Our Genes Make Us Human

Genes do more than just determine the color of our eyes or whether we are tall or short. Genes are at the center of everything that makes us human.

Genes are responsible for producing the proteins that run everything in our bodies. Some proteins are visible, such as the ones that compose our hair and skin. Others work out of sight, coordinating our basic biological functions.

For the most part, every cell in our body contains exactly the same genes, but inside individual cells some genes are active while others are not. When genes are active, they are capable of producing proteins. This process is called gene expression. When genes are inactive, they are silent or inaccessible for protein production.

At least a third of the approximately 20,000 different genes that make up the human genome are active (expressed) primarily in the brain. This is the highest proportion of genes expressed in any part of the body. These genes influence the development and function of the brain, and ultimately control how we move, think, feel, and behave. Combined with the effects of our environment, changes in these genes can also determine whether we are at risk for a particular disease and if we are, the course it might follow.

This brochure is an introduction to genes, how they work in the brain, and how genomic research is helping lead to new therapies for neurological disorders.
From DNA

In order to understand how genes work in the brain, we have to understand how genes make proteins. This begins with DNA (deoxyribonucleic acid).

DNA is a long molecule packaged into structures called chromosomes. Humans have 23 pairs of chromosomes, including a single pair of sex chromosomes (XX in females and XY in males). Within each pair, one chromosome comes from an individual’s mother and the other comes from the father. In other words, we inherit half of our DNA from each of our parents.

DNA consists of two strands wound together to form a double helix. Within each strand, chemicals called nucleotides are used as a code for making proteins. DNA contains only four nucleotides – adenine (A), thymine (T), cytosine (C), and guanine (G) – but this simple genetic alphabet is the starting point for making all of the proteins in the human body, estimated to be as many as one million.
A gene is a stretch of DNA code that makes or regulates a protein.

When it is time to make a protein, the section of DNA that contains the code unzips.

To Gene

A gene is a stretch of DNA that contains the instructions for making or regulating a specific protein.

Genes that make proteins are called protein-coding genes. In order to make a protein, a molecule closely related to DNA called ribonucleic acid (RNA) first copies the code within DNA. Then, protein-manufacturing machinery within the cell scans the RNA, reading the nucleotides in groups of three. These triplets encode 20 distinct amino acids, which are the building blocks for proteins. The largest known human protein is a muscle protein called titin, which consists of about 27,000 amino acids.

Some genes encode small bits of RNA that are not used to make proteins, but are instead used to tell proteins what to do and where to go. These are called non-coding or RNA genes. There are many more RNA genes than protein-coding genes.
The cell’s protein-making machinery reads the mRNA and produces a chain of amino acids.

To Protein

Proteins form the internal machinery within brain cells and the connective tissue between brain cells. They also control the chemical reactions that allow brain cells to communicate with each other.

Some genes make proteins that are important for the early development and growth of the infant brain. For example, the ASPM gene makes a protein that is needed for producing new nerve cells (or neurons) in the developing brain. Alterations in this gene can cause microcephaly, a condition in which the brain fails to grow to its normal size.

Certain genes make proteins that in turn make neurotransmitters, which are chemicals that transmit information from one neuron to the next. Other proteins are important for establishing physical connections that link various neurons together in networks.

Still other genes make proteins that act as housekeepers in the brain, keeping neurons and their networks in good working order.

For example, the SOD1 gene makes a protein that fights DNA damage in neurons. Alterations in this gene are one cause of the disease amyotrophic lateral sclerosis (ALS), in which a progressive loss of muscle-controlling neurons leads to eventual paralysis and death. The SOD1 gene is believed to hold important clues about why neurons die in the common “sporadic” form of ALS, which has no known cause.
DNA Binding Proteins
About 10 percent of the genes in the human genome encode DNA binding proteins. Some of these proteins recognize and attach to specific bits of DNA to activate gene expression. Another type of DNA binding protein, called a histone, acts as a spool that can keep DNA in tight coils and thus suppress gene expression.

sRNA
Scattered throughout the genome are many types of small RNA (sRNA) that actively regulate gene expression. Because of their short length, they are able to target, match, and deactivate small bits of genetic code.

Epigenetic Factors
The word epigenetics comes from the Greek word epi, meaning above or beside. In a broad sense, epigenetics refers to long-lasting changes in gene expression without any changes to the genetic code. Epigenetic factors include chemical marks or tags on DNA or on histones that can affect gene expression.

How Gene Expression Is Regulated
We know which protein a gene will make by looking at its code, also called its DNA sequence. What we cannot predict is the amount of protein that will be made, when it will be made, or what cell will make it.

Each cell turns on only a fraction of its genes, while it silences the rest. For example, genes that are expressed in brain cells may be silenced in liver cells or heart cells. Some genes are only turned on during the early months of human development and then are silenced later.

What determines these unique patterns of gene expression? Like people, cells have a unique lineage, and they tend to inherit traits from their parents. So, a cell’s origins influence the genes it turns on to make proteins. The cell’s environment – its exposure to surrounding cells and to hormones and other signals – also helps determine which proteins the cell makes.

These cues from a cell’s past and from its environment act through many regulatory factors inside the cell, some of which are described in the following sections.
Variations In Genetic Code

A genetic variation is a permanent change in the DNA sequence that makes up a gene. Most variations are harmless or have no effect at all. However, other variations can have harmful effects leading to disease. Still others can be beneficial in the long run, helping a species adapt to change.

**Single Nucleotide Polymorphism (SNP)**

SNPs are variations that involve a change in just one nucleotide. It is estimated that the human genome contains more than 10 million different SNPs. Because SNPs are such small changes within DNA, most of them have no effect upon gene expression. Some SNPs, however, are responsible for giving us unique traits, such as our hair and eye color. Other SNPs may have subtle effects on our risk of developing common diseases, such as heart disease, diabetes, or stroke.

