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Research Paper

Genotype-Phenotype Interrelationships in The Etiology of Malocclusions: A Narrative Review

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ABSTRACT: *Malocclusions are complex dentofacial alterations with multifactorial origins, involving interactions between genetic, epigenetic and environmental factors. This work proposes a literature review to investigate how the interaction between genotype and phenotype influences the etiology of malocclusions, in addition to specific variations, such as mandibular retrognathia and prognathism. Recent studies indicate that single nucleotide polymorphisms (SNPs) in genes related to craniofacial growth, such as those encoding growth factors and their receptors, are associated with mandibular and maxillary alterations. In addition, epigenetic research has shown that environmental factors can modulate gene expression, contributing to the observed phenotype. This review will address the main advances in the genetic and epigenetic bases of malocclusions, evaluating genomic and functional studies that explore potential biomarkers for early diagnosis and personalized treatments. The objective is to provide an integrated view that aids in the development of more accurate therapeutic strategies, aligned with the principles of precision diagnosis.*

KEYWORDS: *Orthodontics, malocclusion, maxillofacial abnormalities, genetics, phenotype.*

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I. INTRODUCTION

A Craniofacial growth and development represent a complex and fascinating phenomenon of human biology, derived from the continuous and dynamic interaction between genotype and phenotype. The genotype, a set of inherited genetic information, provides the initial biological architecture, determining the potential for the development of bone, muscle and dental structures; however, there is no isolated action, needing to be interpreted and modulated by the phenotype, which encompasses the expression of genes and the influence of environmental, functional and epigenetic factors [1, 2].

The prevailing view in orthodontics has long prevailed that genetics plays the primary role, while the environment has a limited impact. Studies with twin brothers, for example, have helped confirm the strong genetic influence on characteristics such as skull shape, mandibular growth pattern, and dental occlusion [3, 4]. However, as scientific research has advanced, it has become apparent that this relationship is much more complex. The genotype defines "what can be," but it is the phenotype that reflects the "what really is" shaped by a network of internal and external influences.

Craniofacial growth is a dynamic process, in which the facial skeleton responds to functional and biomechanical stimuli from the environment. Thus, Moss's Functional Matrix Theory (1962) [19] already highlighted that this growth does not occur independently, but in response to the functional demands of adjacent soft tissues. This concept has recently been enriched with new evidence demonstrating how the neuromuscular system, breathing, and even the oral microbiome can modulate facial growth [6, 7, 8].

Knowledge in digital technologies and molecular biology has brought powerful tools to investigate these processes. The use of tridimensional scanning, cone beam computed tomography (CBCT), digital cephalometric analyses, and advanced biomechanical modeling has allowed for a more accurate analysis of

morphological changes over time (Shuto et al., 2025). At the same time, genome-wide association studies have identified new genetic factors associated with specific craniofacial traits, expanding the understanding of the genetic basis of facial asymmetry, maxillomandibular discrepancy, and complex malocclusions [9, 10].

Another relevant aspect is the application of artificial intelligence (AI) and machine learning in predicting craniofacial growth. Predictive models based on large genetic and morphological datasets are being developed to anticipate growth patterns and aid in personalized orthodontic planning, which paves the way for precision orthodontics, in which interventions can be tailored to each patient's individual biological characteristics [22].

Craniofacial growth and development represent a complex synergy between genetic potential and the external influences that modulate its expression. The genotype provides the genetic "score," but it is the phenotype, with its ability to adapt and respond to the environment, that dictates the "rhythm" and "melody" of facial development. This new understanding not only enriches the field of craniofacial biology but also transforms clinical practice, allowing for more individualized and effective approaches in orthodontic diagnosis and treatment.

II. MATERIAL AND METHODS

Eligibility criteria

The bibliographic search was carried out in the Pubmed database (https://pubmed.ncbi.nlm.nih.gov). As inclusion criteria, articles were established in any language, through translation for reading, with a limitation of 10 years of publication in the literature (2015-2025). As search results, articles from clinical studies, systematic reviews and other literature reviews were included on the genetics and epigenetics involved in craniofacial growth and development, as well as malocclusion. There was no restriction regarding the language and status of the publications; however, there was a limitation of 10 years of publication in the literature (2015-2025), maintaining current knowledge on the subject.

