# TRABAJO FIN DE GRADO

## Grado en Odontología

# GENETIC POLYMORPHISMS INVOLVED IN CLASS III MALOCCLUSION

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## ABSTRACT

**Introduction**: Class III malocclusion is a complex dental condition characterized by a protruded mandible that can result from both environmental and genetic factors. A better understanding of its genetic etiology may help in the development of more effective and personalized treatment approaches; **Objectives**: The main objective of this work was to explore and analyze the existing literature on genetic polymorphisms that may be associated with the development of Class III malocclusion; **Materials and Methods**: This study followed the PRISMA guidelines for systematic reviews. A documentary research was conducted using PubMed and Scopus databases. The search strategy focused on terms related to Class III malocclusion and genetic polymorphisms. After applying inclusion and exclusion criteria, 25 articles were selected. Information regarding population, genotyping method, diagnostic criteria, genes and SNPs studied, and p-values was extracted and analyzed; **Results**: Among the 67 SNPs studied, 11 showed a final significant association with Class III malocclusion. The most frequently associated genes were FGFR2, MYO1H, GHR, and RUNX2. However, methodological variability and limited sample sizes reduced the generalizability of these findings; **Conclusions**: This review supports a potential genetic involvement in Class III malocclusion, although further research is needed to confirm these associations and explore their clinical relevance.

## KEYWORDS

Class III malocclusion, single nucleotide polymorphism, craniofacial development, genetic factors, orthodontics.

## RESUMEN

**Introducción**: La maloclusión Clase III es una condición craneofacial compleja identificada por una prominencia mandibular que puede variar en severidad. En el paciente, esto se traduce con repercusiones funcionales y estéticas. Aunque su etiología es multifactorial, la contribución genética ha cobrado cada vez mayor relevancia; **Objetivos**: El objetivo principal de esa investigación fue identificar polimorfismos genéticos específicos que estén potencialmente asociados al desarrollo de la clase III, y evaluar la posible variabilidad de estas asociaciones geneticas entre distintas poblaciones; **Metodología**: Este trabajo de investigación documental siguió las directrices PRISMA. Se realizó una búsqueda sistemática en bases de datos como PubMed y Scopus. Se incluyeron 25 estudios que cumplían con criterios de inclusión y exclusión rigurosos. Se extrajeron datos sobre población, diagnóstico, técnicas de genotipado, genes/SNPs estudiados y significación estadística; **Resultados**: Se identificaron inicialmente 33 SNPs potencialmente asociados, de los cuales 11 mantuvieron significancia tras correcciones estadísticas. Los genes más asociados fueron FGFR2, MYO1H, RUNX2 y GHR. La heterogeneidad metodológica y poblacional dificultó la interpretación concluyente; **Conclusiones**: Existe una implicación genética importante en la maloclusión Clase III. A pesar de la identificación de varios SNPs relevantes, se necesitan estudios más amplios, homogéneos y estandarizados para clarificar su papel y mejorar su aplicabilidad clínica.



## PALABRAS CLAVE

Maloclusión Clase III, polimorfismo genético, SNP, desarrollo craneofacial, ortodoncia.

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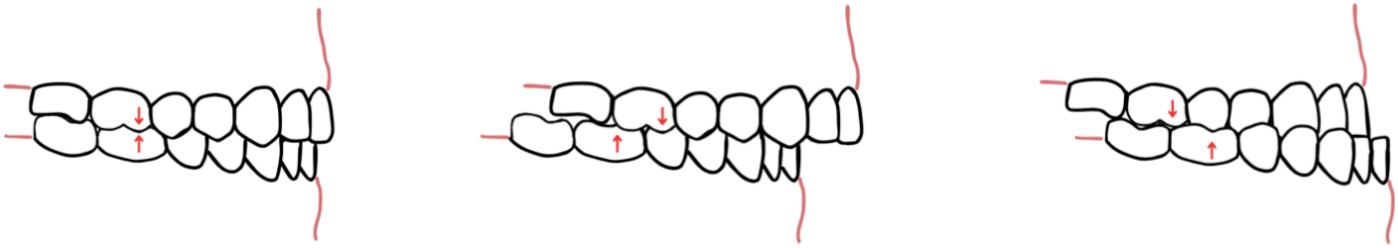
# 1. INTRODUCTION

## 1.1. Definition of Malocclusions

Class III malocclusion is a dental condition characterized by a protruded mandible. A malocclusion refers to any deviation from a normal occlusion, which is the normal physiological contact and teeth alignment between the upper and lower jaws during jaw closure. Class III malocclusion can be categorized into three types based on etiology: dental, pseudo, and skeletal(1). Dental Class III results from misaligned or incorrectly angulated teeth, without underlying skeletal involvement. Pseudo-Class III arises from premature teeth contact that forces the mandible into a forward position, mimicking skeletal discrepancy. Skeletal Class III involves a discrepancy between the maxilla and the mandible.

The specific facial profile associated with the Class III malocclusion can negatively impact an individual's quality of life, both functionally and aesthetically. With treatment often challenging, a deeper understanding of its genetic etiology could help improve outcomes and develop effective treatment strategies. This thesis will explore and discuss the literature regarding the genetic factors underlying Class III malocclusion to better understand the condition, focusing on its dental and skeletal etiology.

In 1899, Dr. Edward Hartley Angle, known as “the father of modern orthodontics”, classified for the first time the different types of dental malocclusions, focusing on the mesiodistal relationship of the first permanent molars in the sagittal plane. This classification is divided into three categories: Class I, Class II, and Class III (2). Class I is considered the standard physiological occlusion, where the mesiobuccal cusp of the first permanent maxillary molar aligns with the buccal groove of the first permanent mandibular molar. Class II is characterized by a distal occlusion with a retruded mandible and a convex profile. In this type of occlusion, the mesiobuccal cusp of the first permanent maxillary molar aligns mesially with the buccal groove of the first permanent mandibular molar. Finally, Class III defines a mesial occlusion with a protruded mandible and a concave profile, where the mesiobuccal cusp of the first permanent maxillary molar aligns distally to the buccal groove of the first permanent mandibular molar (3–7),(Figure 1).



Dental Class I  Dental Class II  Dental Class III

**Figure 1.** Illustration of the dental Class I, II, and III. The upper arrow indicates the position of the mesiobuccal cusp of the first permanent maxillary molar and the lower arrow indicates the position of the buccal groove of the first permanent mandibular molar.

In addition to Angle's classification, which focuses on dental alignment, skeletal classification evaluates the relationship between the maxilla and mandible based on their relative positions. This classification is determined through cephalometric analysis, which involves measuring and analyzing the skull and facial bones using X-ray images. Specific anatomical landmarks, such as the ANB (A-point to Nasion to B-point), SNA (Sella-Nasion to A-point), and SNB (Sella-Nasion to B-point) angles, are used to differentiate between Class I, Class II, and Class III.

The ANB angle measures the sagittal relationship between the maxilla and mandible, the SNA angle between the cranial base and the maxilla, and the SNB angle between the cranial base and the mandible. In permanent dentition, a Class I relationship typically corresponds to an ANB angle of around 2°, with increased values indicating Class II and decreased values indicating Class III. Likewise, the average SNA angle of 82° ± 1° is typically associated with a Class I relationship, with increased values (maxillary protrusion) usually linked to Class II and decreased values (maxillary retrusion) linked to Class III. The average SNB angle of 81° ± 1° is typically associated with a Class I relationship, with decreased values (mandibular retrusion) usually linked to Class II and increased values (mandibular protrusion) linked to Class III (8,9). A visual representation of these angles in each Class can be seen in Figure 2.

