ASSOCIATION BETWEEN P561T POLYMORPHISM IN GROWTH HORMONE RECEPTOR GENE AND MANDIBULAR PROGNATHISM: SYSTEMATIC REVIEW AND META-ANALYSIS

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Palavras-chave: Polimorfismo Genético. Classe III de Angle. Prognatismo. Nucleotídeo Único. Proteína Ligante à Somatotropina.

RESUMO

Objetivo: Por meio de uma revisão sistemática e meta-análise, o objetivo deste estudo foi avaliar a associação entre o polimorfismo P561T em GHR (rs6184) com a maloclusão de Classe III esquelética em diferentes populações. **Métodos:** Uma ampla pesquisa de estudos foi realizada utilizando os bancos de dados PubMed, Web of Science, Scopus, Cochrane, Google Scholar e Open Grey até dezembro de 2018. O desenho do estudo de acordo com o PECOS foi: P-Pacientes ortodônticos; Polimorfismo P561T em GHR; C-ausência de polimorfismo P561T em GHR ; O-alterações na dimensão linear das medidas maxilares e mandibulares; S- Estudos transversais. Os estudos selecionados foram qualificados pela qualidade metodológica em uma escala de 10 pontos. A avaliação em subgrupos. O subgrupo foi realizada de acordo com as medidas lineares avaliadas em dois ou mais estudos, como a seguir: altura corporal, N-S, A'-PTM ', Gn-Go, Pog'-Go. Foi utilizado o modelo de efeito fixo e as diferenças médias foram realizada usando a metanálise de variância inversa. O I^2 (95%) foi utilizado para medir heterogeneidade estatística entre estudos, em que valores de I^2 de 25%, 50% e 75% significaram baixa, média e alta heterogeneidade, respectivamente. **Resultados:** A pesquisa inicial identificou 146 estudos. Após excluir resumos duplicados, 138 foram selecionados. Sete estudos foram incluídos na revisão sistemática. Apenas 1 estudo foi classificado como de baixa qualidade metodológica. Três estudos foram incluídos na meta-análise. A meta-análise demonstrou uma associação entre a medida linear Co-Go e o genótipo CC ($p<0,0001$), com diferença média e intervalo de confiança de 3,79 [2,06; 5,52]. CC foi associado com maior altura mandibular. **Conclusão:** O polimorfismo P561T em GHR está associado à medida Co-Go em asiáticos, com baixo nível de evidência.

Keywords: Genetic Polymorphism. Angle Class III. Prognathism. Single nucleotide. Somatotropin-Binding Protein.

ABSTRACT

Objective: Through a systematic review and meta-analysis, the aim this study was evaluating the association between the P561T polymorphism in *GHR* (rs6184) with skeletal Class III malocclusion in different populations. **Methods:** A broad search for studies was conducted using the databases: PubMed, Web of Science, Scopus, Cochrane, Google Scholar and Open Grey until December 2018. The study design according to PECOS was: P-Orthodontic patients; E- polymorphism P561T in GHR; C- absence of polymorphism P561T in GHR; O- linear dimension alterations in maxilla and mandibular measurements; S- Cross-sectional studies. The selected studies were qualified by 10-point scoring sheet methodological quality. The subgroups evaluation was performed according to the linear measurements evaluated in two or more studies, as follows: body height, N-S, A'-PTM', Gn-Go, Pog'-Go, and Co-Go.A fixed effect model was used and the mean differences were performed using the inverse-variance meta-analysis. The I^2 (95%) was used to measure statistical heterogeneity between studies, where I^2 values of 25%, 50%, and 75% signified low, medium, and high heterogeneity, respectively. **Results:** The initial search identified 146 studies. After excluding duplicate abstracts, 138 were selected. Seven studies were included in the systematic review. Only one study was classified as having low methodological quality. Three studies were included in the meta-analysis. The meta-analysis demonstrated an association between the Co-Go linear measure and CC genotype ($p<0.0001$), with a mean difference and confidence interval of 3.79 [2.06, 5.52]. CC was associated with greater mandibular height. **Conclusion:** The polymorphism P561T in *GHR* is associated with Co-Go measurement in Asians, with low level of evidence.