Search strategy and sources of information

A search strategy was developed for the Pubmed database using controlled vocabulary (MeSH terms), synonyms and free terms. All search terms were worked on in English. Generic terms maxillofacial abnormalities, genetics, orthodontics-related phenotype and malocclusion were selected. The searches were conducted in Pubmed until June 2025.

Selection, data extraction and synthesis of information

The records retrieved from PubMed were downloaded from the scientific articles, performing a manual selection process. The titles and abstracts of the papers were initially reviewed to identify potentially eligible studies. Then, the studies selected in this phase were read in full to confirm their eligibility. In case of doubts, a second reviewer was consulted to make the final decision. After selection, the information was extracted in an Excel spreadsheet (Microsoft.). After data extraction, the information was synthesized in a narrative way.

III. RESULTS

Genetic mechanisms involved in malocclusion

The concept of gene used to have a rigid and immutable definition, as an indivisible part of DNA, in a similar way even to how the atom was understood in the early nineteenth century [27]. Currently, this concept in genetics constitutes that the essence of the gene can be defined as a segment of DNA, a unit of transmission that is characterized by the construction of physical characteristics that constitute the phenotype [27].

However, failures in this functioning constitute, in Orthodontics, alterations in bone and dental development, characterizing malocclusions.

Angle, in 1899 [1], described malocclusions for a better understanding among professionals in their diagnosis and classifications. Class I malocclusion stands out, although it presents a normal relationship between the maxilla and mandible bones, its etiology may be influenced by genetic factors, especially about genes associated with craniofacial and dental development. In this context, some of them have already been identified, such as MXS1, PAX9 and AXIN2, whose SNP variations (mutations that alter the genetic coding) predispose to this malocclusion. Other genes, such as ES-RRB, FGF3, FGF4, FGF9, GREM2, IRF6, JAG1, LHX8, and TWIST1 have also been detected as genes associated with dentofacial morphogenesis [17].

While Class I has a genetic basis but does not present considerable bone discrepancies, Class II and Class III malocclusions are characterized by these discrepancies between bone bases. Bone growth is known to be modulated by networks of epigenetic molecular interactions that regulate physiological processes such as metabolic pathways and signaling pathways. By participating in this process, some of these signaling pathways are essential in the construction of craniofacial morphology, whose phenotypic variations constitute Angle Classes II and III [10].

Among these pathways, fibroblast growth factor (FGF) and its receptors (FGFRs) stand out. FGFR2 has been recognized as a receptor of clinical interest due to its role in intramembranous ossification, a process in

which most facial bones are formed. SNP mutations in this specific receptor have been related to certain craniofacial changes, such as hypoplasia of the middle third of the face, craniosynostosis, and prognathism. Many studies have linked variations of this receptor, such as SNPs s2162540, rs2981578, rs1078806, rs11200014, and rs10736303 directly with Class II and Class III malocclusions [15].

Many genetic association studies, including cross-sectional surveys, case-control studies, and crossover studies, have identified those positively linked to Class II. Some studies have confirmed the relationship between this malocclusion and the MSX1, MATN1, MYOH1, ACTN3, GHR, KAT6B, HDAC4, and AJUBA genes. In total, at least 19 genes related to Class II malocclusion have been identified [16, 18].

Transforming growth factor beta 1 (TGFB1) is also relevant in bone development, especially about mandibular retrognathism, where four SNPs of transforming growth factors were associated with physiological bone control: rs1800469 and rs4803455 (TGFB1 gene), and rs3087465 and rs764522 (TGFBR2 gene). The SNPs rs3087465 and rs2237051 were associated with mandibular retrognathism, while the rs2227983 variant was identified as a candidate gene, suspected of being involved in a specific disease or characteristic due to its known location or function [24].

