Chapter 1 : Genetics 101

Understanding the underlying concepts of human genetics and the role of genes, behavior, and the environment will be important to appropriately collecting and applying genetic information and technologies during clinical care. This chapter provides some fundamental information about basic genetic 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.

Almost every human trait and disease has a genetic component, whether inherited or by modifying the body's response to environmental factors such as toxins or behavioral factors such as exercise. Understanding the underlying concepts of human genetics and the interactive role of genes, behavior, and the environment will be important in improving disease diagnosis and treatment. This section presents a broad overview of concepts in basic genetics and the molecular and biochemical basis of disease.

1.1 Cells, Genomes, DNA and Genes

Cells are the fundamental working units of every living system. All the instructions needed to direct their activities are contained within a DNA (deoxyribonucleic acid) sequence. DNA from all organisms is made up of the same chemical units (base pairs) abbreviated as A, T, C, and G. 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 million to 250 million base pairs. Human cells contain two sets of chromosomes, one set inherited from each parent. Each cell, except sperm and eggs, contains 23 pairs of chromosomes which consist of 22 autosomes (numbered 1 through 22) and one pair of sex chromosomes (XX or XY). Sperm and eggs contain half as much genetic material (in other words, 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 on 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 20,000-25,000 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 genes active in a brain cell since 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 Major Types of Genetic Disease

Many, if not most, diseases have their roots in genes. 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.

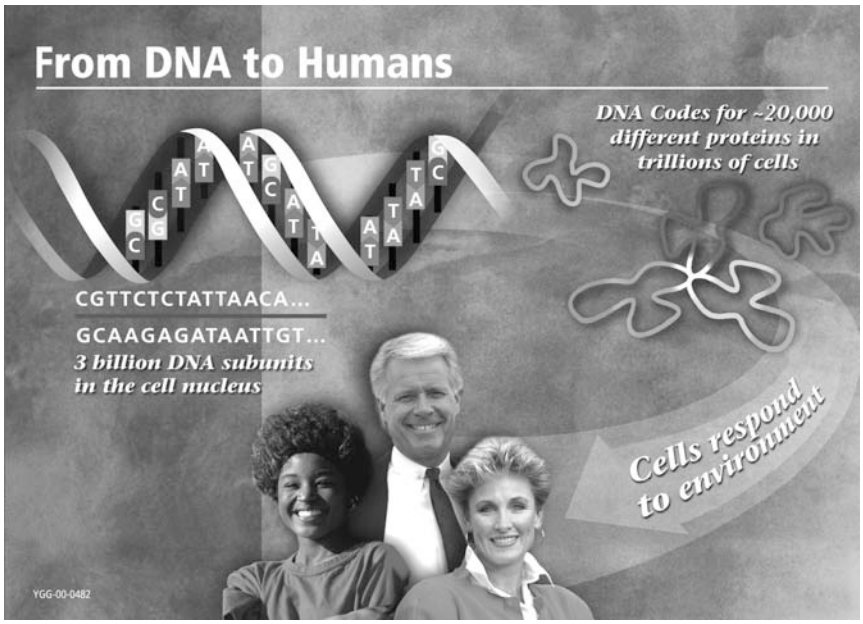


Image Credit: U.S. Department of Energy Human Genome Program, *http://www.ornl.gov/hgmis.*

Thousands of diseases are known to be caused by changes in the DNA sequence of single genes. A gene can be changed (mutated) in many ways resulting in an altered protein product that is unable to perform its 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 bases. The altered protein product may still retain some 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.

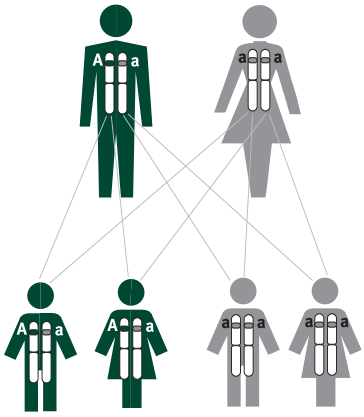
In addition, genetic diseases can be caused by larger changes in chromosomes. Chromosomal abnormalities may be either numerical or structural. The most common type of chromosomal abnormality is known as aneuploidy, an abnormal number of chromosomes due to an extra or missing chromosome. A normal karyotype (complete chromosome set) contains 46 chromosomes including an XX (female) or XY (male) sex chromosome pair. Structural chromosomal abnormalities include deletions, duplications, insertions, inversions, or translocations of a chromosome segment. [See Appendix H for more information about Chromosomal Abnormalities.]

