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Polymorphic Variants across Population of the Growth Hormone Receptor with Mandible Prognathism: A Systematic Review

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Abstract

Genetic influences are critical for determining mandibular protrusion in class IIImalocclusion cases, and growth hormone receptors (GHRs) are thought to have an essential impact on craniofacial bone growth. This review aimed to assess the association between GHR gene polymorphism variants and mandibular morphology. Studies were extensively searched using PubMed and Google Scholar until December 2020. The study design according to PECOS was: P, class III malocclusion; E, GHR polymorphism; no polymorphism in C, GHR; O, linear dimensional changes in maxillary and mandibular measurements; and S, cross-sectional and case-control studies. Selected studies were of acceptable methodological quality on a 10-point scale. A preliminary search identified 107 studies; after excluding duplicate abstracts, 63 studies were screened. Nine studies were subsequently included in the systematic review. Conclusion Polymorphic variants at rs6180, rs6182, and rs6184 in the GHR gene were associated with condylion-gonion measures in Asians and Turks but not in Colombians and Egyptians.

Keywords

- polymorphism
- *GHR* gene
- class III malocclusion
- mandible prognathism

Introduction

Craniofacial morphology is influenced not only by genetic components but also by environmental complexes. The effects of these components are related to size and craniofacial characteristics. Growth hormone (GH) also has a vital role in the growth of the craniofacial complex and its development through direct or indirect size regulation. The angular relationship between craniofacial structures and GH receptor (GHR) affects mandibular condyle growth.[1,2]

The anterior pituitary gland facilitates the regulation of the maxillofacial complex growth development, which produces GH. Insulin-like growth factor-1 (IGF-1) in the axis plays a role in normal metabolism and thus significantly regulates the effect on the growth and development of postnatal hard tissue. GH originates in the anterior pituitary and produces GH, acting directly on tissues through IGF-I production.[1,3]

Several previous studies have investigated the association between the variants of the *GHR* gene and craniofacial morphology in the population in general, and the results

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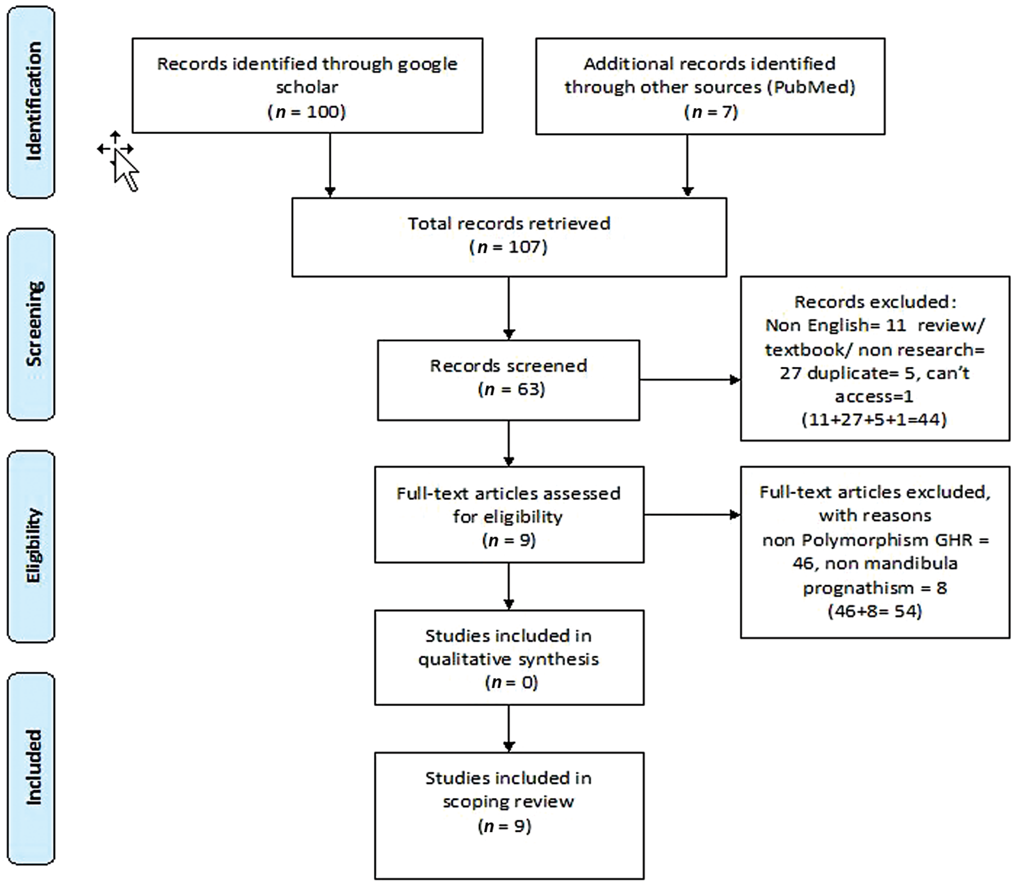