Regarding mandibular prognathism, present in Class III, the associated growth factors are IHH, PTHLH, VEGF, DUSP6, FGF23 and ADAMTS1. The genes ANT1, HSPG2, ALPL, EPB41 (gene 1p36) and IGF-1, COL1A1, COL2A1, HOX3 (genes 12q23 and 12q13) are genes known to play a role in condylar growth, and consequently, in mandibular prognathism [38]. In addition to these, genes ADAMTSL1, BEST3, C1orf167, CALN1, FGF12, FGF20, FGF23, FGF3, GLI2 (rs3738880 and rs2278741) and GLI3 were also identified, with a total of 53 genes determining Class III malocclusion [18].

The signaling pathways involved in craniofacial growth

The main genes that interact with the development of malocclusion are expressed by signaling pathways that modulate the maturation of bone and cartilage tissues. Among the most important are the pathways related to FGFR2, FGF (fibroblast growth factor) receptor, the insulin receptor cascade, and the transcription factors RUNX2 and NOTCH3 [10].

The role of the FGFR2 receptor in bone growth is given by the cellular differentiation of osteoblasts and apoptosis, and its clinical role is very significant in the construction of the sagittal plane of the facial bones. The most relevant findings related to it are the actions of proteins and metalloproteinases (enzymes that degrade proteins) that regulate their functioning in bone cells. These proteins and enzymes, curiously, have been linked to skeletal malocclusions, either directly through their actions on bone growth, or indirectly, when they are mutagenic encoded by genes already notoriously analogous to malocclusions, such as ALPL and ADAMTS9 [10].

FGFR2 activity is regulated, among other factors, by transcription factor 2 (RUNX2), which promotes the proliferation of pre-osteoblastic cells. In addition to this function, a study with mice demonstrated the action of RUNX2 in the formation of condylar cartilage, suggesting that the deficiency of this factor would be related to mandibular retrognathism, present in Class II [31]. Antagonistically, a deficiency in the NOTCH3 pathway is compatible with an increase in osteogenic differentiation on the lingual surface of the mandible, which can generate mandibular prognathism in skeletal Class III [6].

Environmental and epigenetic factors

Currently, it is known that it is possible to occur modifications in gene expression, orchestrated by environmental factors, without any alteration in the DNA sequence, which configures the study of epigenetics [14].

Epigenetics works by activating or inactivating the expression of genes, without changing the structure of any of them. That is, even when the traits have already been genetically orchestrated, environmental factors can modulate this gene expression. Thus, in craniofacial and dental development, several environmental factors can modify the intermaxillary relationships and their harmony with the skull [4].

Among the main epigenetic factors related to malocclusions are deleterious oral habits, such as pacifier, bottle, and finger sucking during childhood [33], lingual interposition, and abnormal swallowing [11].

Mouth breathing also causes changes in tongue positioning and cervical and body posture, in addition to generating an increase in vertical growth of the face, which generates an elongated facial pattern with greater angulation - characteristic of Class II malocclusion. due to poor sagittal and transverse growth in the maxilla caused by insufficient contact of the tongue against the palate [27, 28, 29].

Another factor known to alter the pattern of craniofacial development is obstructive sleep apnea syndrome (OSAS). This disorder is characterized by a collapse of the airways multiple times during sleep, causing interruptions in breathing and compromising the quality of rest. Junior et al, 2022 demonstrated that individuals with OSAS have variations in the morphological characteristics of soft tissues, such as airway constriction, changes in the diameter of the soft palate, variations in the bones of the face, and inferior positioning of the hyoid bone.

