# Understanding Genetics in Neuroimaging

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**KEYWORDS**

• DNA • Genome • Mutations • Genetic diseases

**KEY POINTS**

- The history of genetics and the Human Genome Project.
- Understanding genetics: from DNA to Protein.
- Identification of different molecular abnormalities.
- Most used technologies to identify genetic injuries.
- Genetics and epigenetics mechanisms identified in neurological disorders.

## INTRODUCTION

*Genome* is the term used to describe the group of genes and regulatory sequences from an individual. Genes carry all the information that distinguishes one organism from others. Genes were discovered in 1865 by Gregor Mendel. His observations led to the creation of laws regarding the transmission of hereditary characteristics from generation to generation, which have constituted the basis of genetics until now.[1] The nature of the genes was understood only in 1952, when the scientist Roselin Franklin showed a distinctive pattern that indicated the helical shape of DNA. One year later, James Watson and Francis Crick revealed the mechanisms of DNA structure: the double helix. In 1977, Frederick Sanger developed a rapid DNA sequencing technique.[2]

In 1983, Kary Mullis improved the technique of PCR for amplifying DNA and the first genetic disease, Huntington disease, was mapped.[3]

Since then, the development of techniques to analyze the genome has grown and different pathologies are associated with genetic abnormalities.

Recently, the DNA sequence of the entire human genome was sequenced by the international, collaborative research program called the Human Genome Project (HGP). The project was idealized in 1984 but launched in 1990. The full sequence of the human genome obtained by the HGP was completed in 2003 and provided the first complete view of human genetic code.

The complete human genome contains approximately 3 billion bases and approximately 20,500 protein-coding genes on 46 chromosomes (22 pairs of autosomal chromosomes and 2 sex chromosomes). The coding regions constitute less than 5% of the genome (the function of the remaining noncoding DNA is not yet well established) and some chromosomes have a higher density of genes than others. James Watson was one of the HGP heads and his own genome was sequenced and published on the Internet.[4]

Scientists are studying how the DNA sequences of human genes can vary among individuals and populations and how genetic changes can generate diseases.

A genetic disease is any illness caused by an abnormality in an individual's genome. The abnormality can range from a discrete mutation in 1 base in the DNA of a single gene to a chromosome aberration involving the gain or loss of the genes in

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an entire chromosome or set of chromosomes. Some genetic disorders are hereditary (inherited from the parents) whereas others are caused by acquired mutations in a somatic gene or group of genes. Mutations can happen either randomly or due to some environmental exposure.[5]

Most genetic diseases are the direct result of mutations in 1 or many genes. One of the most difficult questions to be further elucidated, however, is how genes contribute to diseases that have a complex pattern of inheritance, such as diabetes, asthma, cancer, and mental illness.[6]

In the nervous system, from depression to Alzheimer disease, familial genetic heritage has been observed. Other conditions, such as Parkinson disease and tumors in the central nervous system, have been associated with a variety of gene deregulations.[4]

In these cases, more than 1 mutation is responsible for the disease arising, and several genes may contribute to a person's susceptibility to a disease.[7] Moreover, genes may affect how someone reacts to environmental factors. To understand how genetics are involved in the genesis of a disease, it is important to understand the mechanisms of gene expression, cell cycle, and proliferation/death control.

## FROM DNA TO PROTEIN

DNA is the molecule that carries hereditary information in almost all organisms. DNA consists of 2 polynucleotide strands. Each nucleotide comprises a sugar, a phosphate molecule, and a nitrogenous base (adenine, guanine, thymine, or cytosine). DNA is arranged in spiral forming a structure, called the double helix.[1]

During DNA replication each strand acts as a template for the synthesis of its complementary strand. The disposition of nucleotides along the DNA strand constitutes the genetic code. Every three nucleotide sequence, called codon, encodes one specific amino acid. A gene is a sequence of nucleotides along the DNA strand that determines the sequence of amino acids in a protein.[1]

Gene expression is a process of DNA sequence reading into protein synthesis. This process has 2 major steps: transcription and translation. During transcription, the information is shifted from the DNA to a messenger RNA (mRNA). The DNA serves as template for complementary base pairing catalyzed by an enzyme called RNA polymerase, forming a precursor RNA molecule (pre-mRNA). Then the pre-mRNA is processed to form a mature mRNA. During this phase, called splicing, noncoding regions named introns are excluded from the molecule and only the coding region, the exons, remain in the mRNA structure. Alternative splicing occurs and different sequences are processed, giving rise to a huge variety of mature mRNAs. The mature mRNA receives some structural markers that signal for cytoplasmic exportation. In the cytoplasm, the step of protein synthesis called translation starts. The mature mRNA, a single-stranded copy of the gene, is then recruited by a protein complex in the ribosome and is translated into a protein molecule.

### *DNA Transcription—Control of Gene Expression*

The process of transcription was first observed in 1970 by electron microscopy. During transcription, 1 DNA strand serves as template for RNA synthesis, whereas the other strand is considered noncoding.

The process of transcription starts when RNA polymerase attaches to the template DNA strand and begins to catalyze the production of RNA by matching complementary bases to the original DNA strand.[8]

Transcription factors bind to specific DNA sequences called enhancer and promoter/silence sequences to recruit RNA polymerase to an appropriate transcription site and signal which part of the gene will be transcribed.

The promoters and enhancers or silencers are located within regulatory regions of the gene as well as within introns. Enhancer sequences regulate gene activation by binding proteins and changing the conformational structure of the DNA, helping to attract RNA polymerase. Because DNA is tightly packed into chromatin, transcription also requires several specialized proteins that facilitate the access to the coding strand.

### *The Role of Chromatin Structure*

In human cells, DNA is packaged around histones, which are proteins in chromatin that also perform a function in gene regulation. In general, they control whether transcription factors may access the DNA.

For transcription to occur, the transcription area needs to be unrolled. This process requires the coordination of histone modifications, transcription factors binding, and other chromatin remodeling activities.

Modifications of histones can open up a gene, whereas DNA modifications can shut it down. In general, methylation of DNA makes chromatin more tightly closed and results in down-regulation or inhibition of gene transcription. On the other hand, acetylation of histones unbends bindings and helps transcription. Methylation of histones

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