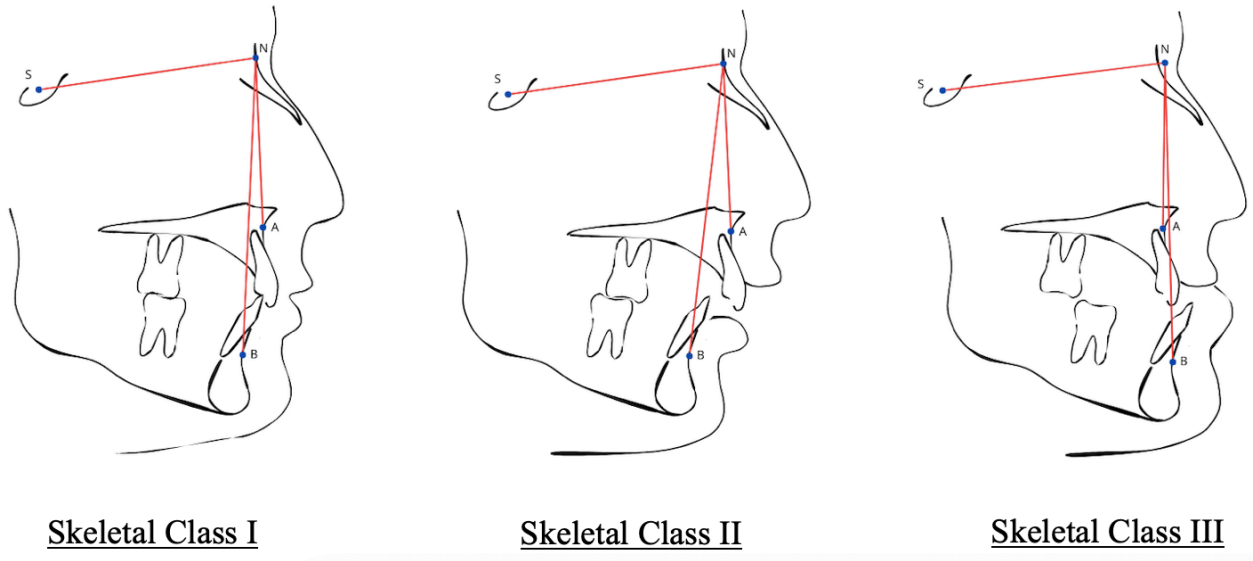



**Figure 2.** Cephalometric representation of the skeletal Class I, II, and III. In each Class, point S (Sella) represents the center of the Sella turcica, point N (Nasion) represents the intersection of the frontonasal suture with the midsagittal plane, point A (Subspinale) represents the deepest point on the contour of the maxillary alveolar process and the point B (Supramental) represent the deepest point on the contour of the mandibular alveolar process. The cephalometric tracing in red shows the angles SNA, SNB, and ANB, which are used to assess the sagittal relationship of the maxilla and mandible.

## 1.2. Prevalence and Impact of Malocclusions

Class I, Class II, and Class III malocclusion present a global incidence of approximately 74%, 20%, and 6%, respectively (7). Despite their lower prevalence, Class III malocclusion is often considered more challenging to treat (10,11). This complexity can be attributed to several factors: firstly, Class III malocclusions often involve underlying skeletal discrepancies, necessitating more invasive treatment such as orthognathic surgery to correct the underlying bone structure. Secondly, the timing of treatment is crucial for improving outcomes, particularly during growth periods. Lastly, maintaining long-term stability can be difficult, as there is a risk of relapse, especially in cases with strong genetic predispositions. This requires careful planning and long-term monitoring (6,11).

Class III malocclusion can have significant negative impacts on individuals, affecting their physical, psychological, and social well-being. Physically, the abnormal forward positioning of the mandible in Class III malocclusion can impair oral function, leading to difficulties in chewing, speaking, and even sometimes breathing in severe cases. The temporomandibular joint can be subjected to stronger forces, resulting in temporomandibular disorder leading to pain, discomfort, and dysfunction. The altered bite can also accelerate tooth wear due to premature contact or uneven forces applied to the teeth. Psychologically and socially, individuals with Class III malocclusion sometimes experience reduced self-esteem and social anxiety due to their distinctive facial appearance. This can impact their overall quality of life and interpersonal relationships (12–14).

## 1.3. Etiology of Malocclusion Class III

### 1.3.1. Environmental

To address these challenges and optimize treatment strategies, a deeper understanding of the underlying etiology is necessary. Research suggests that both genetic and environmental factors may be involved in its development (15). Environmental factors, such as oral habits (thumb-sucking, mouth breathing), parafunctional habits (bruxism), lifestyle factors (poor nutrition), and trauma, can influence the severity and progression of Class III malocclusion (15,16). Additionally, the exact etiology remains partially unknown, as the interaction between genetic factors and environmental influences is not fully understood.

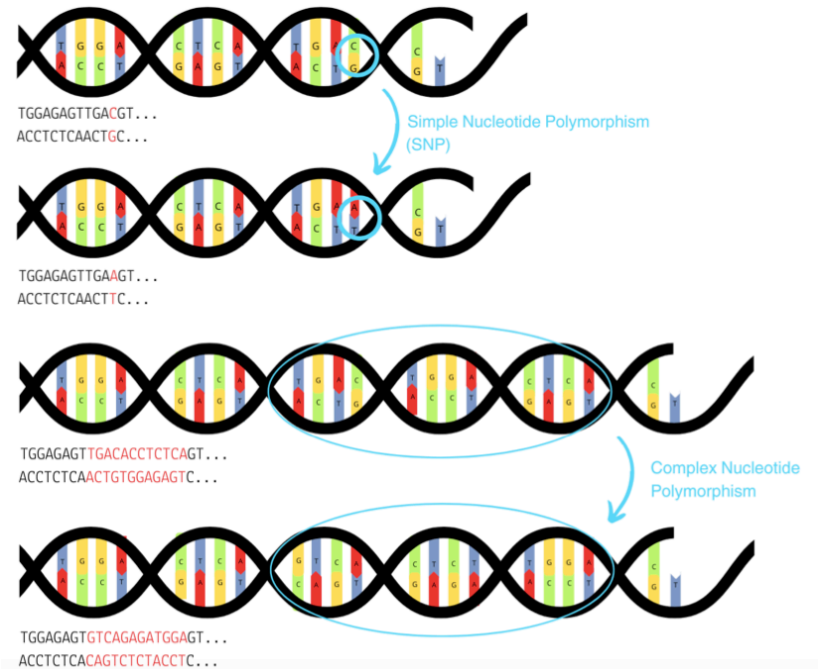
1.3.2. Genetic

Genetic factors, also associated with the development of this dental condition, need to be better analyzed. Understanding the genetic basis of Class III malocclusion may be a key factor in developing effective prevention and treatment strategies. By identifying specific genetic polymorphisms associated with this condition, researchers and dentists can gain valuable insights into the underlying mechanisms and develop personalized treatment plans.

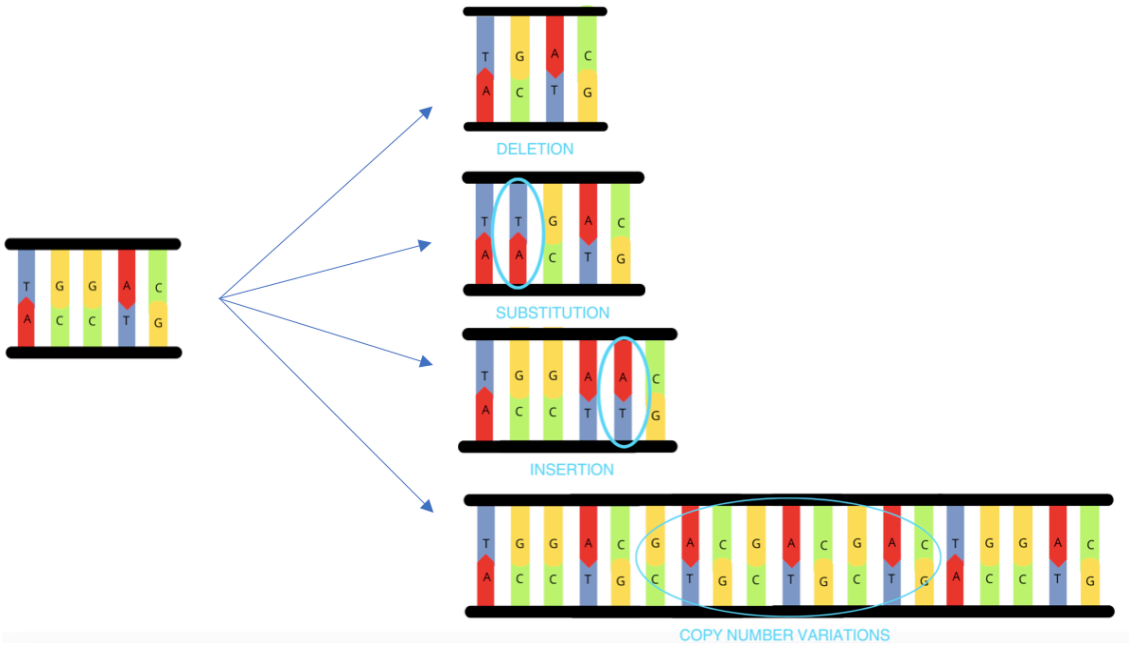
## 1.4. Definition of Genetic Polymorphisms

