Abstract:

In order to make an accurate diagnosis and growth prediction, the orthodontist should consider the role that genetics plays in determining the facial morphology of the patient. One of the major problems which have delayed progress in the investigation of the influence of heredity is the complex nature of multi-factorial inheritance. Though Class III malocclusion is thought to be a result of interaction of genes and environment, studies on family pedigree have pointed a probability of its monogenic dominant inheritance. Studies have also pointed that genes and the variation in their expression can be a factor in development of Class III malocclusion. Vascular endothelial growth factor (VEGF), insulin like growth factor-1 (IGF-1) and HOX 3 are few such genes. On a sub-molecular level, chromosomal loci (1p36, 12q23) harbor genes which increase the susceptibility towards mandibular prognathism. The influence of genetic factors on treatment outcome must be studied and understood in quantitative terms. Only then will we begin to understand how nature (genetics) and nurture (environment) together affect our treatment of our patients. This article reviews the role of nature (genetics) and how its influences the facial morphology.

Key words: genes, chromosomal loci, Class III malocclusion, heredity

Introduction

Class III malocclusion has been the subject of interest in many investigations, because of the challenges in its treatment. Angle (1899) classified the malocclusions based on occlusal relationships, considering the first permanent molar as the "key" of occlusion. Class III malocclusion is defined in cases that mandibular first molar is positioned mesially relative to the first molar of maxilla. A complicating factor for diagnosis and treatment of Class III malocclusion is its etiologic diversity. Its origin can be skeletal or dentoalveolar. The skeletal manifestation can be due to mandibular anterior positioning (prognathism) or growth excess (macrognathia), maxillary posterior positioning (retrognathism) or growth deficiency (micrognathia), or a combination of mandibular and maxillary discrepancies.
A wide range of environmental factors have been suggested as contributing to the development of Class-III malocclusion. Among those are enlarged tonsils, difficulty in nasal breathing, congenital anatomic defects, disease of the pituitary gland, hormonal disturbances, a habit of protruding the mandible, posture, trauma and disease, premature loss of the sixth-year molar and irregular eruption of permanent incisors or loss of deciduous incisors. Other contributing factors such as the size and relative positions of the cranial base, maxilla and mandible, the position of the temporomandibular articulation and any displacement of the lower jaw also affect both the sagittal and vertical relationships of the jaw and teeth. The position of the foramen magnum and spinal column and habitual head position may also influence the eventual facial pattern. The etiology of Class-III malocclusion is thus wide ranging and complex. The prevalence of Class III malocclusion has been described between 1% to over 10%, depending on ethnic background, sex, and age of the sample as well as the diagnostic criteria used. Previous studies have investigated the various skeletal types of Class III malocclusion. Sanborn distinguished 4 skeletal groups in adults with Class III malocclusion: 45.2% with mandibular protrusion, 33.0% with maxillary retrusion, 9.5% with a combination of both, and 9.5% with normal relationship. Similarly, Jacobson et al found that the highest percentage of adults with Class III malocclusion had mandibular protrusion with a normal maxilla (49%), 26% had maxillary retrusion with a normal mandible, and 14% had normal protrusion of both jaws. In contrast, Ellis and McNamara found a combination of maxillary retrusion and mandibular protrusion to be the most common skeletal relationship (30%), followed by maxillary retrusion (19.5%) and mandibular protrusion only (19.1%). In a sample of 50 adults with Class III malocclusion who subsequently had surgical correction, all had some mandibular prognathism; 22% also had an excessive mandible, and 14% also had a retrognathic maxilla. Till date, many investigations have been done to understand the genetics of class III malocclusion and on determining the influence of genes on the response of patients to orthodontic treatment. This article reviews the role of nature (genetics) and how its influences the facial morphology.
MODE OF INHERITANCE IN CLASS III MALOCCLUSION

Skeletal Class III malocclusion clearly has a significant genetic component. Familial studies of mandibular prognathism are suggestive of heredity in the etiology of this condition and several inheritance models have been proposed. It has been observed for many years that mandibular prognathism, and, perhaps to a lesser extent, maxillary deficiency runs in families.

