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Facultad de Odontología

Especialización en Ortodoncia

"POLIMORFISMOS DE LOS GENES ACTN3 Y MYO1H Y SU ASOCIACIÓN CON LAS MALOCLUSIONES ESQUELETALES. UNA REVISIÓN DE LA LITERATURA."

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Autora:

Karen Viviana Novillo Cevallos.

CI: 0104514153

Correo electrónico: vivi_nc@hotmail.es

Autora:

Marcela Alexandra Picón Burbano

CI: 0105599906

Correo electrónico: marce-picon@hotmail.com

Director:

Diego Mauricio Bravo Calderón

CI: 0104514237

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Resumen:

El gen ACTN3 codifica las proteínas α-actininas-3 localizadas en las fibras musculares tipo II e intervienen en la función de los músculos esqueléticos, mientras que, el gen MYO1H codifica las proteínas miosinas de clase I de las fibras del masetero. El objetivo de la presente revisión es discutir los hallazgos sobre las maloclusiones esqueléticas y su asociación con los genes ACTN3 y MYO1H. Fueron consultadas las bases de datos digitales PubMed, Scielo, BVS, AJODO y Google Académico. La literatura indica que el crecimiento de los maxilares está modulado por la actividad muscular, misma que está determinada por la interacción de genes con factores medioambientales. Así mismo, se ha evidenciado que polimorfismos de los genes ACTN3 y MYO1H constituyen un factor de riesgo para maloclusiones esqueletales, por lo que, su detección permitiría la intervención temprana para evitar el desarrollo de alteraciones craneofaciales y en consecuencia tratamientos complejos y costos.

Palabras claves: Maloclusión. Gen. Polimorfismo.ACTN3. MYO1H.

Abstract:

The ACTN3 gene encodes α-actinin-3 proteins that are located in type II muscle fibers and are involved in skeletal muscle function, whereas the MYO1H gene encodes class I myosin proteins of masseter fibers. The present review aims to discuss the findings in scientific literature about the association between skeletal malocclusions and the ACTN3 and MYO1H gene polymorphisms. PubMed, Scielo, BVS, AJO-DO, and Google Scholar databases were consulted. The literature indicates that jaws' growth is modulated by muscle activity, which is determined by the interaction of genes with environmental factors. Furthermore, it has been shown that polymorphisms of the ACTN3 and MYO1H genes constitute a risk factor for skeletal malocclusions; therefore, their detection would allow early intervention to avoid the development of craniofacial alterations and consequently complex and expensive treatments.

Keywords: Malocclusion. Gene. Polymorphism. ACTN3. MYO1H.

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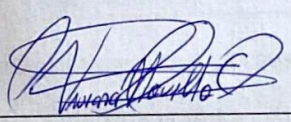

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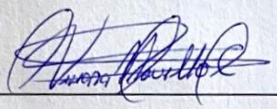

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Marcela Picón B.

MARCELA ALEXANDRA PICÓN BURBANO

C.I 0105599906

1. Introduction:

Orthodontics is the branch of Dentistry involved in the prevention, treatment, and correction of dentomaxillofacial anomalies [1]. In this context, skeletal malocclusion is defined as the abnormal relationship between the bones of the jaws due to inadequate development that affects their volume and proportion, which in turn can distort the normal balance of the face, have an impact on the occlusion due to the inappropriate position of the teeth and cause disorders in the temporomandibular joint [2-3].

Skeletal malocclusions can be transverse, vertical, or sagittal [4]. Specifically, sagittal malocclusions are diagnosed by cephalometric analysis of the measurement of the ANB, SNA, and SNB angles and are classified as [5-6]:

- Skeletal Class I is when there is a normal relationship between the maxilla and mandible.
- Skeletal Class II is characterized by a protruding maxilla, a retruded mandible, or both.
- Skeletal Class III in which there is evidence of maxillary retrusion, mandibular protrusion, or both [4].