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INTRODUCTION

Malocclusion is a misalignment or incorrect relation of teeth and jaws[1] that can lead to alterations in facial profile with esthetic impact,[2] limition in the masticatory function,[3] higher risk for dental trauma[4] and compromised quality of life[5]. Skeletal Class III malocclusion is one of the most severe maxillofacial skeletal alteration in orthodontics. It may be associated to excessive mandibular growth, inefficient maxillary growth or a combination of both conditions.[6-8]

In the past few decades, many association studies with candidate genes[8-13] and genome-wide screenings have evaluated the etiology of skeletal Class III malocclusion in different populations.[14-18] These studies indicated different chromosomal locations shared by the affected subjects. The variety of chromosomal locations identified by these previous studies may be due to the polygenic model of this trait.[18]

The gene growth hormone receptor (*GHR*) has been a widely studied candidate gene in the orthodontic field.[7,9–12,19,20] The polymorphism P561T in *GHR* was a missense mutation, causing a transversion of amino acid from cytosine to adenine and changing codon 56 from proline to threonine.[21] The human *GHR* gene is encoded by a single gene on chromosome 5p13.1. GHR is one of the probable candidates for determining morphological traits, because growth hormone (GH) is a key regulator of bone growth.[10] GH is a peptide hormone made in the anterior pituitary gland that has an important role in the regulation of the growth and development of the maxilla and craniofacial complex. GH binds to specific cell surface receptors to initiate these processes and activate diverse intracellular signaling pathways.[7] Although many studies evaluated the association between the polymorphism P561T in *GHR* with skeletal Class III malocclusion,[7,9–12,19,20] it is unclear if the polymorphism plays a role in its etiology. Therefore, the aim of this study is to perform a systematic review and meta-analysis to evaluate the association between the polymorphism P561T in *GHR* with skeletal Class III malocclusion in orthodontic patients.

MATERIAL AND METHODS

Eligibility criteria

This study was performed in agreement with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement [22] and was registered with PROSPERO (CRD 42016035790).

The inclusion criteria included original, cross-sectional, case-control, or cohort studies that evaluated if the polymorphism P561T in *GHR* is associated with skeletal class III malocclusion in healthy orthodontic patients. Publication dates, sample sizes, and statistical analyses were not a restriction. To certify the broadest possible search, no language restriction was applied. Unpublished manuscripts and theses, book chapters, case reports, and case studies were excluded.

Search strategy

Electronic databases were used for the selection of the primary studies: PubMed (Jan 1996/1966– Dez 2018), Web of Science (1900– Dez 2018), Scopus (1960– Dez 2018), Cochrane (1993/1990- Dez 2018), Google Scholar (Nov 2004- Dez 2018) and OpenGrey (1997- Dez 2018). No filters or limits were used in the searches. The descriptors were selected from a combination of previous searches in MeSH (Medical Subject Headings) terms and the most cited terms in relevant previous publications. The search was conducted using the following terms from Medical Subject Heading terms (MeSH) and their combinations: "genes" (MeSH terms) OR "polymorphism, genetic" (MeSH terms) OR "polymorphism, single nucleotide" (MeSH terms) AND "*ghr*" (MeSH terms) OR "growth hormone receptor" (MeSH terms) OR "somatotropin binding protein" (MeSH terms) AND "malocclusion, Angle class III" (MeSH terms) OR "prognathism" (MeSH terms) OR "mandible" (MeSH terms) OR "skeletal class III malocclusion" (tw). Moreover, the bibliographies of the final selected articles were hand searched to identify any relevant articles that were not identified previous.