Although environmental factors are of paramount importance in the appearance of malocclusions, it is always necessary to remember that they do not act alone. Epigenetics is a science of convergence, where the outside (environmental factors) and the inside (genetic factors) come together to dictate the outcome. In other words, in the same way that external forces can modulate gene expression, genetic predisposition can regulate the impact of these forces. In the case of malocclusions caused by environmental factors, this concept is demonstrated by the ROMA (Risk of Malocclusion Assessment) index, which measures individual susceptibility to the risk of malocclusion based on epigenetic interaction. That is, it determines that the more evident the skeletal craniofacial changes already present in children, the greater their risk of developing malocclusion under the action of deleterious habits [11]. Thus, assessing the habits of a developing patient in conjunction with their skeletal growth is the best way to determine their risk, and therefore to decide the best therapeutic approach for that patient.

In view of this, one of the most enlightening approaches by which this interaction is understood is through studies with monozygotic twins (identical twins). Unlike dizygotic twins, they arise from a single zygote and have the same genetic load, and however, they can present discordant characteristics and manifest genetic diseases differently. Regarding craniofacial development, for example, monozygotic twins usually have the same dental anomalies and malocclusions [2].

However, a study conducted by Carvalho et al. (2019) [2] reported a case of monozygotic twins who had different occlusions. Both had a supernumerary tooth (mesiodens), giroverted and positioned on the left side of the maxillary central incisors, but only one of them had an anterior open bite - the one with a habit of digital suction. The presence and identical positioning of the supernumerary tooth in both demonstrates the strong genetic load in dental development, but the presence of malocclusion in only one of them demonstrates the action of environmental factors. It was also reported that although there was the anterior open bite, it was not severe, which attests to the statement that genetic predisposition regulates the impact of genetic factors.

Another similar study also reported a case of monozygotic twins who had different craniofacial and dental formations, where one had Class I malocclusion, with normal cephalometric parameters and slight crowding, and the other had Class III malocclusion, with accentuated vertical growth and evident disparity between maxilla and mandible. In this study, it was observed that the twin who had skeletal abnormalities had been born underweight compared to her sister, suggesting that aspects of the intrauterine and/or perinatal environment are also external factors that can influence a predetermined gene expression [25, 26].

Characterization of craniofacial phenotypes and morphology

Changes in dentofacial symmetry are not restricted to general facial profile conformations, the three-dimensional investigation of the arches reveals relevant morphological findings. Clinical studies conducted by Ichikawa et al. (2023) [13] compared the morphology of the mandibular arch between individuals with standard measurements (control group), and patients with mandibular prognathism (Class III), and demonstrated significant differences in arch shape and occlusal planes. The mandibular arch with prognathism showed punctual alterations, such as shorter intermolar distance and depth in the canine and molar regions. These changes in the distance between homologous teeth and in the depth of the arch result in a wider mandibular configuration in the anterior portion and narrower in the posterior portion, in relation to the control group. The authors suggest that these differences are due to a compensation of the arch due to a more anterior position of the mandible.

In this malocclusion, the depth of the maxillary arch is greater, and the intermolar distance is smaller [23]. It is relevant to mention that the Class II phenotype also involves variations in the morphology of the mandible, which has a shorter mandibular body than in Class III, in addition to posterior rotation of the mandibular ramus and anteriorization of the skull base [30].

While concepts such as beauty and aesthetics are relatively subjective, it is essential to understand the morphological patterns of the face, such as size, shape, and position, and how orthodontic treatment interacts with them. Dentofacial alterations, such as changes in angulation and protrusion, can also modify the shape of the lips and nose, generating a different perception of the face. Dental interventions that disregard facial contouring can accentuate existing asymmetries.

The genetic methodologies used in the studies

Several approaches have been used to identify point genes, genetic variants, and epigenetic interactions related to the study of craniofacial development and malocclusions. Among the main ones are genome-wide association studies (GWAS), epigenome-wide association studies (EWAS), quantitative trait loci analysis (QTL), RNA sequencing (RNA-seq), and polymerase chain reaction (PCR), including its real-time variation (PCT-RT) [15, 20, 21].

GWAS (Genome-Wide Association Studies) is widely used to associate genetic variants, such as single nucleotide polymorphisms (SNPs), with specific craniofacial phenotypes. Although this method is effective for correlating already identified genes with a given clinical condition, it does not determine causality [10]. PCR-

RT is used for real-time gene expression analysis. For example, Cunha et al. (2020) [5] used it to analyze the transcription levels of myosin heavy chains (MyHC) in Class II and III malocclusions.

