

Review article**Genetics and orthodontics: digging secrets of the past**

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**ABSTRACT:** This paper reviews the changing concepts of genetics in the field of orthodontics from past to present. Orthodontists in past were mainly concerned with the correction of malocclusion by moving teeth into an ideal occlusal relationship, but the inception of the concept of growth modification has provoked a controversial area of interest and activity in orthodontic fraternity. Like every biologically based clinical discipline, there was a significant lag time between the discoveries in the emerging field of genetics and incorporation of these discoveries into concepts. A rapid advance in the field of genetics has provided new insight into craniofacial development and has led to a better understanding of the subject. Advancements are so rapid, that only by keeping our eyes steady on what went before; we can progress with intelligence and confidence.

**Key words:** History; Genetics; Orthodontics; Theories; Experiments; Occlusal.

**PIONEERS IN THE FIELD OF GENETICS**

*“The heritages of the past are the seeds that bring forth the harvest of the future.”*

It has been more than 50,000 years when *Homo sapiens* first appeared on this planet, ever since then we have been curious about the matters of inheritance. It is this never ending desire to know our existence that has led to varied advancements in the field of genetics.

Genetics in simple words is a field of biological science which deals with the mechanisms of heredity. The first name that comes to our mind when we talk about history of genetics is Gregor Mendel. His contributions to the field of genetics cannot be overstated but it is very interesting to know that history of genetics began with Hippocrates. In his theory he concluded the inheritance of acquired characters with the view that each part of the body produces something which is then somehow collected in the “semen” and these form the material basis of heredity, as they develop into the characters of the offspring; hence baldheaded fathers will have baldheaded sons.<sup>1</sup>

Aristotle criticized this hypothesis for the following reasons, (1) Individuals sometimes resemble remote ancestors rather than their immediate parents, (2) Peculiarities of hair and

nails, and even of gait and other habits of movement, may reappear in offspring, and that these are difficult to interpret in terms of simple form of the hypothesis, (3) Characters not yet present in an individual may also be inherited, (4) The effects of mutilations or loss of parts, both in animals and plants, are often not inherited. His general conclusion was that what are inherited are not characters themselves in any sense but only the potentiality of producing them.<sup>2</sup>

It was in the 17<sup>th</sup> century, when Dutch scientists like Leeuwenhoek and De Graaf recognized the existence of sperm and ova, thus explaining how females could also transmit characteristics to her offspring.

The quest to understand sexual reproduction and its mechanism in animals and plants led to varied investigatory studies by the botanist and zoologist of that time. Most satisfactory general account of the state of knowledge at that time was found in Darwin’s discussion in *The Variation in Animals and Plants under Domestication* (1868).<sup>3</sup>

Charles Darwin recognized two more or less distinct types of variations– those that came to be known as continuous and discontinuous, respectively. He concluded that crossing has a unifying effect. Since hybrids are generally intermediate between their parents, crossing

tends to keep population uniform, while inbreeding leads to differences between populations.

Much of our knowledge of laws of genetics and mode of inheritance is due to the outstanding work of Gregor Johann Mendel. In the summer of 1854, Mendel grew thirty – four strains of peas; he tested them for constancy in 1855. In 1856 he began the series of experiments that led to his paper, which was read to the Brunn Society for Natural History in 1865 and was published in their proceedings in 1866. Despite the efforts his conclusions remained unnoticed for many decades.<sup>4</sup>

It was only after 35 years that Mendel's work was rediscovered by joint efforts of Correns, De Vries, Tschermak. The period between the publication of Mendel's paper and its rescue in 1900 was dominated by the development of the theory of evolution and its implications. There were, however, several real advances which helped to make Mendel's result acceptable. Amongst such advances were the knowledge of cytological details of fertilization and cell division, increasing emphasis on the importance of discontinuous variation and germplasm theory by Weismann. Weismann concluded that the cytoplasm found with germ cells is composed of "determinants" that transmit traits from parents to offspring and germplasm is not affected by the life experiences of the parents, which was a clear contradiction of the ideas of Lamarckism (i.e., inheritance of acquired characteristics).<sup>5</sup>