Genetic polymorphism refers to “the presence of two or more variant forms of a specific DNA sequence that can occur among different individuals or populations” (17). These polymorphisms are heritable genetic variations that occur in at least 1% of the population and involve differences in nucleotides, the smallest structural units that make up DNA. The different versions of a gene resulting from these polymorphisms are called alleles, and they contribute to individual diversity. For a genetic polymorphism to exist, the alleles must be homologous in their position within the genome (they occupy the same location on paired chromosomes). The trait must also be carried by chromosomes and be transmissible across generations. These variations, which occur at a defined position in the genome (locus), are heritable and influence higher levels of biological structure, such as the gene, protein, and phenotype of an individual. These different levels of genetic polymorphism show the impact of nucleotide variants on the organism (18).

Genetic polymorphisms can be simple, involving a single nucleotide change (a single nucleotide polymorphism or SNP), which is the most common type, or complex, involving changes to even thousands of nucleotides (Figure 3). SNPs are a common form of genetic variation that are stable, frequent, and easily detectable. These characteristics make them particularly valuable for identifying genetic variations linked to conditions such as Class III malocclusion. Genetic polymorphisms can be divided into four main types: insertions, deletions, substitution, and copy number variations (17,19,20)(Figure 4).




**Figures 3.** This figure illustrates an example of SNP and complex polymorphism within a DNA sequence. In the top two sequences, the SNP is the result of one substitution of the base pair 'CG' to 'AT'. In the two lower sequences, the complex nucleotide polymorphism occurs because of a 12-base substitution, from 'TGACACCTCTCA' to 'GTCAGAGATGGA'.




**Figures 4.** Illustration of the four main types of DNA polymorphism. In the first sequence, the 'GC' base pair is deleted. In the second sequence, the 'GC' base pair is substituted by the 'TA' base pair. In the third sequence, the 'AT' base pair is inserted. In the fourth sequence, a copy number variation is observed where 'GAC' is repeated three times.

Polymorphisms are responsible for the genetic diversity on which natural selection occurs, leading to evolutionary processes. Certain polymorphisms can increase an individual's risk of developing specific abnormal developments, including conditions such as Class III malocclusion. These genetic variations also contribute to phenotypic diversity, as genes directly influence physical traits. In the case of Class III malocclusion, from a skeletal point of view, the observed phenotype can either be caused by a retruded maxilla, a protruded mandible, or an association of both (11,21–23).

### 1.5. Development of the Craniofacial Bones Involved in Class III Malocclusion

To better analyze the role that genetics plays in Class III malocclusion, it is necessary to understand the development of the craniofacial structures implicated in this condition, as genetics directly influence Its development.

Mandibular and maxillary development are complex processes that start at the embryonic stage. The mandible and maxilla originate from the first pharyngeal arch, where neural crest cells migrate and proliferate to form mesenchymal condensations (24,25). This process initiates the development of the two facial bones and is influenced by various genes. Homeobox genes, such as MSX1 and MSX2, regulate cell proliferation and differentiation (26). RUNX1, and more specifically RUNX2, encode transcription factors that regulate osteoblast differentiation (27). Additionally, genes coding for growth factors play an important role in mandibular development. The SHH gene encodes the Sonic Hedgehog (*SHH*) protein, which plays a crucial role in patterning the mandible and maxilla by regulating gene expression and influencing their shape and size. Meanwhile, bone morphogenetic proteins (*BMPs*) induce osteoblast differentiation, regulate cartilage development in areas of endochondral ossification (such as the mandibular condyle), and promote bone remodeling (24,28).

Furthermore, genes coding for fibroblast growth factors (FGFs) are involved in the development of osteogenic condensations and the appositional growth of mandibular bones, as well as the elongation of Meckel’s cartilage (29). Meckel's cartilage is a temporary cartilaginous structure formed from mesenchymal cells derived from the first pharyngeal arch, which differentiate into chondrocytes, and this cartilage also acts as a template for the development of the mandible(24). It will guide the bone formation that will happen by both endochondral and intramembranous ossification. The maxillary bone is formed exclusively by intramembranous ossification, where mesenchymal cells directly differentiate into osteoblasts without forming a cartilage intermediate.

The mandible forms through both intramembranous and endochondral ossification (such as the condylar process), which involves the formation of cartilage intermediates that are subsequently replaced by bone.

In addition to genetic factors, the development of the mandible and maxilla is also influenced by hormones. Growth hormone stimulates bone lengthening by enhancing cartilage production in the condylar region, especially during puberty. Thyroid hormones increase chondrocyte activity in the cartilage, affecting the endochondral ossification and thus the mandibular growth rate. Sex hormones (estrogen and testosterone) influence maxillary and mandibular growth, with effects on bone density and size (30,31). Lastly, estrogen regulates the timing of growth plate closure, which will limit the length of the mandible (32).

The final stages of mandibular and maxillary growth will happen postnatally, when these structures continue to grow and remodel in response to functional demands, like chewing and speaking, that will implicate the orofacial muscles. The mandibular condyle's growth will continue throughout childhood and adolescence, resulting in the lengthening of the mandible. Bone resorption and deposition will continuously remodel the facial bones throughout life.

### 1.6 Justification

As previously described, Class III malocclusion can have a significant impact on the quality of life of an individual, both physically and psychologically. Although environmental factors play a role, the genetic component is increasingly recognized as a key determinant in the development of this condition. By studying the genetic basis of Class III malocclusion, researchers can gain valuable insights into the underlying mechanisms and allow the development of personalized treatment plans. The identification of genetic polymorphisms associated with Class III malocclusion may significantly improve public health by enabling targeted prevention strategies and personalized treatment plans. By identifying individuals at risk based on their genetic profile, we can optimize treatment timing and potentially develop novel therapeutic interventions.

## 1.7 Hypothesis

Specific genetic polymorphisms in genes involved in craniofacial development, bone remodeling, and growth regulation are associated with an increased risk of developing Class III malocclusion.

# 2. OBJECTIVES

## 2.1. Primary Objective

The primary objective of this study is to investigate the genetic basis of Class III malocclusion by identifying if specific gene polymorphisms are associated with the development and severity of this condition.

## 2.2. Secondary Objectives

The secondary objectives are first to evaluate whether these genetic polymorphisms differ across certain populations, and secondly to assess the relevance of potential genetic screening in the treatment of Class III malocclusion.

# 3. MATERIALS AND METHODS

## 3.1. Formulation of Research Question

The study selection process for this systematic review was conducted according to the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). A clinical question was developed using the PICO framework (Patient, Intervention, Comparison, Outcome) to focus the review, based on the information presented in the introduction and justification. The formulated question was:

Among individuals with Class III malocclusion (P), do specific genetic polymorphisms (I) contribute to their condition (O) compared to individuals without Class III malocclusion (C)?

## 3.2. Eligibility Criteria

Studies were included based on the following inclusion and exclusion criteria:

Inclusion criteria: Studies investigating the genetic basis of Class III malocclusion on human subjects, studies published in the last 10 years, studies investigating SNPs, and studies with a clear methodology and results.