The EWAS (Epigenome-Wide Association Studies) approach is applied to the investigation of epigenetic variations such as DNA methylation, histone modifications, and RNA interference, without alteration of the DNA sequence. Histone deacetylation, for example, regulates the contraction of fast muscle fibers encoded by the MHC type IIX gene, whose expression is affected in Class III patients. In addition, the KATB6 gene, with greater expression in the masseter muscle of Class III individuals, stimulates the transcription factor RUNX2, which regulates the expression of the FGFR2 receptor, involved in osteogenesis and development of condylar cartilage [5].

RNA sequencing (RNA-seq) is used to identify which genes are active in different types of tissue at certain times. In the studies by Gedrange et al. (2006) [8], this technique was combined with GWAS to identify myosin heavy chain mRNA levels of the masseter muscles of class II and III patients, before and after orthognathic surgery. MyHC type I levels were found to decrease by 87% after the intervention, while MyHC type II levels increased, which reinforces its impact on malocclusion progression, as well as bone development through muscle action [39].

Quantitative character loci (QTL) analysis is used to identify regions in the genome associated with ongoing traits, such as craniofacial growth patterns. Studies in animal models, such as mice, have identified specific regions on chromosome 7 that are related to the development of Class I malocclusions, such as anterior open bite [17].

These genetic mapping methods are fundamental in predicting and monitoring the development of craniofacial growth, especially about the sagittal growth of the face, as they can correlate variants specific to certain phenotypes and enable the understanding of an intrinsic network of molecular mechanisms that drive signaling pathways, bone development and muscle function. In general, these are techniques that allow a rich mapping of the genetic and epigenetic architecture involved in craniofacial morphology [34-36].

Prospects for genetic-based orthodontic treatment

Orthodontics, by investigating the role of mutations and genetic variations in the formation of the craniofacial complex, has made it possible to categorize biomarkers that cause the manifestation of different types of dentofacial phenotypes [37]. This knowledge, when added to clinical and cephalometric findings, not only enriches the diagnosis, but also opens doors to a new way of planning orthodontic treatment: personalized, accurate, and more predictable.

Gene therapy in orthodontics is complex and exciting; however, it demonstrates some possible limitations, such as triggering immunological reactions, oncogenicity, and gene inactivation due to cellular defense mechanisms [32].

As a result, genetics can no longer be a science away from dental offices to become an adjunct for orthodontists, helping them to establish a safer treatment plan, with predictable intervention choices according to the factors to which they are exposed by genetics as well as the variations imposed by epigenetics [19, 38]. From this, orthodontic treatment can be elaborated according to the biological needs of each patient, which leads Orthodontics to increasingly promising prognoses.

IV. DISCUSSION

The present review shows that craniofacial growth and development are multifactorial phenomena, resulting from the complex interaction between genetic (genotype) and environmental (phenotype) factors. Genetic studies have identified numerous genes associated with skeletal malocclusions, many of which act through critical signaling pathways, which control processes such as ossification, osteoblastic differentiation, and condylar growth, which are essential for facial morphology [12, 25].

In addition, genetic polymorphisms and epigenetic modifications are directly related to sagittal and vertical growth patterns. The presence of common variations between different types of malocclusions and dentofacial changes, such as open bite and prognathism, highlights the functional overlap of certain genes and suggests shared regulatory mechanisms [5].

V. CONCLUSION

Environmental factors, such as deleterious oral habits and mouth breathing, also modulate facial growth through epigenetic mechanisms, reinforcing the importance of early identification. Studies with monozygotic twins corroborate this point by showing significant phenotypic differences despite genetic identity, suggesting that the environment acts as a modulator of gene expression [25, 28].

The identification of genetic and phenotypic markers enables the construction of personalized and predictive orthodontic treatment plans, inaugurating an era of precision orthodontics.

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