

The completion of the Human Genome Project in 2003 revealed much about the role of genes in human development and disease progression, but questions about the functioning of genes remained. Epigenetics has been able to provide answers to some of these outstanding questions. Epigenetics refers to the study of changes that occur in the genome without changing the DNA sequence.

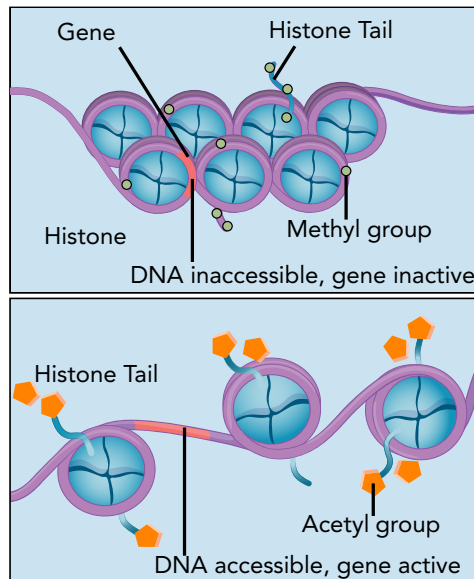
1. What is epigenetics?

Epigenetics is the study of the impact of behavioral and environmental factors on genes. These include both internal and external factors, such as diet, exercise, smoking, and stress, among others. Such activities cause the addition of chemical marks to the genome that change its physical structure but do not modify the DNA sequence. These changes can be inherited and in some cases are reversible. They are significant because they play a key role in gene expression and functioning. The collection of changes to DNA is called the *epigenome*.

2. What mechanisms bring about epigenetic changes?

While several epigenetic mechanisms have been characterized, two have been studied extensively: *methylation and histone modifications*. These mechanisms are associated with either activation or repression of gene expression. Both can be influenced by a range of factors, including maternal hormones during pregnancy, temperature changes, smoking, and exposure to toxins.

The diagram below explains these processes.



Methylation of DNA and histones causes nucleosomes to pack tightly together. Transcription factors cannot bind the DNA, and genes are not expressed.

Histone acetylation results in loose packing of nucleosomes. Transcription factors can bind the DNA and genes are expressed.

DNA methylation refers to the addition of a methyl group, usually to cytosine, one of the bases of DNA. Cytosines are normally in regions rich in cytosine and guanine (another DNA base), called CpG islands. When CpG islands are methylated, transcription, the first step in gene expression, is stopped, causing protein production to stop as well.

Histone modifications are linked to changes that take place when methyl and acetyl groups attach to histone. In the limited volume of a cell's nucleus, DNA is wrapped around histones to form clusters called nucleosomes. Histone modifications are linked to changes that take place when methyl and acetyl groups attach to histones. An example of this occurs on the third histone protein, where the addition of methyl groups causes the nucleosomes to pack tightly together, making the genes in that region less available, and reducing the likelihood of gene activation and expression. Alternatively, the addition of acetyl groups, however, results in looser packing of nucleosomes, resulting in genes becoming more accessible and easily activated. While this is one example of the on/off switch like mechanisms underlying chromatin modifications, there are many others that are involved at different sites of gene expression regulation.

3. What are epigenetic clocks?

Using knowledge about the effect of DNA methylation on aging, researchers have developed epigenetic clocks, mathematical models used to gain a better understanding of how we age. The clocks assess the level of methylation in several genes and CpG sites. In one well-studied clock, the Horvath Clock, 21,000 sites in the genome were considered, from which 353 sites emerged that were predictive of age. From this data, scientists developed an equation that can be applied to other samples to determine an individual's biological age. This number is then compared to the individual's chronological age to determine the rate of aging. Other clocks also evaluate the influence of environmental factors on aging.

What is epigenetics teaching us about genetic changes throughout the lifespan?

Studying epigenetics has revealed that changes from outside influences have a significant impact throughout the lifespan, from early development to old age. Changes in epigenetic patterns can lead to genetic diseases such as asthma and some kinds of cancer. Finally, epigenetic changes can accelerate the aging process, a phenomenon being tracked with epigenetic clocks.



The Future of Epigenetics

It is becoming increasingly possible to harness knowledge gained through epigenetics to discover disease markers early on and develop therapies that target epigenetic pathways. In the future, cancer therapies may be able to reactivate genes that suppress tumor growth or activate oncogenes, which can slow the growth of cancer cells. As personalized medicine becomes more widespread, therapies could be targeted to each patient's unique epigenetic profile.