Fig. 1 PRISMA diagram

show that class malocclusion in the cases of class III is more common in Asian populations than in other populations. In addition, several studies have also reported a low incidence of class III malocclusion (~1–5%) in Caucasian, American, European, and African populations. These results indicate that genetic factors play a role in craniofacial morphology.[4] This review aims to evaluate and discuss variant polymorphisms in GHR in different populations.

Methods

Search Strategy

Electronic databases were used for the initial selection: PubMed (2000–2020) and Google Scholar (2000–2020). No filters or restrictions were used in the search. Descriptors were selected from previously searched Medical Subject Headings (MeSH) terms and the most cited ones from relevant previous publications. Search was performed using the following terms in MeSH and their combinations: "polymorphism, genetic" (MeSH term) or "polymorphism, mononucleotide" (MeSH term) and "Growth hormone receptor" (MeSH term) or "growth hormone-binding protein" (MeSH term) and "malocclusion, angle class III" (MeSH term) or "protrusion" (MeSH term) or "mandible" (MeSH term) or "Skeletal Class III Malocclusion" and "Population." In addition, a manual search of the bibliographies of the final selected articles was performed to identify any relevant articles that were not previously identified. The detailed search protocol is explained in the Preferred Reporting Items Stated by the Systematic Review and Meta-analysis (PRISMA; ►**Fig. 1**).

Eligibility Criteria

This study was conducted concerning the PRISMA.[5] The eligibility criteria were imposed as original, cross-sectional, case-control studies that assessed whether polymorphisms in the GHR were associated with patients' skeletal malocclusion of Angle's class III and mandibular protrusion. Unpublished manuscripts, theses, dissertations, book chapters, and case reports were excluded.

Study Selection

Two reviewers independently read all retrieved article titles and abstracts. The full text was obtained if a reviewer deemed the publication to meet the inclusion criteria. Abstracts that were potentially eligible and those that did not provide sufficient information were included in the full-text analysis. After evaluating the full text, disagreements about eligibility were resolved by consensus, and when disagreements persisted, a third reviewer was invited to make the final decision.

Data Extraction

Two reviewers independently performed data extraction. General information was collected from each article. In addition, specific characteristics were collected: author/year, ethnicity/country, age range, sample size, case definition, cephalometric analysis methods used to assess facial measurements, molecular biology techniques, and authors' conclusions.

Quality Assessment

Articles were scored on a 10-point standard scale for published recommendations to assess the quality of epidemiological and genetic association studies. Each quality criterion was rated as present (yes, score 1) and absent or uncertain (no, 0).[6] Two authors independently graded all articles. In any disagreement, a consensus is reached on the final score. The final quality rating is the sum of all components, and each item is assigned a rating from 0 to 10. Papers are divided into three categories based on the following scores: (1) high methodological quality: eight or more criteria are suggested; (2) medium methodological quality: five to seven criteria are proposed; and (3) low methodological quality: four or more. The recommended standard is less standardized. Therefore, this study was also divided into strong, moderate, and low-quality evidence.

Result

The extracted data from the studies included in this review are listed in ►**Table 1**. Six studies were conducted on Asian populations,[1,2,7–10] and one study each was born in Turkey,[11] Egypt,[12] and Columbia.[13] Other results are the qualitative scores of the articles, presented in ►**Table 2**; seven studies were classified as high methodological quality.[1,2,7,9,10,12,13] One study was classified as methodological quality due to incomplete data reported in the results section.[11]

Discussion

This review suggests that GHR polymorphisms are related to craniofacial development, particularly the mandible, and may be genetic markers of mandibular protrusion.[14] GH is a crucial somatic cell growth regulator through its pleiotropic effect on metabolism systemically and local bone growth plates; it is secreted by the pituitary gland that binds to receptors on the cell surface of target tissues (GHRs) which will trigger a cascade of rapid intracellular signaling.[15]