The inheritance of phenotypic features in mandibular prognathism was first reported by Strohmayer and then by Wolff et al in their analysis of the pedigree of the Hapsburg family. Suzuki studied offspring of parents with mandibular prognathism from 243 Japanese families, and reported a frequency of 31% of this condition if the father was affected, 18% if the mother was affected and 40% if both parents were affected. Nakasima et al assessed the role of heredity in the development of Angle’s Class II and Class III malocclusions and showed high correlation coefficient values between parents and their offspring in the Class II and Class III groups. However the role of cranial base, the midfacial complex and the mandible in the development of class III malocclusion has not been clarified yet.

Saunders et al compared parents with offspring and siblings in 147 families and demonstrated a high level of significant correlations between first-degree relatives. Byard et al analyzed family resemblance and found high transmissibility for components related to cranial size and facial height. Lobb suggested that the shape of the mandible and cranial base are more variable than the maxilla or cranium. Nikolova studied 251 Bulgarian families and showed a greater paternal influence for head height and nose height. Manfredi et al found strong genetic control in vertical parameters and in mandibular structure in twins. In addition Johannsdottir showed great heritability for the position of the lower jaw, the anterior and posterior face heights, and the cranial base dimensions.

Heritability of craniofacial morphology has also been investigated among siblings; from parents to twins or from parents to off-spring in longitudinal studies. Horowitz et al demonstrated a significant hereditary component for the anterior cranial base, mandibular body length, lower facial height and total face height. Fernex et al found that
the sizes of the skeletal facial structures were transmitted with more frequency from mothers to sons than from mothers to daughters. Hunter et al\textsuperscript{35} reported a strong genetic correlation between fathers and children, especially in mandibular dimensions. Nakata et al\textsuperscript{36} demonstrated high heritability for 8 cephalometrics variables and reported that the father–offspring relationship was stronger than the mother–offspring relationship.

**ROLE OF GENES IN EXPRESSION OF CLASS III MALOCCLUSION**

Class III malocclusions can exist with any number of aberrations of the craniofacial complex. Deficient orthocephalization of the cranial base allied with a smaller anterior cranial base component has been implicated in the etiology of Class III malocclusions. Whereas the more acute cranial base angle may affect the articulation of the condyles resulting in their forward displacement, the reduction in anterior cranial size may affect the position of the maxilla. As well, intrinsic skeletal elements of the maxillary complex may be responsible for maxillary hypoplasia that may exacerbate the anterior crossbite seen in the Class III condition. Conversely, with an orthognathic maxilla, condylar hyperplasia and anterior positioning of the condyles at the temporo-mandibular joint may produce an anterior crossbite. Aside from the skeletal components, soft tissue matrices, particularly labial pressure from the circumoral musculature, may influence the final outcome of craniofacial growth of a child skeletally predisposed to Class III conditions. Indeed, as some Asian ethnic groups demonstrate an increased prevalence of Class III malocclusions, it is likely that the skeletal components and soft tissues matrices are genetically determined. Presumably, the co-morphologies of the craniomaxillary and mandibular complexes are likely dependent upon candidate genes that undergo gene-environmental interactions to yield Class III malocclusions.

Condylar cartilage grows in response to functional stimuli or mechanical loading. This in turn leads to mandibular growth. McNamara and Carlson\textsuperscript{37} hypothesized that class III malocclusion might be precipitated under these biomechanical conditions by the inheritance of genes that predispose to a class III phenotype. Studies have documented numerous genes which are involved in the phenotypic expression of mandible. Also
specific growth factors or local mediators are involved in condylar growth. The variable expression of such factors can lead to differential mandibular morphogenesis leading to a prognathic or retrognathic mandible.