Exclusion criteria: Case reports, review articles, research conducted on animals, in vitro studies, studies that do not investigate genetic polymorphisms, studies that investigate mutations or microsatellite variations, patients presenting with syndromic conditions, and studies that focus on a specific family sample.

## 3.3. Search Strategy

3.3.1 Identification of search terms

The identification of search terms was carried out breaking down the PICO question into key terms. The following terms were selected: “Class III malocclusion”, “mandibular prognathism”, “skeletal Class III”, “genetic polymorphism”, “gene polymorphism”, and “genetic factors”. The selection of search terms was designed to ensure a comprehensive and systematic search strategy, allowing the retrieval of relevant articles addressing the genetic polymorphisms associated with Class III malocclusion.

### 3.3.2 Search Equation Creation

A comprehensive literature search was conducted in December 2024 using the databases PubMed and Scopus. The following search equation was used in both databases: (((Class III malocclusion) OR (mandibular prognathism) OR (skeletal Class III)) AND ((genetic factor) OR (genetic polymorphism) OR (genes))).

### 3.3.3 Data Extraction and Analysis

Relevant data were extracted from each included study, including:

Population ethnicity and country

Study design (case-control, cohort, or cross-sectional)

- Sample size
- Class III identification method
- Genotyping methods
- Genes and SNP studied
- Bias and limitations

A synthesis of the extracted data was performed to identify common findings and discrepancies. The focus was on understanding the role of specific polymorphisms of certain genes in the development of Class III malocclusion.

# 4. RESULTS

## 4.1. Study Selection

As Illustrated in the PRISMA flowchart (Figure 4), an initial search across PubMed and Scopus databases using the search equation yielded a total of 587 records. After removing 188 duplicates, 399 records underwent title and abstract screening.

During this initial screening, 361 records were excluded based on the following criteria: excluded based on publication year (published before 2015) (n=207), exclusion of animal and in vitro studies (n=26), exclusion of review articles and case reports (n=61), excluded because title and abstract where not align with the topic (n=67). This resulted in 37 full-text articles being assessed for eligibility. During the second screening of the full-text, 12 articles were excluded for the following reasons: language (n=1), no full-text access (n=3), focus on temporary anchorage devices for other types of malocclusion (n=1), associated with malocclusion in general, not Class III malocclusion (n=1), focus on gene, not polymorphisms (n=1), focus on mutations (n=2), focus on microsatellite variations (n=1), insufficient methodological details (n=1), case study on a single family, lacks population-level significance (n=1). As a result, a total of 25 studies met all inclusion criteria and were included in this systematic review.

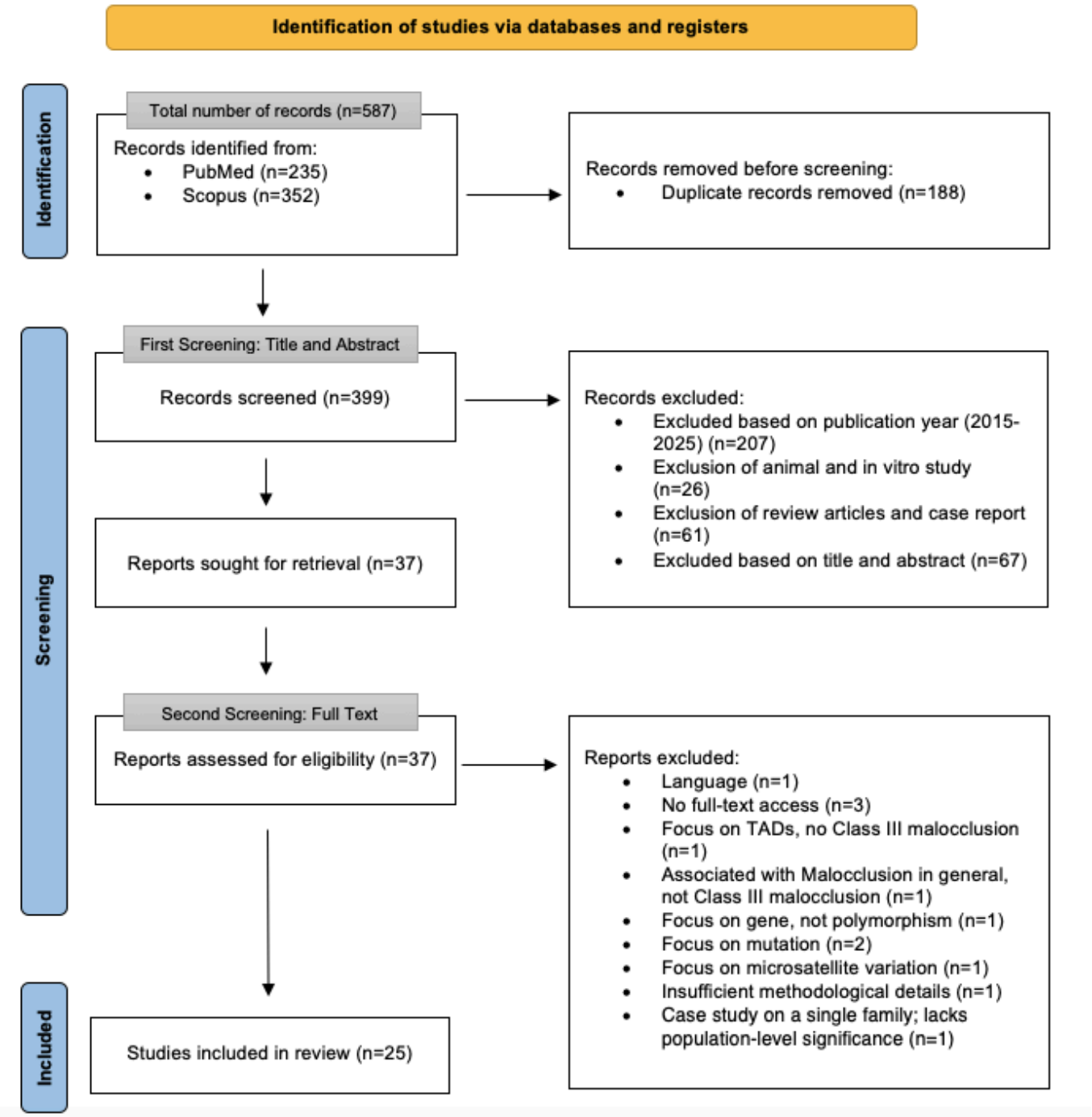



**Figure 4.** Study selection process and literature search results following the PRISMA flow chart.

### 4.1. Data Extraction Table

Summarized in Table 1 is the information extracted from the 25 studies included in the systematic review. Details of the publication's author, year, country/population, sample size (including study and control groups), Class III identification method, genotyping method, genes/SNPs investigated, significant findings, and bias/limitation of the studies were listed. The studies included case-control, cross-sectional, observational, analytical, and pilot studies. The sample size of the population ranged from 10 to 895 participants. Class III malocclusion identification methods varied across studies, but all utilized cephalometric analysis via cephalometric radiography, with specific angular measurements (e.g. SNB, ANB, SNA) used to define the case and control groups. The composition of control groups differed among studies. Some investigations compared Class III malocclusion cases against controls comprising both Class I and Class II individuals, while others restricted controls exclusively to Class I subjects. Other studies employed unspecified non-Class III controls. Genotyping methods also varied, including polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), TaqMan assay, Sanger sequencing, DNA sequencing, and kompetitive allele specific PCR (KASP).

This study prioritized the analysis of single nucleotide polymorphisms (SNPs) due to their higher prevalence, stronger evidence in the literature, and greater analytical reliability compared to other genetic variants. SNPs were the most extensively studied polymorphisms in the context of Class III malocclusion, providing a sufficient dataset for reliable analysis. By comparison, research on mutations and microsatellite variations was limited, with only two studies on mutations and one on microsatellites, reducing their statistical power and generalizability. Furthermore, since most genetic studies on malocclusion concentrate on SNPs, this approach allowed for direct comparisons with existing literature, improving the interpretability and relevance of the findings.

