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Impact of heredity on class III malocclusion

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Abstract
Class III malocclusion is believed to be a polygenic disorder that results from an interaction between susceptibility genes and environmental factors. Recent studies and advances in genetic sciences allowed the orthodontists to better understand the effects of genetics on the etiology of Class III malocclusion. Knowing the relative impact of genetic and environmental factors would greatly enhance the clinician's ability to treat malocclusions successfully. This article includes the current data on the association between Class III malocclusion and genetics, as a review of the etiological factors of skeletal anomalies from the genetic point of view.

Keywords: Genetics, malocclusion, association study

1. Introduction
The pioneering work of Gregor Mendel has initiated an interest in the field of genetics in the 19th century and afterwards genetics has been an important part of the studies carried in both biological and medical sciences [1]. Since the genetic proof is directly related to the diagnosis of familial dentofacial problems, modern orthodontists need to be aware of the basis of the genetic sciences, recent advances in the genetic researches and their application in the orthodontic practice. Once the genetic factors are determined and isolated, the clinician may clearly ascertain and distinguish the environmental factors and carry out the treatment plan according to etiology. Therefore, it is an inevitability to clearly outline the association between genetics and orthodontics.
It has been known for many years that skeletal Class III malocclusion has a significant genetic component. To date, many investigations have focused on understanding the genetic factors that underlie Class III malocclusion and on determining how these genetic factors might influence the response of patients to orthodontic treatment. The objectives of this review were to discuss the impact of heredity on the development of Class III malocclusion and to introduce the cause and the consequence relationships between genetics and Class III malocclusion.

2. Etiology and prevalence of class III malocclusion
According to Angle's classification, Class III malocclusion is defined in cases that mandibular first molar is positioned mesially relative to the first molar of maxilla [2]. It can be skeletal or dentoalveolar. Skeletal manifestations can be due to prognathism or macrognathia, retrognathism or micrognathia, or a combination of mandibular and maxillary discrepancies.
A wide range of environmental factors have been proposed as contributing to the development of Class-III malocclusion. Among those are enlarged tonsil, 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 [3]. Other factors include 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 [4]. The position of the foramen magnum and spinal column and habitual head position[5] may also influence the eventual facial pattern.
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 [5] 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.* [6] 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 [7] 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 [8]

3. 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. The inheritance of phenotypic features in mandibular prognathism was first reported by Strohmayer [9] and then by Wolff *et al.* [10] in their analysis of the pedigree of the Hapsburg family. Suzuki [11] studied offspring of parents with mandibular prognathism, 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.* [12] 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.* [13] compared parents with offspring and siblings and demonstrated a high level of significant correlations between first-degree relatives. Byard *et al.* [14] analyzed family resemblance and found high transmissibility for components related to cranial size and facial height. Lobb [15] suggested that the shape of the mandible and cranial base are more variable than the maxilla or cranium. Nikolova[16], in his study showed a greater paternal influence for head height and nose height. Manfredi *et al.* [17] found strong genetic control in vertical parameters and in mandibular structure in twins.

In addition, Johannsdottir [18] 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.* [19] demonstrated a significant hereditary component for the anterior cranial base, mandibular body length, lower facial height and total face height. Fernex *et al.* [20] 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.* [21] reported a strong genetic correlation between fathers and children, especially in mandibular dimensions. Nakata *et al.* [22] demonstrated high heritability for 8 cephalometrics variables and reported that the father–offspring relationship was stronger than the mother–offspring relationship.

4. Role of genes in expression of class III malocclusion

Condylar cartilage is an important site of growth in the mandible and it forms part of the temporomandibular joint as well. The condylar cartilage is categorized as secondary cartilage, which has distinct biological characteristics, and is considered to support the growth of the mandibular bone. Mechanical loading or functional stimuli might influence the responses of the condylar cartilage and the subsequent growth of the mandible. Experimental generation of Class III malocclusion in monkeys has been attributed to an increased rate of condylar growth. Therefore, McNamara and Carlson [23] hypothesized that the cartilage of the mandibular condyle is responsive to biophysical environmental changes, and it is highly likely that Class III malocclusion might be precipitated under these biomechanical conditions by the inheritance of genes that predispose to a Class III phenotype. A number of reports have documented the influence of various genes that are involved in the regulation of mandibular morphogenesis.

Recent research has focused on the expression of specific growth factors or other signalling molecules that are involved in condylar growth. Growth factors and cytokines are local mediators and can be secreted in response to mechanical strain. These mediators regulate cell proliferation and the expression of differentiation products by activating signal transduction pathways in the target cells. In an experimental model of enhanced condylar growth, Rabie *et al.* [24] 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. In another rat model, the expression of IGF-1 increased significantly when the mandible was repositioned by means of a propulsive appliance.In addition, growth factors such as Vegf and transcription factors such as the sex determining region Y (SRY)-box 9 (Sox9) and runt related transcription factor 2 (Runx2) play important roles in the differentiation of chondrocytes in the growth plate under conditions of mechanical loading or exposure to other stimuli. The genes that have been concerned in condylar growth by studies in the mouse might aid as potential candidates to increase our understanding of Class III malocclusion in humans. The discovery of candidate genes provides the possibility to identify genes that confer susceptibility to this phenotype. In the search for susceptibility genes that are involved in Class III malocclusion, polymorphisms in the afore mentioned genes and the genes for the molecules that they regulate will be prime targets.