Animal studies have shown that IGF-1 significantly increased when mandible was repositioned with a propulsive appliance\(^{38}\). Rabie et al.\(^{39,40}\) indicated that forward positioning of the mandible triggered the expression of Ihh and Pthlh, which promote mesenchymal cell differentiation and proliferation, respectively, and that these proteins acted as mediators of mechano-transduction to promote increased growth of the cartilage. Also an increase in transcription factors like sex-determining region Y and Runx2 was noted during mechanical loading of mandible. These factors induce differentiation of chondrocytes.

The discovery of genes implicated in condylar growth provides the possibility to identify the genes that make an individual susceptible to Class III malocclusion. Human studies support an autosomal-dominant mode of inheritance in two independent studies of the Class III phenotype\(^{41,42}\). Specifically, genome-wide scan and linkage analysis of mandibular prognathism in Korean and Japanese persons revealed that there was a statistically significant, although nominal, linkage of the mandibular prognathic trait to 3 regions\(^{43}\). Studies in mice also support the genetic basis of maxillary and mandibular size. Some investigators have used inbred mouse strains to confirm the hypothesis that the D12mit7 segment on mouse chromosome 12 determines maxillary growth\(^{44}\), while others applied Quantitative Trait Locus (QTL) studies in inbred mice to identify specific QTLs on mouse chromosomes 10 and 11 that are correlated with the anteroposterior length of the mandible\(^{45}\). The Hox families of genes are highly conserved master regulatory genes shown to play a definitive role in patterning the hindbrain and branchial regions of the developing head, up to and including structures derived from the second branchial arch. The HOX3 region contains at least 7 genes in a 160-Kb stretch of DNA, including Hoxc4, Hoxc5, Hoxc6, Hoxc8, Hoxc9, Hoxc10, Hoxc11, Hoxc12, and Hoxc13\(^{46}\). The \textit{COL2A1} (collagen, type II, alpha 1) gene, located between positions 12q13.11 and 12q13.2, encodes the alpha-1 chain of type II collagen found in cartilage. Previous studies in mice point to the rhizomelic effect of
Col2A1 mutations in overall somatic growth, but also confirm the importance of Col2A1 in craniofacial growth\textsuperscript{47}. Results from mouse studies of craniofacial growth show that a region on chromosome 12 is biologically relevant to craniofacial development and may be linked to the Class III phenotype. In an SMXA recombinant inbred strain of mice, the positions of the mouse chromosome 10 and chromosome 11 were determined to be responsible for mandibular length and corresponded to regions 12q21 and 2p13, respectively, in human chromosomes. These results suggest that the major gene(s) responsible for mandibular length are located in these regions\textsuperscript{45}. Though heterogeneity exists in the Class III phenotype, since different populations (Japanese/Korean and Hispanic) reveal that differing subtypes of the Class III phenotype share linkage to loci on chromosome 1\textsuperscript{43}, this may point to a common upstream regulator that affects both maxillary and mandibular development. Progress in the craniofacial genetics field toward human genetic mapping of the Class III trait is gradual but limited. The improved annotation of genetic and physical maps offers great future potential for identifying genes associated with this trait.

**DISCUSSION**

Various treatment modalities prescribed by the orthodontist are expected to lead to improved orofacial function. However some patients fail to show an improvement while others show a relapse. The reasons for this may be a lack of cooperation but other factors like growth, inherent lack of muscle adaptability are difficult to assess. Class III malocclusion, though less prevalent than other phenotypes, expresses in a more severe form. A complicating factor for diagnosis and treatment of Class III malocclusion is its etiologic diversity. Although the etiology is believed to be multifactorial, vast data is available now has paved towards a molecular diagnosis of malocclusion. As we are entering a nano era, with techniques like linkage analysis and association studies, it is now possible to indentify the causative genes responsible for this phenotype. While previous studies have contributed to our understanding of the inheritance of the Class III phenotype, there are still significant gaps
in the knowledge of the specific genetic contribution.
The influence of genetic factors on treatment outcome must be studied and understood in quantitative terms. Conclusions from retrospective studies must be evaluated by prospective testing to truly evaluate their value in practice. Only then will we begin to understand how nature (genetics) and nurture (environment) together affect our treatment of our patients.

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