Of the 47 genes and 67 SNPs investigated, 20 genes and 33 SNPs were found to be associated with Class III malocclusion. The P-values of the genes and SNPs associated are presented in Table 2 and correspond to the values reported in each original publication. The statistical significance in this study is considered at $P < 0.05$, meaning values above this threshold suggest no association. When available, the corrected P-value is used as the final significance threshold; otherwise, the uncorrected P-value is considered.

4 SNPs had p-values greater than 0,05 from the beginning and were considered not significant. 13 SNPs showed initial significance with a p-value lower than 0,05 but lost significance after correction. 4 SNPs showed varying significance among studies: in MYO1H, rs10850110 was significant in three studies but non-significant in three others, while rs3825393 reached significance in one study even after multiple-testing correction but was non-significant in another study that did not apply corrections. rs6184 (GHR) was significant in one study but not in two others and rs11200014 (FGFR2) remained significant after both initial and follow-up analyses in one study but lost significance after correction in another. The p-value of rs4434184 (SOX2) was not specified.

The 11 SNPs that showed final significance were: rs7351083 (FNB3), rs20566 (MATN1), rs6930053 (RUNX2), rs2973015 (GHR), rs1051415 (JAG1), rs2981578, rs1078806 and rs10736303 (FGFR2), rs372127537 (FGF7), rs593307 (FGF10), and rs985246 (TWIST1). The most frequently analyzed genes were FGFR2, MYO1H, GHR, RUNX2, MATN1, NOTCH4, and COL1A1. Among these, NOTCH4 and COL1A1 did not reach statistical significance, though COL1A1 showed borderline significance in its association.

It should be noted that P-value is a statistical assumption, not absolute proof of the absence of a relationship. The strength of the association also depends on the magnitude of the P-value. A very low P-value indicate a stronger degree of association than a P-value of 0.05. Additionally, some SNPs have P-values close to the 0.05 threshold, which may indicate a potential association that was not detected due to limited sample size or study design limitations.

**Table 1.** Data extraction table of the studies included in the systematic review.

| Author, year | Country / population | Study Type | Sample Size | Class III identification method | Genotyping method | Gene : SNP investigated | Bias/ Limitations |
|---|---|---|---|---|---|---|---|
| Bahya et al. 2024(33) | Bagdad, Iraq | Pilot study | 10<br>Study group: 5<br>Control group: 5 | Cephalometric analysis, lateral Cephalometric Radiographs | Sanger sequencing | - **COL1A1**: rs2249492<br>- **SOX2**: rs4434184<br>- **FGFR2**: rs2162540<br>- **MAFB**: rs11696257<br>- **FGFR1**: rs881301 | Small sample size, limited ethnic population |
| Topârcean et al. 2024(34) | Romania | Case-control | 57<br>Study group: 22<br>Control group: 35 | Cephalometric analysis | Sanger sequencing | - **FBN3**: rs7351083 | Small sample size, limited ethnic population |
| Topârcean et al. 2024(35) | Romania | Case-control | 78<br>Study group: 25<br>Control group: 53 | Cephalometric analysis | Sanger sequencing, PCR amplification | - **MATN1**: rs1065755 | Small sample size, limited ethnic population |
| Doke et al. 2024(36) | India | Case-control | 40<br>Study group: 30<br>Control group: 10 | Cephalometric analysis using Legan-Burstone method | Sanger sequencing, PCR amplification with synthetic primers | - **MATN1**: rs1065755<br>- **BMP-3**: Tyr67Asn<br>- **HOXA2**: Val327Ile<br>- **MYO1H**: rs10850110 | Small sample size, limited ethnic population gender imbalance, no functional validation |
| Vaishnavi et al. 2024(37) | India | Case-control | 36<br>Study group: 18<br>Control group: 18 | Cephalometric analysis | PCR, Sanger sequencing | - **RUNX2**: rs6930053 | Small sample size |
| Milosevic et al. 2022(38) | Serbia | Case-control | 110<br>Study group: 55<br>Control group: 55 | Study cast analysis, cephalometric analysis | PCR, RFLP | - **MATN1**: rs1149048<br>- **MYO1H**: rs3825393<br>- **BMP-4**: rs17563 | Small sample size, limited ethnic population, exclusion of patients with maxillary retrognathism |
| Milosevic et al. 2022(39) | Serbia | Case-control | 120<br>Study group: 60<br>Control group: 60 | Study cast analysis, cephalometric analysis | PCR, RFLP | - **COL1A1**: rs1107946<br>- **MMP9**: rs3918242 | Small sample size |
| Park et al. 2022(40) | South Korea | Case-control | 325<br>Study group: 173<br>Control group: 157 | Lateral cephalometric radiographs | PCR amplification, sequencing using ABI 3730xl system | - **GHR**: rs6180, rs6182, rs6184 | Exclusion of patients with maxillary retrognathism |
| Gullianne et al. 2022(41) | Jackarta, Indonesia | Cross-sectional | 150<br>Study group: 50<br>Control group: 100 | Cephalometric analysis using the Steiner method | PCR, RFLP | - **MYO1H**: rs10850110 | Small sample size, use of different DNA sources |
| Han et el. 2021(42) | China | Case-control | 396<br>Study group: 199<br>Control group: 197 | Dental study model, cephalometric analysis | Targeted region sequencing using Illumina Hiseq2000 platform, Sanger sequencing validation | - **NOTCH1**: rs3125001<br>- **NOTCH2**: rs372504208<br>- **NOTCH3**: rs1044006, rs1044009<br>- **NOTCH4**: rs415929, rs423023, rs520688, rs386591752, rs915894<br>- **JAG1**: rs1051415<br>- **JAG2**: rs2272591, rs10149229, rs1057744<br>- **NUMB**: rs75236173<br>- **DLL3**: rs2304223<br>- **EP300**: rs20551<br>- **NCOR2**: rs3741513<br>- **PSEN2**: rs8383 | Limited ethnic population, most pairwise comparison lacked Bonferroni adjustment |
| Olsson et al. 2021(43) | Brazil | 3 step cross-sectional, comparative | 150<br>Study group: 21<br>Control group: 129 | Cephalometric analysis based on Steiner's ANB and Ricketts' NBa-PtGn angles | TaqMan assay (from saliva sample) | - **RUNX2**: rs59983488, rs1200425<br>- **BMP2**: rs235768, rs1005464 | Small sample size for gene expression analysis, limited ethnic population |