**Copy Number Variation (CNV)**

At least 10 percent of the human genome is made up of CNVs, which are large chunks of DNA that are deleted, copied, flipped or otherwise rearranged in combinations that can be unique for each individual. These chunks of DNA often involve protein-coding genes. This means that CNVs are likely to change how a gene makes its protein.

Since genes usually occur in two copies, one inherited from each parent, a CNV that involves a single missing gene could lower the production of a protein below the amount needed. Having too many copies of a gene can be harmful, too. Although most cases of Parkinson’s disease are sporadic (without a known cause), some cases have been linked to having two or more copies of the SNCA gene, which encodes a protein called alpha-synuclein. The excess alpha-synuclein accumulates in clumps inside brain cells, and appears to jam the cells’ machinery. For reasons that are not clear, similar clumps are associated with sporadic Parkinson’s disease.

**Single Gene Mutation**

Some genetic variations are small and affect only a single gene. These single gene mutations can have large consequences, however, because they affect a gene’s instructions for making a protein. Single gene mutations are responsible for many rare inherited neurological diseases.

For example, Huntington’s disease is the result of what is called an expanded “triplet repeat” in the huntingtin gene. Normal genes often have triplet repeats, in which the same triplet amino acid code occurs multiple times like a stutter. These repeats are usually harmless.

In the huntingtin gene, triplet repeats of 20 to 30 times are normal. But in people with Huntington’s disease, the number of repeats reaches 40 or more. The mutation creates an abnormally shaped protein that is toxic to neurons. As cells start to die, the symptoms of Huntington’s disease appear – uncontrollable writhing movements of the legs and arms, a loss of muscle coordination, and changes in personality and thinking.
Most of the single gene mutations that cause rare neurological disorders such as Huntington’s disease have been identified. In contrast, there is still much to learn about the role of genetic variations in common neurological disorders and conditions, like Alzheimer’s disease and stroke. A few things are clear. First, for most people, a complex interplay between genes and environment influences the risk of developing these diseases. Second, where specific genetic variations such as SNPs are known to affect disease risk, the impact of any single variation is usually very small. In other words, most people affected by stroke or Alzheimer’s disease have experienced an unfortunate combination of many “hits” in the genome and in the environment. Finally, beyond changes in the DNA sequence, changes in gene regulation – for example, by sRNAs and epigenetic factors – can play a key role in disease.

Scientists search for connections between genes and disease risk by performing two kinds of studies. In a genome-wide association (GWA) study, scientists search for SNPs or other changes in the DNA sequence, comparing the genomes of subjects (people, laboratory animals or cells) that have a disease and subjects that do not have the disease. In another type of study called gene expression profiling, scientists look for changes in gene expression and regulation that are associated with a disease.

Both kinds of studies often use a device called a DNA microarray, which is a small chip, sometimes called a gene chip, coated with row upon row of DNA fragments. The fragments act as probes for DNA (in a GWA study) or RNA (in gene expression profiling) isolated from a sample of blood or tissue.

Increasingly, scientists are conducting these studies by direct sequencing, which involves reading DNA or RNA sequences nucleotide by nucleotide. Sequencing was once a time-consuming and expensive procedure, but a new set of techniques called next-generation sequencing has emerged as an efficient, cost-effective way to get a detailed readout of the genome.
Genes At Work For Better Treatments And Cures

Doctors can prescribe DNA-based tests to look for the mutations that cause single gene mutation disorders such as Duchenne muscular dystrophy, neurofibromatosis type 1, and Huntington’s disease. Genetic tests are often used to confirm the diagnosis of disease in people who already have symptoms, but they can also be used to establish the presence of a mutation in individuals who are at risk for the disease but who have not yet developed any symptoms.

In the laboratory, GWA studies and gene expression profiling studies are leading to insights into new possibilities for disease prevention, diagnosis and treatment. When scientists identify a gene or gene regulatory pathway associated with a disease, they uncover potential new targets for therapy.

Understanding the relationships between genes and complex diseases also is expected to play an important part in personalized medicine. One day, microarray-based genome scanning could become a routine way to estimate a person’s genetic risk of developing diseases like stroke, Alzheimer’s disease, Parkinson’s disease and certain brain cancers. Also, researchers hope to develop customized drug “cocktails” that are matched to a person’s unique genetic profile. Researchers believe that these customized drugs will be much less likely than current medicines to cause side effects.

RNA interference (RNAi) is a technique that takes advantage of the ability of small RNAs to modify gene expression. In the future, RNAi could be used therapeutically to power up a gene that has been abnormally silenced, or to turn down one that is overactive. There are still many technical hurdles to overcome before these kinds of treatments become a reality. For example, researchers do not yet know how to best deliver these molecules to the nervous system.

These are just a few of the ways scientists are using newfound knowledge about gene expression to make life better for people with neurological disorders.
The National Institute of Neurological Disorders and Stroke

Since its creation by Congress in 1950, the National Institute of Neurological Disorders and Stroke (NINDS) has grown to become the nation’s leading supporter of biomedical research on the brain and nervous system. Most research funded by the NINDS is conducted by scientists in public and private institutions such as universities, medical schools, and hospitals.

Government scientists also conduct a wide array of neurological research in the more than 20 laboratories and branches of the NINDS itself. This research ranges from studies on the structure and function of single brain cells to tests of new diagnostic tools and treatments for those with neurological disorders. For more information, write or call the Institute’s Brain Resources and Information Network (BRAIN) at:

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