Epigenetics and Sleep Disordered Breathing

by Amalia A. Geller, MD

Educational Aims

This self-instructional course for dentists aims to discuss the role of epigenetics and craniosacral-fascial therapies on sleep-disordered breathing.

Expected Outcomes

Dental Sleep Practice subscribers can answer the CE questions online at https://dentalsleeppractice.com/continuing-education/ to earn 2 hours of CE from reading the article. Correctly answering the questions will demonstrate the reader can:

1. Identify some characteristics of the science of epigenetics.
2. Realize how the epigenetic code works in the human body.
3. Recognize epigenetics' connection to general oral health.
4. Realize epigenetics' role in periodontal medicine.
5. Identify the role of epigenetics in orthodontics.
6. Recognize the role of craniosacral fascial therapy in using the patient's natural genes to correct and straighten the teeth in jaws in conjunction with the use of biomimetic appliances.

Child neurologists have much exposure to many different types of genetic conditions that lead to sleep-disordered breathing. For many years, the tonsils were the prime culprit. However, discoveries show more than simply the tonsils leading to the problem – the relationship of upper airway resistance, malocclusion, and the role of epigenetics also must be considered. An aligned body is essential to working with malocclusion. Malocclusion and broken teeth cannot be fixed on a body frame that is not in proper alignment. Concepts of craniosacral fascial therapy also are an essential component to treating sleep/breathing issues. All of these factors are a part of the study of epigenetics.

What is Epigenetics?

Epigenetics is the study of phenotypic changes that occur via mechanisms that are not related to DNA sequence alteration. Epigenetics means that something is acting up on the genome.

In 2007, the human genome project was completed, and it was after this that the *epigenetic code* was recognized. Besides the genetic code, we also have an epigenetic code that essentially tells the genes in our genetic code when and where they are to be expressed. The simplest example of this would be what drives many different tissues to come from one specific cell line. The genetic code contains all the information that humans need to function, but it does not contain the program that determines when and how genes are going to be expressed. The epigenetic code tells where genes are to be activated and deactivated during embryogenesis and growth throughout our lives.

How Does the Epigenetic Code Work?

According to SD Williams, et al., "it is our epigenetic code that allows genetically identical cells to express different patterns of genes."

The epigenetic code works through chemical modifications and key elements — namely DNA methylation and histone-protein acetylation. Epigenetic modification also can be involved in switching genes on and off by preventing RNA and messenger RNA formation. These epigenetic modifications can be inherited from cell cycle to cell cycle dating back to grandparents, passed on to parents, to the current generation, and passed on to our children.

Factors that can lead to epigenetic modifications of our genetic code come from various sources such as the environment and emotional adaptations to stressful situations — all of which can have an impact on our epigenetic code. An important clinical aspect of this is when certain populations appear to be more susceptible to certain diseases. This leads us into the medical issues of autoimmune disease, mental health issues, and cancers. The environment is a very important factor in this because of its capacity to regulate genetic expression.

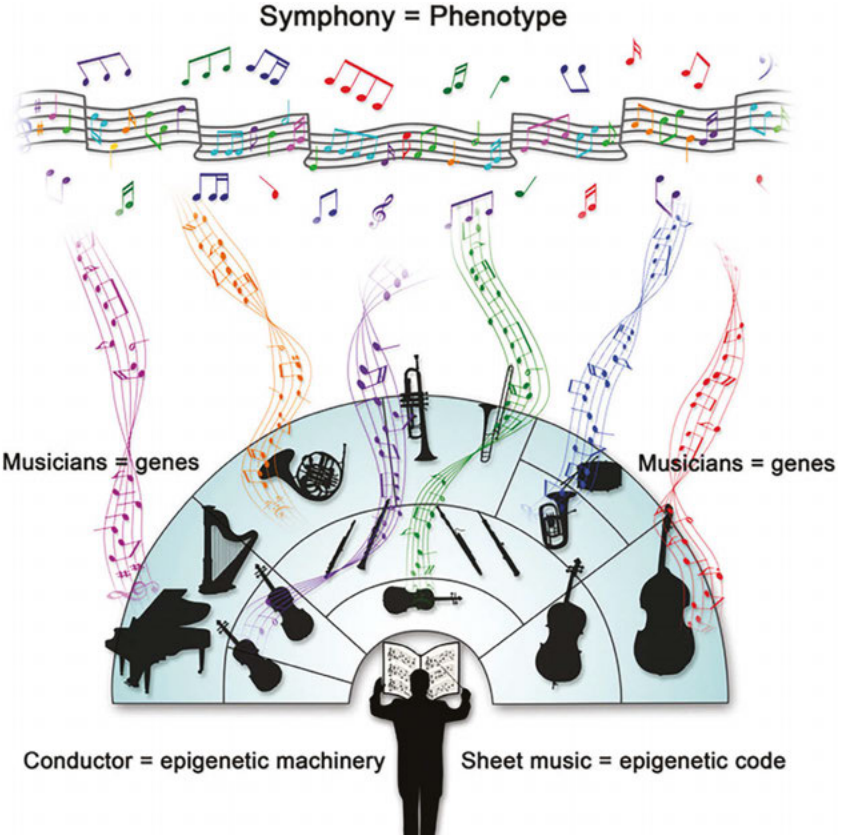

Figure 1: "The music of life" illustration of epigentics

Another way to see this concept of epigenetics is in Figure 1 titled "the music of life." The genetic code can be described essentially as the orchestra. The orchestra has different instruments played by different musicians. Many different types of melodies are produced from this orchestra. But without the conductor to interpret the music and conduct the orchestra,

