The gene and epigenetics: the dental and maxillofacial characteristics are related to environmental factors

or

The genes do not control everything!

or

Is the genetic determinism over?

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The word gene was coined in 1909 by Wilhelm Johannsen to replace the concept of units of inheritance called "gemmules", created by Charles Darwin. Before Darwin, the prevailing concept was the "determinants" created by Weismann. Before these, there was the concept of "pangenes" initially proposed by Hugo de Vries[9,13].

The concepts of gemmules, determinants and pangenes had a built-in meaning: *they were preformationists, i.e. everything was predetermined*. However, Johannsen knew this was wrong: the transmissibility of characteristics between generations was not as such, and thus the term gene was created to eliminate this meaning[9,13].

The creation and concept of gene ultimately gave rise to the genetic determinism: *the characteristics of live beings are determined by units of inheritance called genes.* This concept was very keen and closed and was finally dogmatically used. The transmissibility of characteristics between generations does not depend *exclusively* on the genes; we should consider the cell as a whole with the cytoplasm, mitochondria and genetic material present in its structure, as well as the entire organism and the complexity of the environment.

The didactic meaning of the word gene implies translating it as a DNA fragment that stores complete information related to the cell function. In the human body, we have nearly 337g of DNA[1]. Some years ago, we assumed that the mankind would have the highest number of genes among all species. Nowadays, we know that we have fewer genes than the rice, the cow or even the rat. We imagined we had 100 thousand genes, yet the current knowledge indicates that we have nearly 25 to 30 thousand. *The low number of genes reveals that the biology is more complicated than many people would like*, as stated by Craig Venter, founder of Celera Genomics, a company that has its own version of the human genome[8]. The onset and end of a gene in the DNA structure may be permeated by another gene that uses only part of this gene. The genes are interspersed and superimposed one over the others, and maybe for this reason there was a feeling of frustration when the sequencing by the human genome project was announced[1,8,9,13]. Spectacularly, conclusions were expected such as: *"... here are the genes,*

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distributed this way in each chromosome, each with a defined function".

This project detected the sequencing of the DNA, yet did not describe the onset and end of all genes involved in the formation and functioning of mankind. This is still ongoing, or at least attempting. To demonstrate the complexity of this system, there are also jumping genes that may change their position in the DNA in the context of chromosomes, which are very hard to identify and isolate.

The epigenetics influences the inaccurate transmissibility of dental and maxillofacial characteristics

Many aspects not related to the genes influence the transmissibility of our characteristics. There is no genetic determinism and the importance of the concept of epigenetics has been increasingly highlighted based on the ideas of four renowned geneticists, Lewontin, Keller, Parentoni and Piza[9,13]:

1) the gene-particle does not exist;
2) the chromosome works as a whole;
3) the cytoplasm plays a more important role than the nucleus in hereditary phenomena. Remember the RNA, mitochondrial DNA, cytoplasmic enzymes and proteins.
4) for the cell, the environment is the organism in which it lives; for the organism, the environment is represented by the place where it lives and its variables in the interaction with the outside world.

The epigenetics considers the biochemical factors that turn genes on and off, which is related to the environment of the cells and of the organism as a whole. The genes are often present, yet they are "turned on and off" by enzymes, proteins, hormones and other mediators. The genes may undergo adaptations to conform the cell or organism to the environment. This may occur without alterations in their nucleotides or "letters", i.e. the genes may be simply turned off.

The difference between epigenetics and a mutation lies on the fact that the latter changes the sequence of letters or nucleotides of the genes, usually by the action of external factors such as chemical or physical agents during the process of genome reduplication, or by a simple biochemical accident.

The environmental factors are among the epigenetic factors most often cited, including the diet, pollution, drugs and exercises that may modify the pattern of turning the genes on and off during the cell division. In 2001 many frustrations occurred when the sequencing of the human genome was announced. Many responses were expected to diseases such as obesity, diabetes and cancer; however, these responses were not achieved, because the genes represent one of several factors involved. Many other factors related to cell functioning have not been elucidated, yet the epigenetics begins to explain this variability.

The teeth present shape, structure, size, number, shade and position, besides other characteristics that are strongly influenced by environmental factors in the years of extra-uterine life in which the odontogenesis occurs. Four such environmental or epigenetic factors that may be involved in the final determination of dental characteristics are presented below4:

a) growth forces guiding the final format of the jaws. In this process, the position and shape of tooth buds still in the soft tissue stage or undergoing mineralization may be altered. The face formation is initiated in the fourth to eighth week of intrauterine life, called embryonic period. In this period there is intensive cell differentiation and migration. The forces generated during face formation and growth and during the formation of embryonic processes may change the original, genetically determined position of the tooth buds and their harmonious alignment with the deciduous tooth buds,

FIGURE 1 - Epigenetics may explain why the teeth of any given patient are not exactly the same on both sides, although it is highly likely that the genetic information in the DNA determines that they be bilaterally identical. However, this does not occur owing to the influence of environmental factors. Epigenetics must be deeply embedded in the morphological formatting of human teeth.

alveolar ridge and the other permanent teeth. This may occur during the initial period of odontogenesis, still in the dental lamina stage.