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|---|---|---|---|---|---|---|---|
| Küchler et al. 2021(44) | Brazil | Cross-sectional | 143<br><br>Study group: 19<br><br>Control group: 124 | Cephalometric analysis using the software Dolphin Imaging version 8.0 | TaqmanTM assay (from saliva samples) | - **BMP2**: rs1005464, rs235768<br>- **BMP4**: rs17563<br>- **RUNX2**: rs59983488, rs1200425<br>- **SMAD6**: rs3934908, rs2119261<br>- **WNT3A**: rs708111<br>- **WNT11**: rs1533767 | Small sample size |
| Laviana et al. 2021(45) | DeuteroMalay population | case-control | 94<br>Study group: 47<br>Control group: 47 | Cephalometric analysis with Steiner analysis | PCR (from buccal mucous epithelia) | - **MATN1**: rs20566, rs371564845, rs201283860, rs376020917, rs181457111 | Small sample size |
| Atteeri et al. 2021(46) | India | Case-control | 60<br>Study group: 30<br>Control group: 30 | Cephalometric analysis | PCR-RFLP | - **MYO1H**: rs10850110 | Small sample size |
| Yusoff et al. 2020(47) | Malay population | Case-control | 57<br>Study group: 27<br>Control group:30 | Cephalometric analysis | PCR-RFLP (from saliva sample) | - **MYO1H**: rs3825393 | Small sample size |
| Rodriguez et al. 2020(48) | Brazil | Cross-sectional | 594 | Cephalometric analysis | Taqman assay (from saliva sample) | - **MSX1**: rs1042484<br>- **PAX9**: rs8004560<br>- **TGF-α**: rs2902345<br>- **FGF10**: rs900379<br>- **FGF3**: rs1893047<br>- **FGF13**: rs12838463, rs5974804, rs5931572 | Small sample size of individuals with TA, sampling limitations, failure rate of genotyping procedures |
| Dalaie et al. 2020(49)1/29/25 8:53:00 PM | Iranian population | Case-control | 124<br>Study group: 64<br>Control group:60 | Cephalometric analysis | PCR, RFLP | - **MYO1H**: rs10850110, rs11611277 | Small sample size, limited ethnic population |
| Dalaie et al. 2020(50) | Iranian population | Case-control | 125<br>Study group: 65<br>Control group:60 | Cephalometric analysis | PCR-RFLP, Sanger sequencing | - **GHR**: rs6184 (P561T), C422F polymorphisms | Small sample size, limited ethnic population |
| Jiang et al. 2019(51) | Nanjing, China | 2 stages case-control cohorts | 895<br>Stage 1: 330<br>Stage 2: 565 | Cephalometric analysis (ANB angle, Wits appraisal, Overjet) | TaqMan assays | - **FGFR2**: rs755793, rs1047100, rs1047057, rs2162540, rs11200014, rs2981578, rs1078806, rs10736303 | Limited ethnic population |
| Yahya et al. 2018(52) | Malay population | Case-control | 31<br>Study group: 17<br>Control group:14 | Cephalometric analysis using Eastman and Wits Analysis | PCR and DNA sequencing (from saliva sample) | - **MYO1H**: rs10850110 | Small sample size, limited ethnic population, preliminary study |
| Tobón-Arroyave et al. 2018(53) | Colombian population | Cross-sectional, observational, analytic | 306<br>Study group: 44<br>Control group: 162 | Cephalometric analysis | PCR-RFLP | - **GHR** : rs6184, rs6180 | Limited ethnic population |
| Xiong et al. 2017(54) | Chinese population | Case-control | 331<br>Study group: 176<br>Control group:155 | Cephalometric tracing performed using NemoCeph NX software | Sanger sequencing | - **FGF7** : rs372127537<br>- **FGFR1** : rs13317<br>- **FGF20** : rs149242678<br>- **FGF12** : rs79176051 | Limited ethnic population |
| Gupta et al. 2017(55) | North india | Cross-sectional | 133<br>Study group: 98<br>Control group:35 | Facial profile and intraoral examinations, cephalometric analysis | PCR, gene sequencing with 3730XL DNA analyser (from blood sample) | - **MSX1** : rs186861426 | Small sample size, limited ethnic population |
| Cruz et al. 2017(56) | Brazil | Case control | 174<br>Study group: 54<br>Control group:120 | Cephalometric analysis | TaqMan assay | - **MYO1H** : rs10850110<br>- **GHR** : rs2973015<br>- **FGF10** : rs593307 | Small sample size, limited ethnic population |
| Da Fontoura et al. 2015(57) | Iowa, USA | Cross-sectional | 269<br><br>Study group: 88<br><br>Control group:181 | Lateral cephalometric radiographs + Principal Component Analysis (PCA) for skeletal classification | TaqMan asssay + KASP (competitive allele-specific PCR) | - **PAX5** : rs3780138<br>- **PAX7** : rs766325<br>- **COL1A1** : rs2249492<br>- **FGFR2** : rs2162540, rs11200014<br>- **ARHGAP29** : rs1576593<br>- **SNAI3** : rs4287555<br>- **MYO1H** : rs11066446<br>- **TWIST1** : rs985246<br>- **LTBP2** : rs3742794<br>- **SHH** : rs1233560<br>- **EDN1** : rs2070699<br>- **TBX5** : rs1248046 | Limited ethnic population |

**Table 2.** Genes and SNPs associated with Class III malocclusion and mandibular prognathism

| Gene | SNP | P-value | Significance | Gene function |
|---|---|---|---|---|
| SOX2 | rs4434184 | - Not specified | - | Involved in early head and face formation during embryonic development |
| FBN3 | rs7351083 (G allele) | - 0.0004998(34) | Yes | Contributes to connective tissues structure, influencing craniofacial morphology |
| MATN1 | rs1065755 (C>T) | - 0.471(36)<br>- 0.7984(35) | No | Directly impact cartilage formation in jaw and facial skeletal development |
| | rs20566 (T>C) | - 0.027(45) | Yes | |
| MYO1H | rs10850110 | - 0.000(52)<br>- <0.0001(56)<br>- < 0.05(41)<br>- 0.766(36)<br>- 0.680(49)<br>- 0.72(46) | Yes-No | Influences cell shape and movement, potentially affecting craniofacial growth patterns |
| | rs3825393 | - 0.010 (uncorrected), 0.025 after correction(38)<br>- 0.328(47) | Yes-No | |
| | rs11066446 | - 0.006 (uncorrected), > 0.05 after correction(57) | No | |
| RUNX2 | rs59983488 | - 0.036 (uncorrected), > 0.05 after correction(43) | No | Essential for bone formation in jaws and facial bones |
| | rs6930053 | - < 0.001(37) | Yes | |
| | rs1200425 | - 0.874 (uncorrected), > 0.05 after correction(43) | No | |
| COL1A1 | rs1107946 | - 0.055(39) | No | Provides structural support to bones and connective tissues in the orocranial region |
| | rs2249492 | - 0.008 (uncorrected), > 0.05 after correction(57) | No | |
| GHR | rs6184 | - < 0.001(53)<br>- 0.644(50)<br>- > 0.05(40) | Yes-No | Mediates growth hormone signaling, impacting overall skeletal growth, including craniofacial development |
| | rs2973015 | - 0.001(56) | Yes | |
| NOTCH4 | rs415929 | - 0.030 (uncorrected), > 0.05 after correction(42) | No | Plays a role in vascular development, essential for orocranial tissue growth |
| | rs423023 | - 0.037 (uncorrected), > 0.05 after correction(42) | No | |
| | rs520688 | - 0.049 (uncorrected), > 0.05 after correction(42) | No | |
| NOTCH3 | rs1044006 | - 0.049 (uncorrected), > 0.05 after correction(42) | No | Influences vascular smooth muscle, relevant to blood supply in the orocranial region |
| JAG1 | rs1051415 | - < 0.01 (42) | Yes | Involved in cell fate decisions during craniofacial development via Notch signaling |
| NUMB | rs75236173 (T allele) | - 0.045 (uncorrected), > 0.05 after correction(42) | No | Regulates cell fate, impacting tissue patterning in the developing face and jaws |
| EP300 | rs20551 | - 0.045 (uncorrected), > 0.05 after correction(42) | No | Influences gene expression related to craniofacial development |
| NCOR2 | rs3741513 | - 0.01499 (uncorrected), > 0.05 after correction(42) | No | Regulates gene expression, impacting craniofacial development |
| PSEN2 | rs8383 | - 0.02666 (uncorrected), > 0.05 after correction(42) | No | Involved in Notch signaling, significant for craniofacial development |
| SMAD6 | rs3934908 | - 0.02 (uncorrected), > 0.05 after correction(44) | No | Regulates BMP signaling, influences skeletal development, including jaw and facial bone formation |
| FGF3 | rs1893047 | - 0.037 (uncorrected), > 0.05 after correction(48) | No | Influences skeletal development, including jaw and facial bone formation |
| FGFR2 | rs2981578 | - Stage 1: 0.007, Stage 2: 0.004(51) | Yes | A receptor for FGFs, involved in craniofacial bone and tissue growth |
| | rs1078806 | - Stage 1: 0.001, Stage 2: 0.047(51) | Yes | |
| | rs11200014 | - Stage 1: 0.001, Stage 2: 0.034(51)<br>- 0.005 (uncorrected), > 0.05 after correction(56) | Yes-No | |
| | rs10736303 | - Stage 1: 0.007, Stage 2: 0.004(51) | Yes | |
| | rs2162540 | - 0.204(51)<br>- > 0.05 after correction(57) | No | |
| FGF7 | rs372127537 | - 0.00042(54) | Yes | Supports epithelial tissue development, relevant to oral and facial tissues |
| FGF10 | rs593307 | - 0.001(56) | Yes | Plays a role in craniofacial development |
| TWIST1 | rs985246 | - 0.000076 (uncorrected), < 0.05 after correction(57) | Yes | Involved in craniofacial mesoderm development and bone formation, directly influencing jaw and facial shape |

# 5. DISCUSSION

## 5.1. Findings and Interpretation of Polymorphisms

Malocclusions affect between 39-93% of the global population(58), making it the most common orthodontic problem worldwide. While Class III malocclusion is not that widespread, it is the most challenging to treat due to high surgical need, growth unpredictability, ethnic disparities in prevalence, and high relapse rates after treatment(59). If environmental factors such as oral habits and diet are known to contribute(15), the frequent occurrence of Class III malocclusion within family (with heritability studies estimating genetic factors account for about 60% of the risk(60)) indicates an important genetic component.