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and without the sheet music, only noise will be produced. The conductor is the epigenetic machinery instructing the individual genes (musicians). The conductor tells the musicians when and how to play. The epigenetic code is the sheet music.

Epigenetics' Connection to Oral Health

The history of the concept of craniofacial development connects it to epigenetics. The connections between dentistry and epigenetics have primarily been focused in the fields of periodontics and orthodontics. Over 100 years ago, certain Western societies' diets consisted of high fiber, which required more chewing. Grandparents and great grandparents generations were more accustomed to eating cruciferous vegetables and fruits. Over the years, craniofacial structures changed gradually due to dietary changes where children were offered more opportunities to eat soft foods, soft cereals, macaroni and cheese, etc. Environmental elements such as socio-economic status and early developmental prenatal exposures to toxins and chemicals definitely impact developmental outcome.

Epigenetics' Role in Periodontal Medicine

In the field of periodontics, a complex situation exists with the interaction of the body's immune system and the inflammatory responses that lead to periodontitis. There is a genetic predisposition to this inflammatory state.

Factors that can lead to epigenetic modifications of our genetic code come from various sources such as the environment and emotional adaptations to stressful situations.

Epigenetics involves genes and coding for the pro-inflammatory cytokines that are believed to be associated with periodontitis.

A fascinating link has been made between periodontitis, HIV, and AIDS progression. Periodontitis is believed to be able to reactivate HIV expression through an epigenetic mediator. Research from the early 1990s indicated that HIV-associated gingivitis and HIV-associated periodontitis (HIV-P) were seen only in HIV patients. As discussed earlier, methylation is a very important epigenetic mechanism. An important epigenetic approved therapy in HIV involves DNA methyltransferase inhibitors. These inhibitors target epimutations (the hypermethylation and epigenetic silencing of tumor suppressor genes/etiologies in human cancers). Essentially chemical modifications of DNA and histone proteins cause epigenetic changes that alter cellular function and host defenses.

There is also increasing evidence to support the theory that periodontal disease can increase the risk of cardiovascular disease. That chronic inflammation is what leads to atherosclerosis. Dr. Hatice Hasturk of the Harvard-affiliated Forsyth Institute has identified compounds called *resolvins* that may be able to actually treat chronic inflammation associated with periodontitis and atherosclerosis. Resolvins are molecules derived from omega-3 fatty acids that are believed to help suppress inflammation. Resolvin has been formulated into a topical liquid. When Dr. Hastruk and colleagues exposed rabbits to a cholesterol-rich diet, they developed plaque. These rabbits were then introduced to a bacterium that is known to cause periodontal disease. The rabbits were then treated with Resolvin. They found that not only did Resolvin prevent periodontal disease, but it lowered inflammation and atherosclerosis. Their hypothesis – control one type of inflammation, and you might be able to control another type of inflammation.

The Role of Epigenetics in Orthodontics

Pioneers in the field of epigenetics include:

1. Dr. Conrad Waddington (1942) developed the term epigenetics years before DNA was described by Watson and Crick in 1953. Waddington's definition essentially pointed to something that

acts on the genome in order to regulate it (Figure 2).

2. Dr. Melvin Moss developed the concept of epigenetic processes (mechanical loading) and the processes that cause these changes.
3. Dr. Theodore Belfor who invented the Homeoblock™ applicance device and POD device.
4. Dr. David Singh developed and invented the Vivos DNA appliance.

Dr. Waddington's definition of epigenetics was focused more on molecular mechanisms, but over time in the orthodontics world in particular, the intra-genomics chemical environment is thought to be the location for epigenetic activity. Orthodontic literature focused more on the physical forces acting on the jaw that lead to remodeling at the condyle. Outside forces that act upon the jaw induce epigenetic changes that affect genetic expression.

Another early pioneer in this area is Dr. Melvin Moss who tried to distinguish between epigenetic processes such as mechanical loading and the processes that caused the changes. He described the macro environment, for example joint loading, down to its involvement with DNA methylation. The force acting upon the jaw induces growth or re-modeling at the level of the condyle. Again, the key elements that the epigenetic code works through are chemical modifications of DNA methylation and histone-protein acetylation.