Multifactorial diseases are caused by a combination of genetic, behavioral and environmental factors. The underlying etiology of multifactorial diseases is complex and heterogeneous. Examples of these conditions include spina bifada, diabetes, and heart disease. While multifactorial diseases can recur in families, some mutations can be acquired throughout an individual's lifetime such as in cancer. 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 have influences on genetic traits.

1.3 Laws of Inheritance

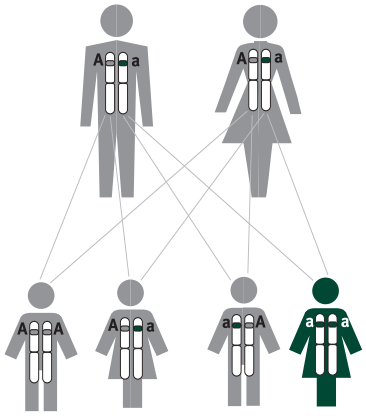
The basic laws of inheritance are important in order to understand patterns of disease transmission. Single-gene diseases are usually inherited in one of several patterns depending on the location of the gene (for example, chromosomes 1-22 or X and Y) and whether one or two normal copies of the gene are needed for normal protein activity. There are five basic modes of inheritance for single-gene diseases: autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, and mitochondrial.

Genetic diseases caused by chromosomal abnormalities are generally not inherited, but usually occur as random events during the formation of reproductive cells. Below is a sample pedigree of each type of inheritance pattern and overview of family history patterns:



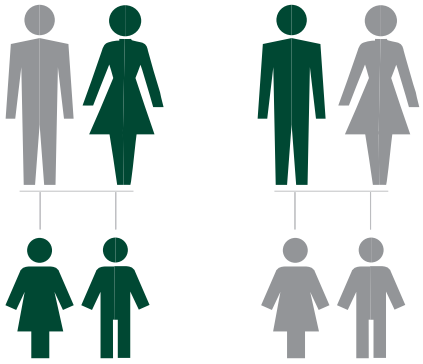
Autosomal Dominant

- 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



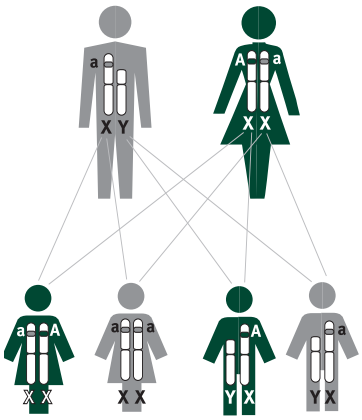
Autosomal Recessive

- 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.



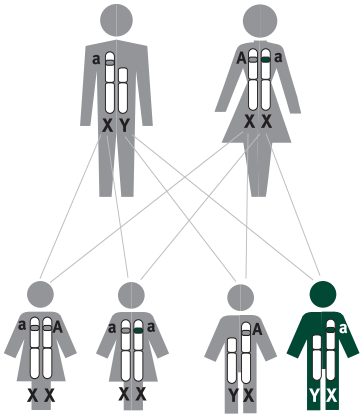
Mitochondrial

- 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 with respect to their DNA sequence. Differences in the sequence of DNA among individuals are called genetic variation. Genetic variation explains some of the differences among people, such as physical traits and also whether a person has a higher or lower risk for certain diseases. Genetic variation is referred to as mutations or polymorphisms. While mutations are generally associated with disease and relatively rare, polymorphisms are more frequent and their clinical significance is not as straightforward. Single nucleotide polymorphisms (SNPs) 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.

While some genetic variation may cause or modify disease risk, others 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 experiment.

Selected References

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

National Library of Medicine, *Genetics Home Reference–Your Guide to Understanding Genetic Conditions.* Available at *http://ghr.nlm.nih.gov/*

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