The dental lamina is shaped as an epithelial wall connected to the ectodermal lining of the primitive mouth, shaped as a horseshoe. Its internal margin gives rise to the tooth buds as round fruits, initially hanging and then loose. These tooth buds are harmoniously aligned in the mesenchyme around them to form the future dental arch. Forces external to the dental lamina and tooth buds may disarrange them or even displace them upward or downward since the onset of formation, when the mesenchyme has not yet originated the bone:

b) tooth migration in the jaws during the process of tooth eruption. Deviations in the tooth long axis may represent changes in the eruption pathway due to the presence of obstacles such as areas of bone condensation, cortical bone or even other teeth in case of lack of space. This probably prevents the contralateral tooth to be exactly equal in volume, shape and position;

c) environmental influences on the organism, as byproducts of the diet and drugs reaching the tissues through the blood circulation, variations in body temperature and byproducts of the metabolism. These factors may influence the shade, mineral density, period of formation and tooth eruption;

d) masticatory load, which may influence the shape of the apical third of teeth. During root formation, the tooth erupts by moving toward the occlusal plane. When the teeth occlude with antagonist teeth, the apical third of the root is still being formed. The tip of the developing root presents the dental papilla, Hertwig's epithelial root sheath and the dental follicle, which in combination constitute the "root forming organ". These tissues have soft texture with reduced ability of physical penetration into the bone tissue; however, their chemical mediators induce the bone resorption, providing space for completion of the apical root formation. Nevertheless, in the presence of obstacles such as cortical bone, bone sclerosis, nerves and blood vessels or even other teeth, the shape and period of formation of these embryonic tissues may be altered, giving rise to different and even shorter apical thirds. Probably the original, genetically determined shape was much different than definitely established in the final tooth morphology.

The epigenetics may explain why the teeth of the same individual are not exactly equal at both sides even though the genetic information in the DNA should probably originate bilaterally equal teeth; however, this does not occur due to the action of environmental factors. The epigenetics should be strongly related to the morphological format of human teeth[5,3].

Tooth positioning, harmony between the dental arches and between the maxilla and mandible and the skull should be genetically programmed, yet environmental factors such as habits, position, change in the growth pattern alter these relationships that may be genetically well established.

Craig Venter, one of the most prominent researchers in the genome project, made the following statement when questioned about the influence of the environment on the occurrence of diseases (Fioravanti): ... genes and the environment have probably the same importance. In each illness, in each human condition there is a different mix of the influence of these two factors. The biological molecule proves that the environment is really an essential part of life, of biology. They are not separated. The people who only look at genes or only at the environment, start out missing the point. By definition, it has to be the two of them together.

The concepts of pleiotropic gene and polygenic system to understand the characteristics and status of the teeth, maxilla and mandible

The genes and chromosomes involved in the determination of our dental and maxillofacial characteristics are not yet accurately known. It is only suggested that the genes *MSX1* and *PAX9* are involved in the origin of partial anodontia. However, clinically, when the number of teeth is altered e.g. in partial anodontia, other characteristics of the present teeth are also altered, such as crown and root shape,[4,5,7,10,14] originating the phenomenon of morphological simplification:

a) the cusps are shorter and less angled,

b) the occlusal surface presents fewer pits and fissures,

c) the mesiodistal diameter is reduced,

d) the Carabelli tubercles disappear or are reduced in the first molar,

e) the cingula are reduced or absent in the maxillary anterior teeth,

f) the distolingual cusp is absent in the maxillary second molar,

g) the roots are shorter in relation to the crown,

h) the triangular shape is predominant in patients with partial anodontia.

Probably, other characteristics may also be altered, such as the shade and tooth positioning in the jaws. As a consequence, the jaws may also present alterations in their growth and shape. This relationship between dental and/or maxillomandibular characteristics with the others influencing the shape and function may be explained by the epigenetics and considering two other concepts:

1° - ***Pleiotropic gene:*** gene responsible for one or more morphological and/or functional characteristics. When one of these characteristics is changed, the others may also be altered, strongly influencing the final phenotype of the structure. Thus, changes in the shape or number of teeth may cause changes in their position and period of eruption, for example.

2° - ***Polygenic system:*** group of genes that would act harmoniously to determine a group of characteristics. When one of these genes presents modifications, the others would be influenced and would alter the phenotypes of structures influenced by them. Changes in tooth shape may be related to alterations in the shade and number of teeth.

Concluding remarks

The knowledge on dental and maxillofacial morphology necessarily involves the concepts of epigenetics, pleiotropic gene and polygenic system to explain the relationship between different characteristics, such as the shade, size, number, shape, structure and position of teeth and of the jaws. Knowledge on the etiopathogenesis of dental and maxillofacial developmental disturbances also involves these three concepts.

The analysis of the relationship between dental and maxillofacial morphology, as well as their developmental disorders, also called disgenesias, may give rise to insights to studies on the identification of genes, chromosomes and epigenetic mechanisms responsible for the characteristics of human teeth and jaws.

We should not state that the genome project was a historic landmark, since it is not over yet. We do not know exactly how many genes we have, in which chromosomes they are located, or their onset and end in the DNA sequence[11].

When asked if the human genome might be considered the "book of life" and if the genetic determinism had been knocked, Venter stated[8]: *... the genetic code is not a portrait of a human being, nor the dictionary of life. It holds important parts to our history, important instructions for our cells, about how to modify them. However, you cannot go into a chromosome and find the instructions on how to make a heart, a brain. This discussion has to do with the complexity of the human being. The information is on the following levels, in the interplay between the proteins and between the structures of the cells. All of this is not directly codified in our DNA.*

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