Interestingly, studies report those skeletal malocclusions are the third most prevalent oral disease worldwide, preceded by dental caries and periodontal disease, and therefore represent a public health problem, generating functional alterations in mastication, swallowing, phonation, respiratory obstruction, alterations in the digestion, and temporomandibular

dysfunction [2-7]. In addition, to these physiological disorders, skeletal malocclusions have been reported to adversely affect intellectual well-being, social skills, and economic and psychological status due to facial aesthetic dissatisfaction [8].

The prevalence of craniofacial anomalies varies among populations, depending on genetic characteristics, socioeconomic status, geographic location, and various environmental factors [2]. For example, it has been verified that in Korea the most prevalent skeletal malocclusion is class III (47.49 %); but, in other regions of Asia class II (47 - 70%), followed by class III (12 - 21%) are more commonly observed [9-10]. Specifically, in Latin America there is also great variability in the results, for example, in Peru, the most frequent skeletal pattern was class II with 69%, while in Brazil the diagnosis of skeletal class III prevailed over classes II and class I [11-13].

Regarding the etiology of skeletal malocclusions, it should be understood that the size and growth of the facial bones and dental arches vary among themselves in the three planes of space and is determined by a genetic basis, with familial aggregation and hereditary tendency together with the influence of local or environmental factors including harmful habits and local or systemic diseases [3-14-16]. Therefore, skeletal malocclusions have a multifactorial origin, due to the interrelationship between the genome and environmental factors that influence their phenotypic expression, being that it has been proposed that the identification of the main genes and the determination of their biochemical action to a particular discrepancy of the jaws is the first approach necessary for the search of a solution [3-14-17].

Specifically, from the genetic point of view, it has been shown that the growth and development of the bones of the craniofacial complex are modulated by several genes such as ACTN3 and MYO1H; and that their variations can produce alterations in the composition and function of these structures, generating disturbances in maxillary and mandibular growth [18]. Therefore, this manuscript aims to discuss the scientific literature findings regarding the influence of ACTN3 and MYO1H gene polymorphisms in the development of skeletal malocclusions.

1. Materials And Methods

For this review article, databases including PubMed, Scielo, BVS, AJO-DO, and Google Scholar were consulted. The following keywords were malocclusion, gene, polymorphism, ACTN3, and MYO1H. Twenty studies were chosen for the final review and writing of this narrative review article.

1. Results

3.1 Genetic basis of disease

Molecular studies have shown that facial primordia's growth, structure, and pattern are controlled by a series of complex interactions involving growth factors and several genes [19].

The gene is the basic unit of inheritance, each gene has two copies called alleles, which control the development of each trait and determine the characteristics of individuals [19]. Structurally, genes are made up of nucleotide sequences with two types of nitrogenous bases: pyrimidines containing a single ring, thymine (T) and cytosine (C); and purines with two

rings, guanine (G) and adenine (A) [20]. Alterations in the nucleotide sequence of a gene modulate phenotypic variations and contribute to the etiology of various diseases [21].

When the nucleotide alteration occurs in ≤0.01% of a population, it is considered very rare, is called a mutation and has a significant physiological impact, and is, therefore, an etiopathogenic determinant of diseases with a simple transmission pattern such as syndromes [22]. Mutations are caused by errors during the DNA synthesis and include substitutions, insertions, deletions of nucleotides, and other DNA rearrangements [23].

On the other hand, there are other genetic variants denominated polymorphisms, which are considered common because they are more than 1% prevalent in a population, the most common of which is the single nucleotide polymorphism (SNP) that results from the substitution of a single nitrogenous base in the sequence of a gene [21-22]. Polymorphisms can contribute to the etiopathogenesis of complex diseases, but there is no one-to-one correlation between the presence of a polymorphic genetic allele and the occurrence of the disease since alleles associated with a disease are also found in unaffected individuals and some individuals with the disease do not have the associated allele [22]. Therefore, in complex diseases, the presence of polymorphism will not represent a definitive diagnosis of the disease and its development requires the interaction of genetic variation with multiple environmental factors [22].