Study selection

Two reviewers independently read all retrieved articles' titles and abstracts. If one reviewer considered a publication as having met the inclusion criteria, the full article was obtained. Abstracts potentially eligible, as well as abstracts that did not presented enough information, were included for full-text analysis. Differences regarding eligibility after evaluation of the full text was resolved through consensus, and, when differences still persisted, a third reviewer was accessed to reach a final decision.

Data extraction

Two reviewers independently performed the data extraction. General information was collected from each article. The specific characteristics were collected: author/year, ethnicity/country, age range in years, sample size, case definition, methods used in the cephalometric analysis to evaluate facial measures, molecular biology technique, and author's conclusion.

The authors of the included articles were contacted by email for the identification of additional information.

Quality assessment

The authors adopted a 10-point scoring sheet, based on published criteria recommendations on the assessment

of the quality of epidemiological genetic association studies.[23] Each quality criterion was assessed as present (yes, score of 1 point) and absent or undetermined (no, score of 0 points). Two authors independently scored all the articles. In any case of disagreement, a consensus regarding the final score was reached. A final quality score was obtained by summation of each component, providing a range of 0–10 for each article. Based on the score, the articles were classified into three categories: i) high methodological quality: presenting 8 or more criteria; ii) moderate methodological quality: presenting 5–7 criteria; iii) low methodological quality: presenting 4 or fewer criteria. Therefore, the studies were also classified as having high, moderate, and low quality of evidence. Only studies with high and moderate evidence were used in the meta-analysis.

Meta-analysis

Data synthesis and meta-analysis

The outcome was presented in all included studies as continuous data. For the meta-analysis, we extracted the mean and the standard deviation. The subgroup evaluation was performed according to the linear measurements evaluated in two or more studies, as follows: body height, N-S, A'-PTM', Gn-Go, Pog'-Go, and Co-Go.

Two studies with high and moderate evidence were used in the meta-analysis. A fixed effect model was used for the meta-analysis. The mean differences in CC and CA genotypes were performed using the inverse-variance meta-analysis. The I^2 was used to measure statistical heterogeneity between studies, where I^2 values of 25%, 50%, and 75% signified low, medium, and high heterogeneity, respectively.[24] The meta-analysis calculation and Forest plot creations were performed with Rev Man 5.3. with the studies that present moderate and high methodological quality, full data regarding linear measurements.

Assessment of the quality of evidence using GRADE

We graded the quality of the evidence for each outcome across studies (body of evidence) using the Grading of Recommendations: Assessment, Development and Evaluation (GRADE) (http://www.gradeworkinggroup.org/). This technique allows one to determine the overall strength of evidence for each meta-analysis.[25] Using the GRADE framework, body of evidence for observational studies is initially classified as low quality. This body of evidence can be rate up if there is special strengths or the study lack limitations. Factors that may rate up the quality of evidence for observational studies is the presence of a large magnitude of an effect (upgrade in one or two levels), presence of a dose-response gradient (upgrade one level) and by the effect of a plausible residual confounding (upgrade one level).

The GRADE pro Guideline Development Tool, available online (www.gradepro.org), was used to create Summary-of-findings table as suggested in the Cochrane Handbook for Systematic Reviews of Interventions.[26]

RESULTS

The search strategy is presented in Table 1, which describes the study selection process and the total number of references. After the analysis of the full text and summary, 6 studies were included. We manually searched one study, totaling 7 studies included in the systematic review.

The data extracted of the included studies are presented in Table 2. Five studies were performed on Asian populations,[9–11,19,20] one study was performed in Turkey,[7] and one was performed in the United States of America.[12]

Table 3 reported the qualitative scoring of the included articles. Four studies[10–12,19] were classified as high methodological quality, 2 studies were classified as moderate methodological quality[7-9] and 1 study[20] was classified as low methodological quality.