The biological role of growth hormone is to bind to the GHR, so the protein on almost every cell membrane in the body has domains of a 246 long extracellular (GH-binding) amino acid, the transmembrane, and a 350 long intracellular (cytoplasmic) amino acid. The GHR protein itself consists of a total of 638 residues. Furthermore, GH binds to GHR and induces a serial conformational event in homodimer receptors, promoting receptor interaction through their relative rotation and location closer to the cell membrane.[16]

The location of the *GHR* gene is proximally on the short arm of chromosome 5 (region p13.1-p12) that encodes the human GHR protein. Nine coding exons are contained in these genes spanning at least 87 kilobase pairs of chromosome 5. The last 11 base pairs of the untranslated 5′ region are encoded by exon 2 and the first amino acid of the extracellular domain. The remaining bulk extracellular domains are encoded by exons 3 to 7; exon 8 encodes the transmembrane domain; and exons 9 to 10 encode the untranslated intracellular and 3′ domains. Moreover, the gene contains several additional exons in the 5′ region, which are not translated.[16]

The family of transmembrane cytokine receptors from which GHR is derived has no intrinsic enzymatic activity; the cytoplasmic domain of GHR associates with tyrosine kinase Janus kinase 2 (JAK2) rather than activating intracellular signaling.[15] An enzyme-like receptor is a protein that passes through the membrane only once. Enzyme-linked receptors have hormone-binding sites outside the cell membrane, while on the inside are the catalytic or enzyme-binding sites. Hormones bind to the extracellular portion of the receptor; thus, enzymes directly inside the cell are activated. A small number of various hormones are facilitated by receptor tyrosine kinase signaling (e.g., fibroblast growth factor, growth factor, hepatocyte growth factor, IGF-2, leptin, prolactin, vascular endothelial growth factor).[17] Binding of growth hormone to GHR results in rapid binding of JAK2; JAK activation is associated with most pathways in GHR and plays a crucial role in signal transduction in the pro-growth axis. GHR is primarily transduced through the JAK2 signal transducer and activator of the transcription (STAT) pathway.[18]

The GH promotes dimerization upon binding the two GHR proteins, resulting in a conformational change triggering the activation of the associated JAK2 tyrosine kinase due to the exposure to its kinase domain. Furthermore, the activation of JAK2 will induce cross-phosphorylation of two adjacent JAK2 proteins and phosphorylation of tyrosine residues in the cytoplasmic domain of GHR. Signal converters and activators of transcription (STAT) are recruited to phosphorylated tyrosine, where they become substrates for JAK2. While STAT1, STAT3, and STAT5a can also be recruited to the GHR, STAT5b is an essential mediator of GH signaling.[13] Members of the JAK family are mainly expressed in different cell types, except for JAK3, whose expression is restricted to the hematopoietic lineage. JAK1 and JAK2 are involved in various physiological activities such as hematopoiesis, immunity, development, and growth.[19]

A polymorphism in the GHR results in a deletion of exon 3 (d3-GHR) with a homozygous allele frequency of approximately 12%. The entire GHR exon 3 sequences were deleted, resulting in a GHR protein lacking 22 amino acids in the extracellular binding domain. The resulting protein (d3-GHR) contains aspartate residues instead of alanine residues at the exon 2 to 4 junction. The consequent deletion affects exons and sections on introns 2 and 3.[12,16]

The mandibular protrusion is a strange relationship between the mandible and the base of the skull, characterized by excessive protrusion of the mandible. Facial contours and soft tissue relationships can quickly diagnose defects. The lower area is enlarged due to the protrusion of the mandible.