As research has progressed, several genetic polymorphisms associated with conditions of the stomatognathic system have been identified; for example, the -1112 polymorphism of the IL-13 gene may be associated with susceptibility to chronic periodontitis [24]. In addition, some

polymorphisms can affect different parts of the organism, as is the case of the -1082*A polymorphism of the IL-10 gene, which is considered a risk factor for many diseases such as Epstein Barr virus infection, inflammatory bowel disease, sporadic Alzheimer's disease, chronic hepatitis, and gingivitis [25-29].

On the other hand, polymorphisms can also exert a protective effect, for example, a study carried out in a Mexican population found a higher frequency of the -308 A/A polymorphism of the TNF-α gene in healthy individuals than in people with gingivitis [30].

3.2 Influence of genetics on skeletal malocclusions

The onset of the genomic era at the beginning of the 21st century gave way to important scientific contributions, including the identification of genes responsible for craniofacial anomalies such as those for growth factors and transcription factors that control craniofacial morphogenesis, as well as genes that affect the growth of the condylar cartilage of the mandible both normally and during treatment [31-32].

In this context, candidate molecules have been identified as responsible for certain diseases and syndromes of genetic origin, such as Pierre Robin syndrome and Crouzon syndrome [33-34]. Specifically, Pierre Robin syndrome is caused by the alteration of the SOX9 gene on chromosome 17 and presents the classic triad of glossoptosis, micrognathia (hypoplastic and retropositionated jaw), and airway obstruction, while Crouzon syndrome was described in 1912 and consists of an autosomal dominant hereditary disease caused by a mutation in the C342Y gene, located on the short arm of chromosome 10, and is characterized by premature

closure of the cranial sutures, exophthalmos, hypertelorism, mental retardation, headaches, and mandibular prognathism [33-34].

Similarly, studies have verified that the most common variations such as polymorphisms are also related to alterations of the facial structures, for example, it was shown that cleft lip and palate are associated with SNPs of the FGF and TGFB3 genes, specifically, the latter gene participates in the processes of membrane degradation, remodeling of the extracellular matrix and in the transformation of the epithelial mesenchyme, which is indispensable for the confluence of the processes during the formation of the palate [35-36]. However, despite the extensive study of cleft lip and palate, the presence of a single candidate gene has not been consistently identified, so the variability found in the results of genetic studies seems to be directly related to the wide phenotypic diversity and ethnic heterogeneity of the populations studied [36-38].

Likewise, it has been estimated that approximately 150 genes/loci are associated with craniofacial conditions that present malocclusions among their clinical characteristics and studies in twins have determined a strong genetic influence on facial and dental characteristics such as middle and lower facial dimensions, dental space, dental arch dimensions, and tooth size [16-39-40].

Interestingly, it has been verified that masticatory muscles contribute to facial growth, specifically, vertical dimensions are influenced by the size and proportion of masseter muscle fiber types, and associations have even been described between genes involved in muscle activity and skeletal malocclusions [18-41-43].

In summary, these findings changed the paradigm of research in orthodontics, orienting it towards the search for biomarkers predictive of growth and tissue response to specific forms of treatment [31-43].

3.3 ACTN3 gene polymorphisms and skeletal malocclusion

The α-actinins are a family of cytoskeletal proteins responsible for actin-binding and cross-linking, are found in both muscle and non-muscle cells, they play an important role in the organization of thin actin filaments and the interaction between the sarcomeric cytoskeleton and the muscle cell membrane [44-46]. In skeletal muscle, α-actinin-2 and -3 are major structural components of sarcomeric Z-lines, cross-linking actin filaments with dense bodies located at the sarcomeric Z-line, to help arrange the myofibril matrix during muscle contraction [47]. Specifically, a-actinin-3 may act directly through structural functioning or cell signaling pathways for skeletal muscle composition and function [48].

The α-actinin-2 is found in all skeletal muscle fiber types, whereas an α-actinin-3 is restricted to most fast-twitch type II fibers thus potentially associated with good muscle performance [49-50]. In a study by Sciote et al; in neonates, three patients with congenital muscular dystrophy were identified who were deficient in a-actinin-3 and who clinically manifested muscle weakness, hypotonia, and arthrogryposis [41]. The α-actinin isoforms in skeletal muscle are important for maintaining sarcomeric registration through interactions with other proteins [44].