5. Linkage analysis and association study of class III malocclusion

5.1 Linkage analysis

Linkage analysis is performed to determine the chromosomal loci that might harbour genes associated with a particular disease or phonotype. The helps to identify a genetic marker that is inherited by all family members that are affected by the disorder or trait, but is not inherited by any of the unaffected family members [25]. During linkage analysis, the segregation of chromosomal regions that are marked by genetic variants is followed in affected families to identify regions that co-segregate with the disorder or trait. However, this approach can only provide an approximate location of the gene of interest relative to a genetic marker, and further association studies are needed to identify the susceptibility genes. The results of genome-wide linkage analyses have suggested

several chromosomal regions that might harbour susceptibility genes for Class III malocclusion.

Yamaguchi *et al*. [26] were the first to map susceptibility loci to chromosomes 1p36, 6q25, and 19p13.2 in affected sibling pairs from Korean and Japanese families. Recently, another genome-wide study, which was carried out in four Hispanic families from a Colombian background, revealed five suggestive loci, namely 1p22.1, 3q26.2, 11q22, 12q13.13, and 12q23 [27]. Therefore, there is support for the existence of susceptibility loci on chromosome 1. The region 1p36 harbours positional candidate genes of interest, which include heparan sulfate proteoglycan 2 (HSPG2), matrilin 1, cartilage matrix protein (MATN1), and alkaline phosphatase (ALPL). Recently, it has been reported that HSPG2 is related to the formation of cartilage and to craniofacial abnormalities[28], and Matn1 and Alpl are considered to be markers for the formation of cartilage and bone, respectively.

Furthermore, in studies of craniofacial growth in mice, loci on murine chromosomes 10 and 11 were determined to be responsible for mandibular length, and these correspond to the human chromosomal regions 12q21 and 2p13, respectively [29]. This comparative result supports the hypothesis that the regions 12q23 and 12q13 are relevant to craniofacial development and might be linked to the Class III phenotype. Candidate genes of interest are located within these regions, which include the homeobox region (HOX3), IGF-1, and the collagen, type II, alpha 1 (COL2A1) gene. The HOX genes are believed to be pivotal in craniofacial development IGF-1 has been proven to be involved in the proliferative activity of condylar cartilage; and Col2a1 encodes type II collagen in cartilage and is important for craniofacial growth. Therefore, studies have proposed that the major gene(s) that are responsible for Class III malocclusion might be located at chromosomal loci 1p36, 12q23, and 12q13.

5.2 Association study

The aim of association study is to identify differences in the frequencies of genetic variants between ethnically matched cases and controls to find variants that are associated strongly with the disease [30]. If a variant is more common in cases than in controls, an association can be inferred. Such studies require relatively large sample sizes and phenotypes that are defined accurately. Association study can be based on candidate genes or can be genome-wide and free of hypotheses [31].They can be used to resolve and refine the candidate interval further [32]. Research on a Japanese population showed that polymorphisms of the gene growth hormone receptor (GHR) are associated with mandibular height. Zhou *et al*. [33] reported a similar conclusion from research on a Chinese population, but there is no direct evidence that shows an association with Class III malocclusion. In a case–control association study that included 158 people with mandibular prognathism, genotyped 106 single nucleotide polymorphisms (SNPs) on 1p36 across an 8.6-Mb critical interval and four candidate genes. The results of the study suggested that the EPB41 gene might be a new positional candidate gene that is involved in susceptibility to mandibular prognathism.

Genome-wide association study (GWAS) uses statistical tools that are comparable to those used in association studies based on candidate genes. However, instead of depending on candidate genes that are selected on the basis of previous knowledge of the disorder or phenotype, GWAS involves an unbiased scan of the whole genome and therefore is more probable to reveal genetic and physiological connections. It is known that the human genome contains many millions of SNPs, which can either cause changes in the phenotype directly or might tag nearby mutations that influence variation among individuals and susceptibility to specific phenotypes. Such GWASs allow researchers to sample 100 000 or more SNPs from each subject to capture the variation across the genome [34]. With the completion of the human genome project (HGP) in 2003, the pace of GWAS has been accelerated by several developments in science and technology: the availability of sequence data from the HGP; improved bioinformatic and statistical tools for handling large volumes of data [35], and high-throughput genotyping platforms [36].

6. Conclusion

Complicating factors for the 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. Progress in molecular biology has made it possible to recognize different genes that are involved in mandibular growth. A number of genes have been described as key regulatory factors that contribute to condylar growth under mechanical strain, and these genes could play a major role in the development of Class III malocclusion. As we are entering a nano era, with techniques like linkage analysis and association studies, it is now possible to identify the causative genes responsible for this phenotype. It has been suggested that a better understanding of the genetic variables that contribute to the Class III phenotype is necessary to develop new preventive strategies for the condition. These promising approaches could allow the clinician to select early courses of dentofacial and orthodontic treatments that are aimed at preventing the development of Class III malocclusion.

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