Significant contribution was also made by Pierre de Maupertuis, who studied hereditary traits such as extra digits (polydactyly) and lack of pigmentation (albinism), and showed from pedigree studies that these two conditions were inherited in different ways. John Dalton observed inheritance pattern in patients with color blindness and hemophilia. Color blindness is still sometimes referred to as Daltonism.<sup>3</sup>

Bateson was most active proponent of Mendel's work and he introduced many of now-familiar terms- such as *genetics*, for the subject itself; *zygote*, for the individual that develops from the fertilized egg, as well as for the fertilized egg itself; *homozygote*, *heterozygote*, and

*allelomorph*. Bateson usually used the word *factor*, which was later termed *gene* by Johannsen.<sup>6</sup>

Among this period, a quite different approach to study of heredity was developed by Francis Galton, cousin of Darwin, considered the father of Eugenics. He carried out various breeding experiments with animals.

Galton introduced the classic '*Twin method*', a methodology that studies twins and attempts to differentiate between genetic and environmental effects on the manifestation of a trait. This is usually done by comparing monozygotic (identical) and dizygotic (fraternal) twins. It is assumed that identical twins have the same chromosomal DNA and the two are genetically identical so any difference between them should be solely the result of environmental influence.<sup>7</sup>

The other classic method of estimating the influence of heredity is to study the family members, observing similarities and differences between mother-child, father-child, sibling pairs, since they share similar (50% of their genes in common on average) genetic background. In case of a strong genetic influence the trait of interest is usually more common in certain families compared with the general population.<sup>8</sup>

#### CONCEPTS OF CRANIOFACIAL GROWTH, ORTHODONTICS, AND GENETICS

Mathematical laws of inheritance of trait could be appreciated after the rediscovery of Mendel's experiments but the knowledge about of nature of gene, mechanism of gene action and its control was largely unknown. Orthodontists were practically interested in the postnatal craniofacial growth and the possibilities of modifying it. As a result many theories of craniofacial growth was proposed and investigated by variety of methods.

Major concern in the middle of the 20<sup>th</sup> century was the role of unique structures- such as sutures, cranial base, synchondroses, and mandibular condyle in craniofacial growth. Early research of postnatal development focused on nature of bone growth.

Influenced by the experiments of Sir John Hunter (1771), first general theory of craniofacial growth- the *Remodeling Theory* was proposed by Brash. He concluded that: 1) bone grows by apposition at surfaces; 2) growth of maxilla and mandible is characterized by deposition at posterior surface; 3) calvarial growth occurs via ectocranial deposition and endocranial resorption.<sup>9</sup>

By the end of first half of 20<sup>th</sup> century, Brodie (1941) gave his *Genetic Theory* of craniofacial growth, which stated that the persistent pattern of facial configuration is under genetic control and genes determine the overall growth control. Thus the primary role of orthodontist was to treat a malocclusion by moving teeth into a more harmonious position relative to the facial type; facial growth could not be affected by orthodontic treatment.<sup>10</sup>

Later in 1940s Weinmann and Sicher proposed the *Sutural Theory*, which considered sutures as an active area of bone growth and stated that the expansive proliferative growth of sutural connective tissue force the bones of the vault and circummaxillary complex apart.

James H. Scott and Melvin Moss were not convinced with the *Sutural Theory*. Scott in 1950s, through his descriptive histological analysis postulated the *Nasal Septum Theory* and stated that sutures are merely secondary and compensatory sites of bone formation and growth. The essential primary element directing craniofacial growth is the cartilages within the cranial base, particularly nasal septal cartilage.<sup>11</sup>

All these theories generally assumed that craniofacial growth is largely inherited, intrinsically regulated, predetermined and immutable. Major question that still remained unanswered was about “where do heredity and genes act, what is the mode of its action and control.”

This period also marked the beginning of the science of Developmental Genetics. In particular, research by Waddington clearly established the linkage between embryology and genetics by proposing to think of genes as organizers and “evocators” of development.<sup>12</sup>

In 1950, two major breakthroughs in genetics were (1) discovery of double helical structure of DNA by Watson and Crick and (2) the *Operon Theory* by Jacob and Monod.<sup>13</sup> These provided an explanation for how genes and whole groups of genes operate within common regulatory sequences that can be turned on and off to control transcription of mRNA and gene expression. This also provided a better understanding of the mechanism of development.