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The genes encoding these 2 closely related isoforms are located on different chromosomes, the ACTN2 gene located on the long arm of chromosome 1 and the ACTN3 gene on chromosome 11 [47].

Several years ago, a common genetic variation was identified in the ACTN3 gene that results in the replacement of an arginine (R) by a stop codon (X) at residue 577 (R577X) [51]. This variation creates two different versions of the ACTN3 gene, which are common in the general population: the 577R allele is the normal, functional version of the gene, whereas the 577X allele contains a sequence change that completely prevents the production of the functional α-actinin-3 protein [49]. Therefore, this second type of genetic variation can cause changes in muscle fiber proportions and metabolism, alterations in bone mineralization and has been associated with skeletal class II malocclusion [18]. Masseter muscle biopsies have shown that increased size or proportion of type II fibers is associated with skeletal deep bite, and decreased type II fibers are associated with skeletal open bite [41-52]. Interestingly, in European Caucasian populations, 18% of individuals have a total deficiency of α-actinin-3 protein due to homozygosity for the 577X polymorphism of the ACTN3 gene [45].

Specifically, two polymorphisms of the ACTN3 gene are related to masseter muscle function and Class II skeletal malocclusion, it is suggested that bone growth may be altered with the ACTN3 genotype, these are the SNPs located at rs1815739 and rs678397 [18]. The SNP rs1815739 is a substitution of cytosine for thymine at nucleotide 1586 located in exon 16, which results in the change of an arginine codon for a stop codon at residue 577 (R577X) and produces 3 genotypes: CC (normal), TC (heterozygous) and TT (without α-actinin-3) [18]. Additionally, SNP rs678397 is a cytosine to thymine substitution at nucleotide 15193

of an intron of the ACTN3 gene, producing 3 genotypes: CC (normal), TC, and TT, but, has no reported functional changes [18].

Interestingly, a clinical study, performed on Class II patients, found that 42% of the participants presented the TT genotype, 44% presented the heterozygous CT genotype and 14% were homozygous for the wild-type CC alleles, furthermore, it was demonstrated that the presence of the TT genotype, which lacks α-actinin-3, is a risk factor for developing Class II skeletal malocclusion [53].

Another study by Godel et al. identified the association between the R577X polymorphism of ACTN3 and skeletal Class II, deep bite, and the presence of temporomandibular joint disorders, manifested by muscle pain during mastication [54].

The results of the study by Zebrick et al. were similar for the rs678397 and rs1815739 polymorphisms and their association with skeletal class II, adding that individuals with the rs1815739 polymorphism showed significantly smaller diameters of type II fast fibers in the masseter muscles and clinically presented variations in vertical dimensions, specifically deep bite [18]. Likewise, a study conducted on 646 patients from 4 different regions of Brazil concluded that there is an association between the rs678397 and rs1815739 polymorphisms of the ACTN3 gene and skeletal malocclusions II and III [43].

3.4 MYO1H gene polymorphisms and skeletal malocclusions

Class I myosins are a superfamily of molecular motor proteins that are necessary for the structural and functional integrity of skeletal muscle, they bind actin and use energy from

adenosine triphosphate hydrolysis to generate force and movement along actin filaments, eight isoforms are expressed in mammalian cardiac and skeletal muscles [55-56].

Specifically, in the masseter and other fast-twitch skeletal muscles of the orofacial area, four myosin class I protein isoforms are expressed [57]. Myo1a to Myo1h isoforms are prominent in facial muscles as they are involved in several motile processes, including organelle translocation, ion channel activation, and cytoskeletal reorganization [58-59].

Muscles have broad effects on bone development, these effects influence the muscle forces generated in the areas of insertion to the bone, and this results in the modification of these specific areas, therefore, genetic alterations that affect muscles would also affect these skeletal areas [60-62].