Table 1 Characteristics of the included studies

No.	Title	Author (year)	Objective	Specimen	Polymorphism GHR	Mandible prognathism	Year of research	Research methodology	Population	Samples	Result
1	Growth hormone receptor gene variant and three-dimensional mandibular morphology	Nakawaki et al (2017)[1]	Examine the relationship between three-dimensional (3D) mandibular morphology and growth hormone receptor (GHR)	Saliva	*GHR* genes rs6184 and rs6180	Mandibular length and volume were measured by Autotracer in the outer circumference of the cortical bone in all slide using Analyze			Japanese	178	Associated between GHR single nucleotide polymorphisms (SNPs) rs6180 with distances left and right coronoid
2	Association of the P516T and C422F polymorphism of the growth hormone receptor gene with facial dimensions	Dalaie et al (2019)[7]	Evaluate growth hormone receptor (*GHR*) gene polymorphism in relation to facial dimensions	Blood	Polymorphism of *GHR* genes P516T and C422F	Mandibular prognathism group: skeletal class III appearance (ANB and Wits less than zero) and mandibular prognathism (SNB $>$ 82 degrees); Control group: patients' appearance 2 degrees $\leq$ ANB $\leq$ 4 degrees and 0 mm $<$ Wits $\leq$ 2 mm	2015–2016	Observational case-control study	Iranian	125: 65 mandibular prognathic; 60 control	• No correlation between mandibular prognathism and SNPs rs6184 • P516T polymorphism associated with ramus and lower facial height in mandibular prognathism
3	The P516T polymorphism of the growth hormone receptor gene has an inhibitory effect on mandibular growth in young children	Sasaki et al (2009)[8]	Assess whether this mutation affects mandibular during early childhood	Saliva	Single nucleotide polymorphism *GHR* gene P516T	Cephalometry trace for mandibular size (Cd-Go, ramus length; Pog'-Go, mandibular body length and Gn-Cd mandibular length)			Japanese	60: 33 mandibular prognathic; 27 control	P516T heterozygous mutation did not account for the difference between mandibular protrusion and normal occlusion
4	Association analysis between rs6184 and rs6180 polymorphism of growth hormone receptor gene regarding skeletal-facial profile in a Columbian population	Tobón-Arroyave et al (2018)[13]	Examine the association between the rs6184 and rs6180 polymorphic variants of the growth hormone receptor (GHR) gene and skeletal-facial profile in Columbian people	Saliva	Single nucleotide polymorphisms (SNPs) GHR rs6180, rs6182, and rs6184	Analyze skeletal-facial profile, lateral cephalogram, with digital pan/ceph system		Cross-sectional, observational, analytic study	Columbian	306	Result do not support that rs6180 SNP in the gene GHR rs6184 alone or in combination with other SNP in GHR may account for significant horizontal and longitudinal variations in mandibular morphology

Table 1 (*Continued*)

No.	Title	Author (year)	Objective	Specimen	Polymorphism GHR	Mandible prognathism	Year of research	Research methodology	Population	Samples	Result
5	Association of growth hormone receptor gene variants with mandibular form in an Egyptian population	Adel et al (2017)[12]	Confirm GHR variants rs6180 and rs6184 associated with variations in mandibular form	Saliva	Single nucleotide polymorphisms rs6180 and rs6184	11 points from lateral cephalogram and 6 from posterior anterior cephalogram: Point A (the most posterior on the anterior contour of the upper alveolar process); Point B (the most anterior on the anterior contour of the lower alveolar process); Cd (condylion); Cor (coronoid); Gn (gnation); Go (gonion); Id (infradentale); Me (menton); N (nasion); Pog (Pogonion); S (sella turcica)		Cohort	Egyptian	191	No correlation between the rs6180 variant and mandibular form; rs6184 frequency very low; the present study shows that both the rs6180 and rs6184 variants have no association with variations in the mandibular form in the Egyptian population
6	Relationship between P516T and C422F polymorphism in growth hormone receptor gene and mandibular prognathism	Bayram et al (2014)[11]	Evaluate allele and genotype frequencies of the P516T and C422F polymorphic sites of the *GHR* gene and the relationship between mandibular prognathism and these two SNPs	Blood	Single nucleotide polymorphisms P516T and C422F	Mandibular prognathism group: ANB and Wits values less than 0 degrees; Control Group: ANB angle 2–4 degrees and Wits value 0–2			Turks	200: 101 class III malocclusion after or before orthognathic surgery; 99 normal occlusion	C422F and P516T heterozygous polymorphisms of the GHR gene did not justify the difference between the mandibular prognathic group and control group in this population; subjects with CA genotype of P516T have a greater effective mandibular length (Co-Gn) and lower face height (ANS-Me) than those with genotype CC
7	Association of the growth hormone receptor gene polymorphism with mandibular height in a Korean population	Kang et al (2009)[9]	Study the association between a GHR polymorphism (d3/fl-GHR) that result in genomic deletion of exon 3 and craniofacial	Saliva	Single nucleotide polymorphisms (SNPs) C422F (rs6182), S473S (rs6176), P477F (rs6183), I526L (rs6180), and P516T (rs6184)	Cranial base length (nasion sella; N-S), maxillary length (A'-PTM'), overall mandibular length (gnation-condylion; Gn-Co), mandibular corpus length			Korean	159: 87 class I, 44 class II, and 28 class III	There is a significant association between the P561T and C422F polymorphisms of GHR and mandibular