Tassopoulou-Fishell et al., did not evaluate linear measurements.[12] Two studies did not fully report the data in the result section.[7,19] We sent a request for additional data by email to the corresponding authors, who did not reply to the request. Sasaki et al. was excluded due its low methodological quality.[20] Therefore, only 3 studies were eligible to be subject to the meta-analyses (Figure 1).[9-11]

Forest plots of the subgroups are presented in Figure 2. The overall heterogeneity (I^2) among the articles was low. The only linear measure that presented statistical association with the polymorphism P561T in *GHR* was Co-Go. A statistical difference was found for Co-Go linear measurements, in which the CC genotype presented greater measurements than the CA genotype ($p<0.0001$), with a mean difference and confidence interval of 3.79 (2.06, 5.52). The body height and the other facial linear measurements (N-S, A'-PTM', Gn-Go and Pog'-Go) were not associated with polymorphism P561T in *GHR* ($p>0.05$).

Assessment of the quality of evidence is described In the summary-of-findings table (Table 4), the meta-analysis was graded as low quality for body height, N-S, A' PTM', Gn-Go, Pog'-Go, and Co-Go. The reasons for downgrading the evidence were that the studies were cross-sectional and were at "unclear" risk of bias and presence of a dose-response gradient (Table 4).

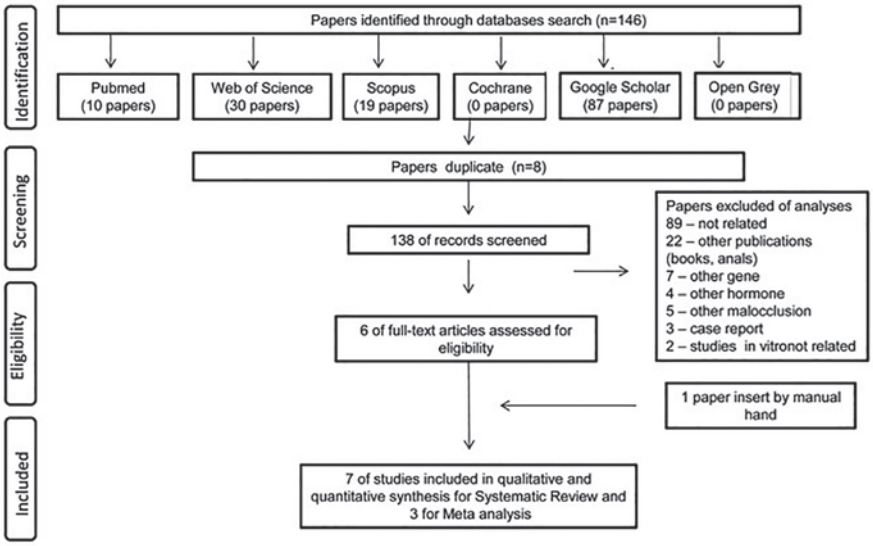

***Figure 1**: Stages of the studies selection progression according to Prisma Statement.*

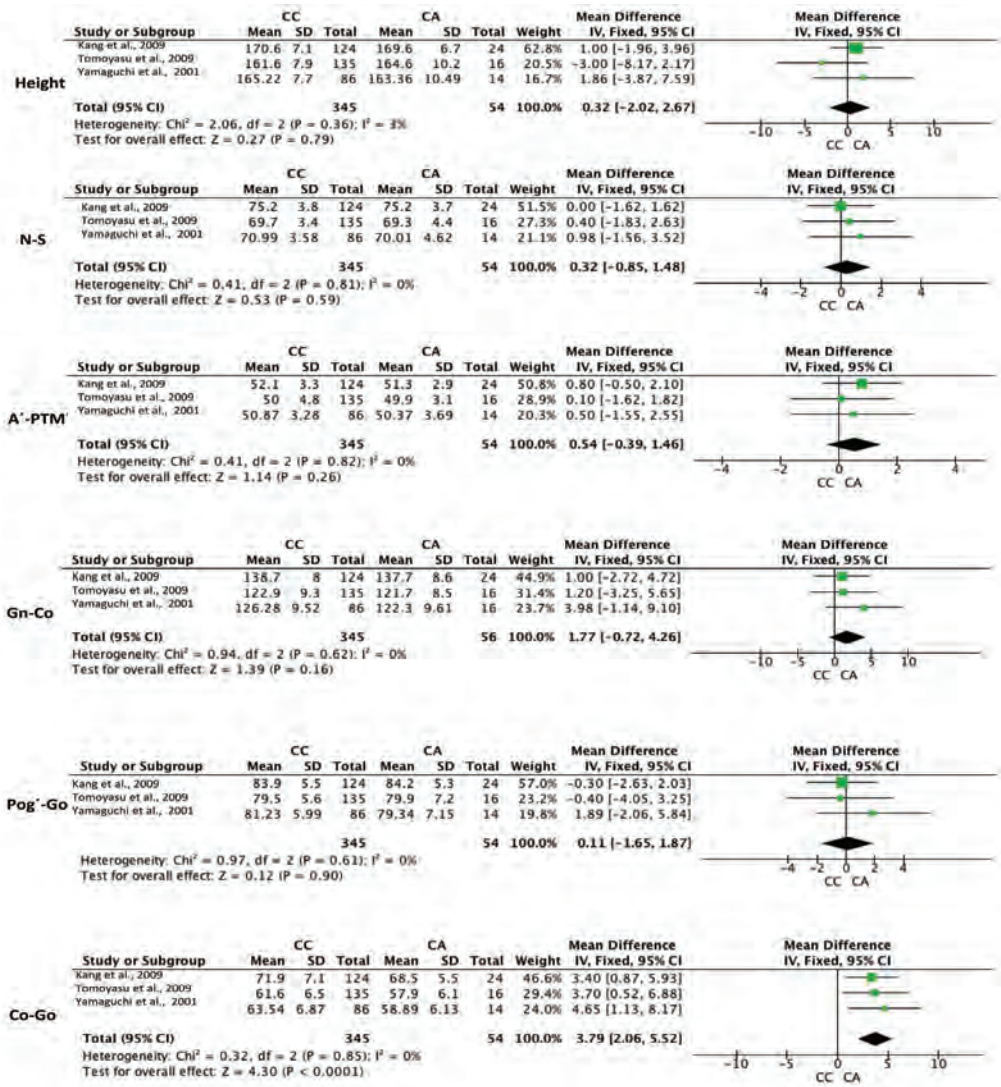

***Figure 2**: Forest plot of cephalometric measures.*

Table 1: *Search Strategy in databases*

Type of term	Search terms used: MeSH terms	PubMed	Web of Science	Scopus	Cochrane	Google Scholar	Open Grey
Phenotype	Malocclusion OR Angle class III OR Prognathism OR Mandible	96046	35155	164423	190	514000	0
Genetics	Genes OR Polymorphism, Genetic OR Polymorphism, Single nucleotide	1442659	2545514	5850356	602	500,000	0
	GHR OR Growth hormone receptor OR Somatotropin binding protein	27783	22696	22699	266	23900	0
Combined terms	(Malocclusion OR Angle class III OR Prognathism OR Mandible) AND (Genes OR polymorphism, genetic OR polymorphism, single nucleotide) AND (GHR OR growth hormone receptor OR somatotropin binding protein)	14	37	106	2	13400	0