During 1950s and 1960s the major emphasis in orthodontics was on the specific location(s) of the “center(s)” at which the inherited traits determining craniofacial growth and form were actually expressed. Areas of growing skeleton that exhibit “tissue separating capabilities,” which included all craniofacial cartilages that are primarily under the control of heredity, were referred to as *growth centers*. Locations at which active skeletal growth occurs as a secondary, compensatory effect, lacking direct genetic influence were defined as *growth sites*.<sup>14</sup>

In early 1960s, Melvin Moss extending the concept of van der Klauuw, proposed the *Functional Matrix Hypothesis* of craniofacial development. This acted as a catalyst for functional paradigm, which emphasized the plasticity of development and growth of craniofacial skeleton. It also supported consideration of the use of dentofacial orthopedic techniques to correct a developing malocclusion or facial deformity.<sup>15</sup>

Moss, in a revisitation of the *Functional Matrix Hypothesis* and resolving synthesis of the relative roles of genomic and epigenetic (environmental) processes and mechanisms that cause and control craniofacial growth and development, concluded both are necessary. Neither genetic nor epigenetic factors alone are sufficient, and only their integrated activities provide the necessary and sufficient cause of growth and development. Moss further considered genetic factors as intrinsic and prior causes and epigenetic as extrinsic and proximate.<sup>11,17</sup>

In 1970s, Petrovic gave the *Servosystem Theory* of craniofacial growth based on cell physiology

and integrated biology, the major significance of this theory is that it emphasizes an approach to craniofacial growth research dealing with the expression of growth factors and signaling molecules that are true gene products influencing growth. It added that all craniofacial tissues are not alike in their ability to express intrinsic growth potential and to respond to functional, epigenetic and extrinsic factors.<sup>16</sup>

Thus it was clear that the development of craniofacial region is complex and there is no *Holy Grail* of craniofacial biology- no single theory of craniofacial growth.

### FIELD AND CLONE THEORIES

The *Servosystem Theory* emphasized the importance of genes and signaling molecules but the basic mechanism of gene action and its pathway was unknown until new discoveries unfolded the role of *Neural Crest Cells* and *Homeobox genes*.

It was postulated that different *neural crest cells* migrate to different specific parts of cranial face and dentition and form different *developmental/morphogenetic fields*.<sup>18,26</sup> Concept of *morphogenetic fields* originated from Ross Harrison's (1918) studies on newt forelimb development and was supported by *Spermann's embryological organizing centers*.<sup>19,25</sup> Weiss reaffirmed the interpretative value of the field concept.<sup>20,29</sup>

Opitz states that processes in *developmental fields* are self-organising, spatially coordinated and ordered, epimorphically hierarchial, temporarily synchronized, epigenetically interactive, developmentally constrained, and phylogenetically conserved.<sup>21,26</sup>

*Butler's Field Theory* states that mammalian dentition can be divided into several *developmental fields*, which include molar/premolar field, the canine field and the incisor field. Within each developmental field, there is a *key tooth*, which is more stable developmentally and on either side of this key tooth, the remaining teeth within the field become progressively less stable. Within molar/

premolar field, maximum variability will be seen for the third molars, second molars can also show variations, second premolars are more commonly affected than the first premolars. Within incisor field, the maximum variability will be seen for lateral incisors and within the canine field, maxillary canines are commonly impacted or ectopically erupted.<sup>21-23</sup>

Inger Kjaer described the *developmental fields* in human cranium and in the dentition. Different fields included the occipital and cervical spine field, theka field, frontonasal field, maxillary field, palatal field, and the mandibular field.<sup>13</sup> Spranger et al concluded that an intrinsic, nondisruptive disturbance of a developmental field will lead to a field defect.<sup>26,27</sup>

Osborn proposed the *Clone Model*, stating that a single clone of pre-programmed cells leads to the development of all the teeth within a particular class. Most recent work invokes a reaction-diffusion model in the region of a presumptive tooth, where activators induce placode formation while negative regulators are higher in interplacodal regions, which prevents tooth formation and, thus, accounts for orderly spacing of teeth.<sup>28,29</sup>