This study was designed to evaluate the genetic variants most consistently associated with Class III malocclusion, focusing on their functional mechanisms and potential interactions with environmental factors.

Given the large number of genetic polymorphisms analyzed, this discussion focuses primarily on genes that showed strong statistical signals in the results and have robust support in the literature for their role in craniofacial development and Class III malocclusion. Among these, MYO1H stands out as the most relevant gene, as well as FGFR2, RUNX2, and GHR. While other genes such as FBN3 and MATN1 are biologically plausible genes of interest and were included in the analysis, their associations were weaker or less consistent, and evidence from previous studies remains limited. Other genes including FGF7/FGF10 and JAG1 showed potential associations but require further validation, while NOTCH4 and COL1A1 demonstrated inconsistent signals and will not be discussed in depth due to insufficient supporting evidence.

### 5.1.1 Mechanisms Linking Polymorphisms to Phenotype

Several genes have been identified in this research as potentially contributing to Class III malocclusion and mandibular prognathism, including FNB3, MATN1, RUNX2, GHR, JAG1, FGFR2, FGF7, FGF10, and TWIST1. Each of these genes is involved in craniofacial growth pathways. This research suggests that polymorphisms within these genes likely contribute to the development of Class III malocclusion. Moreover, it highlights the presence of varied mechanisms of influence across different genes and their associated polymorphisms.

FBN3 encodes fribrillin-3, which regulates TGF-β signaling and is implicated in the formation of the extracellular matrix in mandibular condylar cartilage. The rs7351083-G allele, located in a regulatory region of FBN3(34), could increase the expression or function of FBN3 in the mandibular condylar cartilage, leading to excessive vertical and horizontal mandibular growth.

Similarly, MATN1 encodes matrilin-1, a protein important for cartilage structure, and its rs20566 variant could affect how cartilage organizes itself, possibly resulting in abnormal condylar growth and changes in jaw length(36).

RUNX2 encodes the runt-related transcription factor 2, a regulator of osteoblast differentiation which is essential for intramembranous ossification, maintaining cranial suture and tooth development. The rs6930053 variant is located in an intron (non-coding sequence of a gene), but it could still affect the gene expression by influencing regulatory mechanisms(61). This could lead to increased mandibular length and gonial angle, as well as the acceleration of osteoblast activity in the mandibular condyle(62).

GHR encodes the growth hormone (GH) receptor, which mediates IGF-1 production and mandibular growth during puberty (it affects endochondral ossification of the condyle). rs2973015 may increase GH sensitivity in condylar cartilage, leading to an increased ramus height(63).

JAG1 encodes a Notch signaling ligand involved in the cranial suture pattern. The rs1051415 variant is located in an exonic region (coding sequence of a gene) of JAG1(42). As the gene plays an important role in mandibular symmetry, rs1051415 could result in asymmetric mandibular growth or disrupt maxillomandibular proportionality due to altered timing of suture fusion.

FGFR2 encodes fibroblast growth factor (FGF) receptor 2, which regulates maxillary development. This gene is also involved in cranial suture homeostasis and osteoblast proliferation. The presence of the rs2981578 variant disrupts normal FGFR2 protein production, contributing to maxillary hypoplasia(54). On the other hand, rs1078806 and rs10736303 are associated with reduced midface projection(64).

Both FGF7 and FGF10 encode FGFs, which play a key role in branchial arch formation, mandibular mesenchymal proliferation, and tooth bud formation. The rs372127537 variant in FGF7 and rs593307 in FGF10 have both been associated with increased mandibular length, and can lead to excessive mesenchymal proliferation in the mandibular process(44). Their potential interaction with FGFR2 may enhance mandibular growth.

TWIST1 encodes the Twist-related protein 1, which is involved in cranial suture maintenance, neural crest cell migration, and osteoblast differentiation. The presence of the rs2189000 variant is associated with a shorter ramus and a longer mandibular body (typical of the Class III model)(57).

MYO1H encodes a myosin protein involved in masticatory muscle function and plays a role in their development. The rs10850110-G allele can modify the expression of MYO1H and thus affect the development and function of jaw muscles(65). As the muscle force exerted on the mandible changes, it could influence the mandible's growth and position. MYO1H's effect may also add to the effect of other genes like FGFR2 and GHR, resulting in an exacerbated mandibular prognathism(66).

### 5.1.2 Comparison with Existing Polymorphism Studies

My findings both support and deny findings from existing literature regarding the genetic basis of Class III malocclusion. Several genes previously implicated in craniofacial development are confirmed to have an effect on Class III malocclusion development in this study. Others, however, showed population-specific variability.

#### *5.1.2.1 MYO1H*

MYO1H also showed a significant association with mandibular prognathism in my study, especially the variants rs10850110 and rs3825393. These findings are consistent with those reported by Tassopoulou-Fishell et al.(65) and Lee et al.(67), who demonstrated MYO1H's role in modulating osteoblast function and mandibular length. However, other studies such as Frazier-Bowers et al.(68) and Dai et al.(69) did not find significant associations**,** suggesting possible differences in sample characteristics or phenotype definition.

#### *5.1.2.2 FGFR2*

Variants in FGFR2 (rs2981578, rs1078806, rs10736303) were also strongly associated with maxillary hypoplasia in my cohort and in prior research. For instance, Xiong et al.(54) confirmed the involvement of these variants in Class III malocclusion in a large East Asian GWAS, supporting FGFR2's critical role in midfacial development. In contrast, Cruz et al.(56) did not find these associations in a Brazilian cohort, indicating that ethnicity may influence genetic expression.

*5.1.2.3 RUNX2*

The transcription factor RUNX2 (rs6930053) was associated with mandibular development in this study data, in agreement with the findings of Vieira et al.(70), who linked this gene to increased mandibular length. However, findings remain inconsistent, as seen in the study by Mokhtar et al.(71), which found no significant associations. The disparity may reflect phenotypic variability or differences in measurement methods between studies.

*5.1.2.4 GHR*

GHR (rs2973015) was also identified as a gene of interest, especially in relation to mandibular growth. This aligns with findings from Park et al.(40) in Korea and Yamaguchi et al.(72) in Japan. On the other hand, no such association was reported by Tobón-Arroyave et al.(53) in Latin America or by Alhammadi et al. (73) in the Middle East. These findings again highlight possible population-specific effects.

*5.1.2.5 MATN1 and FBN3*

Additional genes such as MATN1 (rs20566) and FBN3 (rs7351083) showed more variable results. Fresquet et al.(74) reported that MATN1 interacts with aggrecan production in condylar cartilage, whereas Aszódi et al.(75) found no association. Similarly, FBN3 was linked to Class III malocclusion in Chinese populations by Dehesa-Santos et al.(76), but this was not observed in European populations studied by Topârcean et al(34).

