acquired throughout an individual's lifetime. All genes work in the context of environment and behavior. Alterations in behavior or the environment such as diet, exercise, exposure to toxic agents, or medications can all influence genetic traits.

1.3 Laws of Inheritance

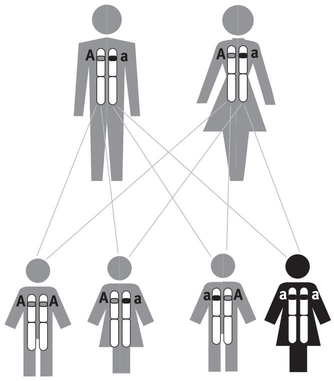
The basic laws of inheritance are useful in understanding patterns of disease transmission. Single-gene diseases are usually inherited in one of several patterns, depending on the location of the gene (e.g., chromosomes 1-22 or X and Y) and whether one or two normal copies of the gene are needed for normal protein activity. Five basic modes of inheritance for single-gene diseases exist: autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, and mitochondria. (See diagram on following page.)

Affected Unaffected



Autosomal Dominant

- Individuals carrying one mutated copy of a gene in each cell will be affected by the disease
- Each affected person usually has one affected parent
- Tends to occur in every generation of an affected family

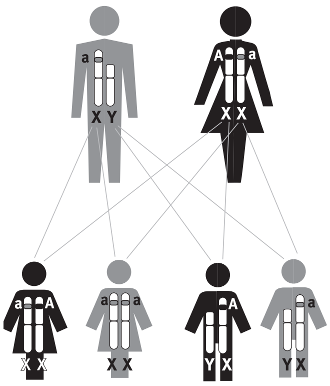


Autosomal Recessive

- Affected individuals must carry two mutated copies of a gene
- Parents of affected individual are usually unaffected, and each carry a single copy of the mutated gene (known as carriers)
- Not typically seen in every generation

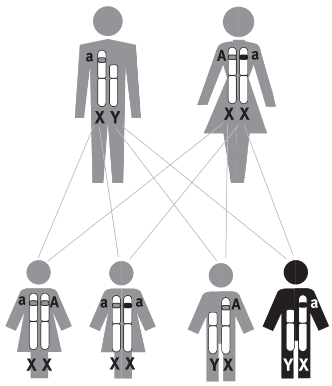
Mitochondrial

- Only females can pass on mitochondrial conditions to their children (maternal inheritance)
- Both males and females can be affected
- Can appear in every generation of a family



X-linked Dominant

- Females are more frequently affected than males
- Fathers cannot pass X-linked traits to their sons (no male-to-male transmission)



X-linked Recessive

- Males are more frequently affected than females
- Families with an X-linked recessive disorder often have affected males, but rarely affected females, in each generation
- Both parents of an affected daughter must be carriers
- Only mother must be carrier of affected son (fathers cannot pass X-linked traits to their sons)

1.4 Genetic Variation

All individuals are 99.9 percent the same genetically. The differences in the sequence of DNA among individuals, or genetic variation, explain some of the differences among people such as physical traits and higher or lower risk for certain diseases. Mutations and polymorphisms are forms of genetic variation. While mutations are generally associated with disease and are relatively rare, polymorphisms are more frequent and their clinical significance is not as straightforward. Single nucleotide polymorphisms (SNPs, pronounced "snips") are DNA sequence variations that occur when a single nucleotide is altered. SNPs occur every 100 to 300 bases along the 3 billion-base human genome. A single individual may carry millions of SNPs.

Although some genetic variations may cause or modify disease risk, other changes may result in no increased risk or a neutral presentation. For example, genetic variants in a single gene account for the different blood types: A, B, AB, and O. Understanding the clinical significance of genetic variation is a complicated process because of our limited knowledge of which genes are involved in a disease or condition and the multiple gene-gene and gene-behavior-environment interactions likely to be involved in complex, chronic diseases. New technologies are enabling faster and more accurate detection of genetic variants in hundreds or thousands of genes in a single process.

Selected References

Department of Energy, **Human Genome Project Education Resources**
www.ornl.gov/sci/techresources/Human_Genome/education/education.shtml

Genetics Home Reference
www.ghr.nlm.nih.gov

National Human Genome Research Institute
www.genome.gov/health

Online Mendelian Inheritance in Man
www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=omim