### EXPERIMENTAL STUDIES IN THE FIELD OF ORTHODONTICS

During 1930s, Professor Stockard conducted the most influential animal breeding experiment by crossbreeding dogs. His experiments indicated occurrence of dramatic malocclusion in his crossbred dogs, more from jaw discrepancies than from tooth size-jaw size imbalances. Thus it was concluded that independent inheritance of facial characteristics could be a major cause of malocclusion and increased outbreeding results in rapid increase in malocclusion accompanying urbanization. However, these experiments turned out to be misleading because many breeds of small dogs used in these experiments carry the gene for achondroplasia, resulting in underdeveloped midface.<sup>30</sup>

Much of the 20<sup>th</sup> century, focused on two major possibilities for the production of malocclusion by inherited characteristics. The first would be an inherited disproportion between the size and

shape of the upper and lower jaws, causing improper occlusal relationships. The second would be an inherited disproportion between the size of teeth and the size of the jaws, resulting in crowding or spacing.<sup>31</sup>

Primitive human populations in which malocclusion are less frequent than in modern groups are characterized by genetic isolation and uniformity. Thus it was concluded that the great increase in outbreeding that occurred as human populations grew and became more mobile was the major explanation for the increase in malocclusion in recent centuries.<sup>31</sup>

In 1971, Chung et al carried out a study in Hawaii, to examine the result of out breeding in human population. He concluded that the most likely explanation for the increased malocclusion seen in “civilization” is changed environment, such as food and airway effects, as the children of racial crosses are at no increased risk of malocclusion. In addition, the increase in malocclusion in populations recently moved into an industrialized lifestyle is too quick to be the result of genetic change.<sup>17,32</sup>

In 1975, Niswander noted that the frequency of malocclusion is decreased among siblings of index cases with normal occlusion, whereas the siblings of index cases with malocclusion tend to have the same type of malocclusion more often.<sup>33</sup>

In 1975, Harris et al showed that the craniofacial skeletal patterns of the children with skeletal class II malocclusion are heritable and that a high resemblance to the skeletal patterns occurs in their siblings with normal occlusion. It was concluded that the genetic basis for this resemblance is polygenic, and family skeletal patterns were used as predictors for the treatment prognosis of the child with a class II malocclusion.<sup>34</sup>

In 1983, Lavelle CL studied mandibular shape in mouse fed on hard and soft diet and showed that difference in shape of mandibular condyle was “slightly greater” among four different inbred strains of mice on a hard diet than on a soft diet for 6 weeks. It was concluded that the genetic background of an individual can influence the

response to environmental factors thus when the environment changed sufficiently, the response was different among animals with different genotypes that was not evident before the environmental change.<sup>35</sup>

King et al, in regards to human beings said that the substantive measures of intersib similarity for occlusal traits reflect similar responses to environmental factors common to both siblings. Malocclusions appear to be acquired, but the fundamental genetic control of craniofacial form often diverts siblings into comparable physiologic responses leading to development of similar malocclusions.<sup>36</sup>

In 1991, Harris and Johnson, from his longitudinal sib analysis, concluded that the heritability of craniofacial (skeletal) characteristics was relatively high but that of dental (occlusal) characteristics was low. For the skeletal characteristics, the heritability estimates increased with increasing age; for dental characteristics, the heritability estimates decreased, indicating an increasing environmental contribution to the dental variation.<sup>18,37</sup>

**Conclusion:** Discoveries about the nature of genome and of specific action of genes in regulation of craniofacial growth are continuing at an unparallel pace through The Human Genome Project and Genome-Wide Association Studies. It is not far when we will be able to identify the specific factors that cause craniofacial dysmorphogenesis, and the location of genes for these factors on the chromosome. A central question in this millennium is: how these discoveries will directly affect concepts and approaches to the treatment, how can the genomic and epigenetic factors be engineered and introduced into the treatment of an individual at appropriate time and in appropriate measure in order to produce a biologically meaningful and clinically efficacious effect.

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