***Table 2**: Characteristics of the included studies.*

Author/Year	Study location	Age in years	Sample size (case/control) Case Definition	Cephalometric landmarks/ measurements	Molecular biology technique	Authors' conclusion regarding the polymorphism P561T
Yamaguchi *et al.* 2001	Japanese	18-49	100 (Case and control was not dicothomized)The phenotype was evaluated as continuous variable	Body height, N-S, A´-ptm, Gn-Co, POG´-Go, Co-Go, and Body height/Co-Go	RFLP-PCR	Associated with Co-Gn measurement.
Zhou *et al.* 2005	Chinese	20-35	140 (Case and control was not dicothomized)The phenotype was evaluated as continuous variable	N-S, N-Ba, N-Ar, S-Ba, S-Ar, A´-PTM´, Co-Go, Ar-Go, Go-Gn, Go-POG, Co-Gn, Ar-Gn, Ar-Pog, N-Me, and S-Go	PCR and sequencing	Was not associated with any measurement parameter.
Tomoyasu *et al.* 2009	Japanese	18-58	167 (Case and control was not dicothomized)The phenotype was evaluated as continuous variable	Body height, N-S, A´PTM´, Gn-Co, Pog´-Go, and Co-Go	PCR and sequencing	Associated with Co-Gn measurement
Kang *et al.* 2009	Korean	18-58	159 (87 Class I/44 Class II/28 Class III)The phenotype was also evaluated as continuous variable - Craniofacial linear measurements	Body height, N-S, A´-PTM´, Gn-Co, Pog´-Go, and Co-Go	PCR and sequencing	Contributes to the mandibular ramal height
Sasaki *et al.* 2009	Japanese	3-13	60 (33 mandibular protrusion/27 Class I)The phenotype was also evaluated as continuous variable - Craniofacial linear measurements	Cd-Go, Pog'-Go, Gn-Cd,A'-Ptm', Gn-Cd, and Ar-Go-Mn	RFLP-PCR	Was not associated with mandibular prognathism
Tassopoulou-Fishell *et al.* 2012	USA	11-52	79 (44 mandibular protrusion/35 Class I)The phenotype was evaluated as Class I and Mandibular prognathism	Steiner´s ANB, Wits appraisal and Downs´ A-B ´lane	Real time PCR	Was not associated with mandibular prognathism.
Bayram *et al.* 2014	Turkish	Older than 16	200 (101 mandibular prognathism/99 Class I)Case defined as ANB and Wits <0°.The phenotype was also evaluated as continuous variable	ANB, Wits, Ar-Go, Go-Me, Go-Pog´, Co-Gn, A´-Ptm, and Co-A	RFLP-PCR	May have an effect on mandibular growth.

***Table 3**: Methodological scoring protocol based on quality assessment for selected studies.*

Criteria evaluated	Included studies						
	Yamaguchi *et al.* 2001*	Zhou *et al.* 2005*	Tomoyasu *et al.* 2009*	Kang *et al.* 2009*	Sasaki *et al.* 2009	Tassopoulou-Fishell *et al.* 2012	Bayram *et al.* 2014
Control group	1	1	1	1	0	1	1
Hardy–Weinberg equilibrium	0	1	1	1	0	1	1
Case group	1	1	1	1	0	1	1
Reproducibility	1	1	1	1	0	1	1
Blinding	0	0	0	0	0	0	0
Power calculation	0	0	0	0	0	0	0
Statistics	1	1	1	1	1	1	1
Corrected statistics	1	1	1	1	0	1	0
Independent replication	1	1	1	1	1	1	1
Compilation of reported associations and outcomes	1	1	1	1	1	1	1
Score	**7**	**8**	**8**	**8**	**3**	**8**	**7**

*Note: Quality assessment criteria were adapted by Clark and Baudouin [23] For the quantification of criteria: "1" means present, and "0" absent. Total score is 10 * Case and control was not defined, the phenotype was evaluated as continuous variable.*

Table 4: *Summary of findings table.*

Patient or population: Orthodontic patients **Intervention:** polymorphism P561T in GHR **Comparison**: absence of polymorphism P561T in GHR					
Outcomes	**Anticipated absolute effects†**(95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
	polymorphism P561T in GHR	**absence of polymorphism P561T in GHR**			
Height	–	–	MD 3.32 SD lower (-2.02 to 2.67)	399 (3 cross-sectional)	**%%LOW QUALITY‡
N-S	–	–	MD 3.32 SD lower (-0.85 to 1.48)	399 (3 cross-sectional)	**%%LOW QUALITY ‡
A'-PTM	–	–	MD 0.54 SD lower (-0.39 to 1.46)	399 (3 cross-sectional)	**%%LOW QUALITY ‡
Gn-Co	–	–	MD 1.77 SD lower (-0.72 to 4.26)	401(3 cross-sectional)	**%%LOW QUALITY ‡
Pog'-GO	–	–	MD 0.11 SD lower (-1.65 to 1.87)	399 (3 cross-sectional)	**%%LOW QUALITY ‡
Co-Go	–	–	MD 3.79 SD lower(2.06 to 5.52)	399 (3 cross-sectional)	**%%LOW QUALITY ‡

Note: †The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group. ‡Imprecision and risk of bias. CI, confidence interval; MD, mean difference; SD, standard difference.