The Moss Functional Matrix Hypothesis led to the concept that genetic control is assumed to be outside the skeletal system. The orthodontic perspective believes that this is the actual epigenetics' model and essentially changes that may occur in bone and cartilage are due to signals coming from other tissues. This concept is the basis for the epigenetics' orthodontics which is also called functional orthodontics.

One of many great pioneers in this field of functional orthodontics is Dr. Theodore Belfor, who after 20 years of research developed an orthopedic/orthodontic appliance that incorporates proper breathing and swallowing practices. His approach is in somewhat of a contrast to Dr. Singh's DNA device that involves focus on palatal expansion and widening of the upper jaw. According to Dr. Belfor, remodeling and repositioning the upper jaw is the focus, and not palatal expansion. The body

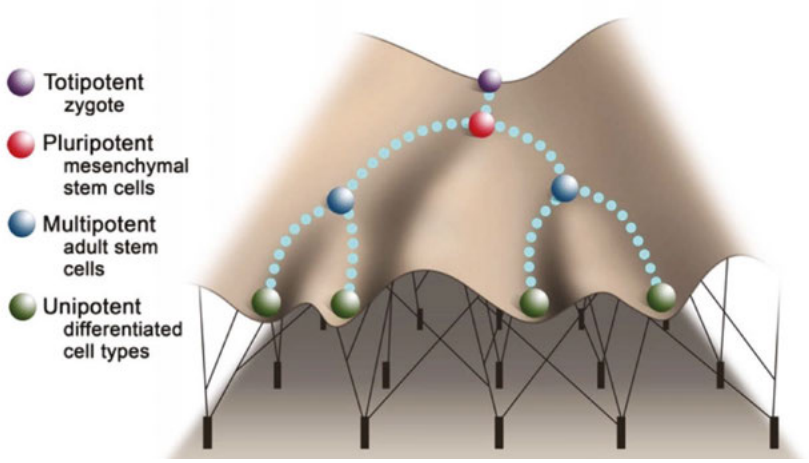

Figure 2: Waddington's Epigenetic Landscape. Waddington's epigenetic landscape is a metaphor for how gene regulation modulates development. Imagine a number of marbles rolling down a hill toward a wall. The marbles will compete for the grooves on the slope, and the ridges between the grooves represent the increasing irreversibility of cell type differentiation. Each marble will come to rest at the lowest possible point, representing eventual cell fates, or tissue types. This concept has been more formalized in the context of a systems dynamics state approach to the study of cell-fate, which has opened the door to the key role played by stochastic fluctuation (cellular noise), as well as physical fields, in both cell differentiation and cell proliferation.

provides a physiologic size and shape change known as maxillary morphogenesis which provides symmetry, balance, and proper jaw alignment. There are no genes for asymmetry. A true epigenetic appliance will provide maxillary and cranial facial symmetry.

Dr. Belfor's device that applies these principles is called the Homeoblock with incorporated Unilateral Biteblock® technology, which generates a cyclical strain on the cranial system when the patient swallows and bites on the block. This action causes osteocytes to generate osteoblasts that can generate new bone. The appliances with the Unilateral Biteblock® technology make more room for the tongue and can strengthen the muscles that prevent airway collapse.

Another fascinating invention, a lower device also designed with the Unilateral Biteblock® technology, is called the Preventive Oral Device (POD)™. The POD™ was FDA approved in 2019 and is designed for those people who suffer from TMD and bruxism. The POD™ allows for dental arches to remain out of contact with each another and allows the tongue to move forward and clear the pathway for breathing.

The Role of Craniosacral Fascial Therapy

In epigenetic orthodontics, orthodontists are using the patient's natural genes to correct

and straighten the teeth in jaws with the use of biomimetic appliances. However, what is the role of preparing patients for these devices?

The concept of craniosacral fascial therapy is very important as it applies to fixing and correcting the occlusion which hopefully will help resolve sleep-disordered breathing. We must not forget the cranium, the neck, and the entire spine. The body's balance and alignment is essential to for appropriate breathing and functioning as healthy human beings. The importance of understanding these concepts beginning at life and continuing through children's developmental stages, will ultimately lead to the prevention of these problems in adulthood.

In Future Articles

Future articles will discuss the relationship of cranial-sacral fascial therapies. Pioneers in this field include:

1. Founder of cranial osteopathy: Dr. William G. Sutherland and his student, Dr. Andrew Taylor Still, DO
2. Founder of cranialsacral therapy/identifying the craniosacral pulse, Dr. John E. Upledger, DO
3. Founder of craniosacral-fascial therapy (Gillespie method), Dr. Barry Gillespie, DMD.

Also, in our upcoming articles, we will compare the different inventions by pioneers of this field, in particular the concepts and theories between Dr. Singh's DNA device and Dr. Belfor's device along with other pioneers in this area and their contributions to this exciting field of sleep dentistry.

The prime source for this article was Williams SD, Hughes TE, Adler CJ, Brook AH, Townsend GC. Epigenetics: a new frontier in dentistry. *Aust Dent J.* 2014; 59 Suppl. 1:23-33. DSP

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