(*Continued*)

Table 1 (*Continued*)

No.	Title	Author (year)	Objective	Specimen	Polymorphism GHR	Mandible prognathism	Year of research	Research methodology	Population	Samples	Result
			morphology and to study association between GHR genotypes in exon 10 and craniofacial morphology			(pogonion-gonion; Pog-Go), and mandibular ramus height (condylion-gonion; Co-Go)					ramus height in a Korean population
8	Further evidence for an association between mandibular height and growth hormone receptors (*GHR*) gene in Japanese population	Tomoyasu et al (2009)[2]	Confirm the SNPs in the *GHR* gene are associated with mandibular height	Saliva	Single nucleotide polymorphisms C422F (rs6180), S473S (rs61176), P477F (rs6183), I526L (rs6180), and P561T (rs6184)	Measured cranial base length (nasion-sella), maxillary length, overall mandibular length (gnation–condylon), mandibular corpus length (pogonion-gonion), and mandibular ramus height (condylion-gonion)			Japanese	167	There is an association between GHR polymorphisms P516T and C422F, and mandibular ramus height
9	Growth hormone receptor gene variant and mandibular height in the normal Japanese population	Yamaguchi et al (2001)[10]	Evaluate quantitatively the relationship between craniofacial morphology and the Pro516Thr (P516T) variant in the GHR gene	Blood	Single nucleotide polymorphism GHR P561T	Cephalometric reference points and lines used to assess: N-S cranial base length; A'-PTM maxillary length; Co-Go mandibular ramus length; Go-POG mandibular corpus length; Co-Gn overall mandibular length; ANB position of maxilla and mandible			Japanese	100: 50 men; 50 women	The normal Japanese population without P516T had significantly greater mandibular ramus length; there is relationship between the P516T variant at the GHR gene locus and mandibular length

Table 2 Methodological scoring protocols

Criteria evaluated	Dalaie et al (2019)[7]	Tobón-Arroyave et al (2018)[13]	Adel et al (2017)[12]	Nakawaki et al (2017)[1]	Sasaki et al (2009)[8]	Bayram et al (2014)[11]	Kang et al (2009)[9]	Tomoyasu et al (2009)[2]	Yamaguchi et al (2001)[10]
Control group	1	1	1	1	0	1	1	1	1
Hardy–Weinberg equilibrium	1	1	0	1	0	1	1	1	0
Case group	1	1	1	1	0	1	1	1	1
Reproducibility	1	1	1	1	0	1	1	1	1
Blinding	0	0	0	0	0	0	0	0	0
Power calculation	0	0	0	0	1	0	0	0	0
Statistics	1	1	1	1	1	0	1	1	1
Corrected statistics	1	1	1	1	1	1	1	1	1
Independent replication	1	1	1	1	0	0	1	1	1
Compilation of reported association and outcomes	1	1	1	1	1	1	1	1	1
Score	8	8	7	8	4	6	8	8	7

Some patients may develop severe long-face syndrome. The prominence of the jaw is also associated with incorrect or no lip contact. Lip and mouth closure is not feasible in many patients because this feature is often associated with anterior crossbite or open bite at the anterior or lateral occlusal site. For most patients, the side effects are not only facial aesthetics but also the ability to speak, chew, and pronounce.[20]

Angle class III malocclusion prevalence varies widely between and within populations, with the highest incidence in Asian populations.[1,2,7–10] The etiology of class III malocclusion is very broad and complex, related to environmental and genetic factors. Class III malocclusion may originate from teeth or bones, so accurate classification of malocclusion is essential for good clinical management. This article describes the optimal timing and management of class III malocclusion in adolescence. Class III malocclusion was relatively high in the Chinese and Malaysian populations (15.69 and 16.59%, respectively), while the prevalence in the Indian population was relatively low compared with other ethnic groups. In the United States, the prevalence of class III malocclusion is only approximately 1% of the general population and only 5% of orthodontic patients.[1,2,7–10,21]

Conclusion

Our systematic review further demonstrated the association between rs6180, rs6182, and rs6184 polymorphic variants in GHR and condylion-gonion measures in Asian populations. On the other hand, the evidence for the relationship between Colombian and Egyptian people was low.

Conflict of Interest
None declared.

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