DISCUSSION

Our study demonstrated that the polymorphism P561T in *GHR* may be biologically relevant to craniofacial development and could act as a genetic marker for mandibular ramus height growth (condyle-gonion). At position 1777 in *GHR*, a transversion of amino acid from cytosine to adenine changes codon 561 from proline to threonine, which affects the cytoplasmic domain of the *GHR*. The Forest plot demonstrated that the homozygotic CC genotype was strongly associated with greater Co-Go measurement.

The others evaluated facial linear measurements were not associated with the polymorphism P561T in *GHR*. However, it is important to consider the heterogeneity of the skeletal Class III malocclusion. It is not surprising that genetic linkage and candidate gene studies have indicated some other candidate genes and loci to be involved in the skeletal Class III malocclusion etiology. It is possible that other genes play a role in other facial linear measurements, such as N-S, A'-PTM', Gn-Go, and Pog'-Go. Additionally, is possible that epistasis is involved, in which the effect of one gene is influenced by one or more modifier genes.

Another important factor that should be highlighted is the multifactorial nature of skeletal Class III malocclusion. Bone development and oral muscles are involved in the development and establishment of the skeletal malocclusion.[27] GH stimulates periosteal apposition within the action of osteoblasts[28] and indirectly through muscle forces that acts on bones, which is regulated by anabolic effects of GH on muscle tissue.[29] Skeletal muscle cells respond rapidly to GH increasing tyrosine phosphorylation of the GHR.[29] This may indicate that the polymorphism P561T in *GHR* may be involved in the mandibular ramal height through bone or muscle function.

One important factor to be taken into consideration in epidemiological genetic studies is the population's ethnic background. The frequency of skeletal Class III malocclusion ranges among worldwide populations, in which the lowest frequencies is in European American populations (0.48 to 4%), moderate frequencies in Sub-Saharan African populations (3 to 8%), and higher frequencies in far-eastern

Asian populations such as Korean, Chinese, and Japanese populations (15 to 23%).[15] In addition, the minor allele frequency of the studied polymorphism varies according to the population (NCBI). It is important to emphasize that the three studies included in the meta-analysis were performed on Asian populations.

Although the included studies were performed on different Asian populations, the heterogeneity of the included studies in the meta-analysis was 0%. In addition, only 2 studies included in the systematic review, that were performed on a Chinese and North American populations, did not find or suggest an association between mandibular ramal height growth and the polymorphisms P561T in *GHR*.[19,12]

It is possible that the differences observed were due to population differences or methodological differences among the studies. None of the included studies performed a sample size calculation[7,9–12,19,20] Two studies did not report if the polymorphism was in Hardy-Weinberg equilibrium.[9,20] The Hardy-Weinberg equilibrium is a principle stating that the polymorphism in a population will remain constant from one generation to the next in the absence of disturbing factors. Studies without Hardy-Weinberg equilibrium could reflect some methodological error in the sample selection or during the genotyping experiment.

Future research in different populations should be performed in order to evaluate if the polymorphisms P561T in *GHR* is associated with the mandibular ramal height in different ethnic backgrounds. This polymorphism may be a genetic marker for mandibular ramal height growth and might impact the orthodontic practice in the near future.

CONCLUSION

Our systematic review and meta-analysis provide further evidence of the association between the polymorphism P561T in *GHR* and the Co-Go measurement, which allows to conclude, with low certainty of evidence, the relation of this SNP with Class III malocclusion Asian patients.

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