Currently, more studies are needed to understand the mechanisms by which asymmetries and changes in craniofacial morphology develop, however one study highlights that alteration in the function of the masticatory muscles has effects on the face and neurocranium [63]. For example, mice with a hyper muscular phenotype presented a homozygous mutation of myostatin, considering that myostatin is a transcription factor that acts as a negative regulator of skeletal muscle growth; the mice presented more brachycephalic with smaller cranial vaults, decreased maxillary length, and the convex mandibular border [64]. Likewise, the morphology observed in the jaws of Eskimos is attributed to the characteristic of vigorous chewing, suggesting that muscular hyperactivity in the orofacial area intervenes in the modification of the bony structures [65]. Therefore, masticatory muscle function is a key environmental influence on these bony craniofacial areas through the application of force

during growth [52]. Human craniofacial skeletal dimensions correlate with masticatory muscle volume, which, in turn, is linked to the loads generated during normal function [66]. Studies of skulls from different Polynesian populations show rocker-shaped jaws with a convex lower edge, which may become evident during puberty due to increased muscle strength with growth [67]. In addition, the mandible loses the antegonial notch and the angle becomes more convex in appearance [68].

On the other hand, immunohistochemical studies in biopsies of the masseter muscle of patients with facial asymmetries due to mandibular deviations have identified that the type II muscle fibers influence the vertical length of the face, specifically the anterior facial height [41-69]. An increase in the area of the type II fiber on the side of the deviation (short side) was identified compared to patients who did not present deviations in which the fibers on the right and left sides had the same dimensions [69]. In general, all these studies indicate that there is an influence of the function of the masticatory muscles on craniofacial growth [41]. Regarding myosin, one study explored the orthologous patterns of myosin 1H (MYO1H) gene expression and identified 2 genes in zebrafish: myo1ha and myo1hb identical to human MYO1H, indicating relatively high conservation in the pharyngeal arches at early stages and in the jaw, brain and little in the trunk at developmental stages [70]. To determine specifically in which jaw tissue the gene is expressed, in situ hybridization was performed using sox9a and myog markers for cartilage and muscle, respectively; and it was verified that MYO1H orthologs were mainly expressed in zebrafish jaw cartilage [70].

Clinically, previous studies evidenced significant associations between anterior facial height and type II isoform in the masseter of orthognathic surgery patients, indicating an association between masseter composition and craniofacial morphology (especially vertical dimension) [18].

The genes encoding myosins are located on chromosomes 11 and 17 (Leinwand, 1983). Studies carried out in adult patients of various races evaluated the association between the SNP rs10850110 polymorphism of the MYO1H gene and Class II and Class III skeletal malocclusions, resulting in a relationship between genetic variation and mandibular prognathism, patients who presented the polymorphism developed Class III malocclusion [71-74].

Likewise, other studies in Class III patients showed a statistically significant association of mandibular prognathism with the rs10850110 polymorphism, and the A/G genotype of subjects with this malocclusion was significantly different from that of controls [75-76]. It was even concluded that the A/G genotype was associated with a significantly higher risk of skeletal Class III due to mandibular prognathism [75].

Additionally, a study in 160 African-American women with the G/G genotype of the rs10850110 polymorphism revealed that four of the eleven measures comprising the Holdaway soft tissue analysis had statistically significant differences, suggesting that genetic variation may play a role in the development of the soft tissue profile in patients with mandibular prognathism [77].

On the other hand, a study conducted on 646 Brazilian patients concluded that there is an association between genetic variation rs10850110 of the MYO1H gene with Class I and II

skeletal patterns, thus reflecting that the association between a polymorphism and malocclusions may differ depending on the population studied [43]. Finally, another MYO1H gene polymorphism, SNP rs3825393, was shown to be associated with the manifestation of mandibular retrognathism in a small population [78].

1. Conclusion

In conclusion, the growth and size of facial bones and dental arches result from the interaction between genotype and multiple environmental factors. In this context, it has been shown that variations in muscle activity genes, ACTN3 and MYO1H, are associated with the development of Class II and III skeletal malocclusions. It is necessary to confirm these results in different populations to consider these polymorphisms as genetic biomarkers predictive of the risk of malocclusions and as determinants of early interceptive intervention that would aim to avoid the high costs of complex treatments necessary to correct skeletal facial alterations.

1. Ethical Statement

This paper has never been published before and is not being considered for publication elsewhere.

2. Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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