*5.1.2.6 Other Findings*

Other significant findings have been identified beyond those directly associated with Class III malocclusion development. For instance, the rs708111 variant in the WNT3A gene emerged as a potential protective factor against mandibular prognathism(44). Additionally, variants in FGFR2, RUNX2, and BMP2 showed an association with Class II malocclusion(44,57), suggesting that different malocclusion types may share overlapping genetic pathways. Such overlap could indicate that these genes influence fundamental processes of craniofacial growth, impacting multiple occlusion types. The specific manifestation as Class II or Class III may be determined by additional genetic or environmental factors. These variants might act as genetic enablers or susceptibility factors, creating a susceptibility to malocclusion that necessitates other triggers for specific phenotypic expression. The association of the FGFR3 rs2284622 variant with both

maxillary constriction and mandibular prognathism strongly supports this enabler hypothesis, demonstrating how a single genetic factor may contribute to divergent malocclusion phenotypes depending on secondary influences(54). In both cases, the findings highlight how subtle genetic variations can establish predispositions that interact with other influences to shape craniofacial development. Importantly, future research should investigate if these variants modify treatment responses. Their potential enabling function suggests that certain malocclusions, where the genetic predisposition is less complex, might be more responsive to biomechanical intervention.

Further supporting the significant role of genetics in craniofacial development, familial inheritance patterns observed in several studies further support the genetic basis of craniofacial variations associated with Class III malocclusion.

### 5.1.3 Influence of Population Variation

The identification of consistent genetic factors associated with Class III malocclusion is often complicated by population variation, which includes both ancestry-specific genetic backgrounds and geographic-specific environmental exposures. Several of my findings suggest that the genetic contribution to malocclusion may differ across populations. For instance, FGFR2 and GHR showed stronger associations with Class III malocclusion in East Asian populations compared to Latin American or European groups. As previously discussed in section 5.1.2.2, while this thesis's FGFR2 findings align with Xiong et al.(54), they were not replicated by Cruz et al.(56), which may reflect ancestry-related effects.

The variability in how Class III malocclusion presents phenotypically also plays a role, as the relevance of genes like MATN1 and RUNX2 may vary depending on whether measurements focus on the condyle, ramus, or the entire mandibular length. Gene-environment interactions may further contribute to discrepancies. For example, the effect of GHR observed by Park et al.(40) in Koreans may be modulated by dietary habits such as high protein intake, a factor potentially lacking in the Latin American sample examined by Tobón-Arroyave et al.(53).

As variations in these findings suggest potential differences in genetic background or environmental factors, it emphasizes the necessity of considering population-specific genetics when developing screening tools and treatment approaches.

## 5.2. Clinical Relevance

Identifying specific genetic markers linked to Class III malocclusion could allow for earlier diagnosis and treatment. This might decrease the need for invasive adult treatments, such as orthognathic surgery.

A genetic screening tool to identify polymorphisms associated with Class III malocclusion could improve treatment planning by distinguishing underlying skeletal causes. For instance, early detection of maxillary retrognathism-related variants could prompt treatment focused on the maxilla, such as maxillary expansion. Similarly, mandibular prognathism markers may guide clinical focus on mandibular growth management, employing facemask therapy or chin-cup devices.

This approach would enable dentists to implement phenotype-specific interventions during active growth periods, potentially enhancing treatment efficacy, as this is when such interventions are more effective (77). Early detection could also help prioritize patients with a higher genetic risk for more careful monitoring**.**

However, treating Class III malocclusion early poses a significant challenge as final results depend on the patient's remaining growth. While interceptive treatment can help, the ultimate outcome is still influenced by the individual's natural growth pattern. Additionally, since Class III malocclusion is influenced by both genes and environment, genetic markers alone may not be enough to accurately predict the development of the condition (78). On top of that, genetic screening raises ethical issues such as potential discrimination regarding price and access, psychological risks including anxiety related to genetic predisposition, and the crucial requirement of informed consent. These concerns necessitate careful management in accordance with ethical guidelines, such as those established in Europe for genetic testing. Looking ahead, the rapid evolution of genomic medicine offers promising solutions to these challenges. The increasing affordability of genetic testing is enhancing accessibility, while established regulations including Europe's GDPR and the U.S. GINA are setting global standards for data protection. Established genetic counseling frameworks and education programs, adapted from oncology and cardiology practice, now provide effective mitigation of psychological risks(79). These protocols, combined with advancing orthodontic research, could enable clinically viable genetic screening applications in the near term.

However, it should be noted that while identified polymorphisms suggest future potential for personalized treatment planning, no clinically available genetic screening tool currently exists for

Class III malocclusion. Emerging research combining genetic and clinical data shows promising predictive accuracy (40), though clinical implementation requires further validation (80).

### 5.3. Study Bias and Limitation

Several limitations and biases must be considered both in the articles reviewed and when interpreting my findings on the genetic basis of Class III malocclusion.

Firstly, as previously stated in section 4.1, variations in control group composition across studies complicate direct comparisons. Additionally, although most studies relied on cephalometric analysis, the specific diagnostic criteria varied, particularly the range of degrees used for ANB, SNB, and SNA angles. Genotyping methods and samples also differed across studies. While some used blood samples, others used saliva samples, which are generally considered less reliable for DNA extraction(81). Moreover, the demographics of the sampled populations varied widely, with some studies focusing on specific populations or countries, limiting the scope of their findings.

Unmeasured environmental factors such as dietary habits or masticatory force could also influence and confound genetic associations, further complicating the interpretation.

A major limitation across all studies was the relatively small sample size. Most did not include enough participants to draw statistically robust or globally applicable conclusions. These discrepancies complicate direct comparisons and highlight the need for larger, standardized studies with harmonized protocols to validate genetic associations. Despite this bias, the present work seeks to bridge that gap by synthesizing findings across diverse populations, potentially yielding a more coherent and broadly applicable understanding of the genetic determinants of Class III malocclusion.

One of the main biases in this study was the decision to focus exclusively on SNPs, excluding other types of polymorphisms, mainly due to the limited availability of studies addressing them. Furthermore, the applied exclusion criteria, while useful in maintaining study quality, may have also led to the omission of relevant findings, potentially narrowing the scope of analysis.

Additionally, relying solely on p-values to assess the strength of the association between genetic markers and Class III malocclusion may introduce bias. As stated previously, a significant p-value does not necessarily imply a meaningful or clinically relevant association, particularly when the measured impact is minimal or replication in independent studies is not observed. Interpretation should therefore be approached with caution.

# 6. CONCLUSIONS

This documentary research aimed to investigate the potential genetic basis of Class III malocclusion by analyzing studies that focused on specific gene polymorphisms. Through the systematic review of 25 articles, 47 genes and 67 SNPs with a possible influence on the condition were identified. Only 11 SNPs demonstrated a statistically significant association with Class III malocclusion. These included SNPs located in genes such as FGFR2, GHR, RUNX2, and MYO1H, which are involved in craniofacial development, bone remodeling, and growth regulation.

However, the results must be interpreted with caution due to several methodological limitations of the analyzed studies. Firstly, there was considerable variability in diagnostic criteria, particularly in the cephalometric angles used to define Class III malocclusion. Secondly, genotyping techniques and DNA sampling methods differed among studies, and sample sizes were often limited, which could reduce the statistical power of the findings.

Despite the biases of the study, it identifies potential genetic links that can serve as a foundation for future research aimed at a more comprehensive understanding of the genetics of Class III malocclusion. Some SNPs showed initial significance but lost it after multiple testing corrections, while others were close to the significance threshold, potentially reflecting underpowered study designs or population-specific effects. These aspects highlight the need for cautious interpretation and for further validation in larger, more diverse cohorts.

Overall, this research supports the hypothesis that genetic factors, particularly certain SNPs, may contribute to the development of Class III malocclusion. Nevertheless, future studies should aim to adopt standardized diagnostic criteria, increase sample sizes and include more ethnically diverse populations to improve the reliability and generalizability of the findings. The integration of genetic screening in orthodontic diagnosis and treatment planning remains a promising yet developing area that warrants further exploration.

# 7. SUSTAINABILITY

The study of genetic polymorphisms involved in Class III malocclusion aligns with social sustainability by contributing to personalized and preventive orthodontic care. By identifying genetic markers associated with skeletal malocclusions, this research could enable early diagnosis and intervention, reducing the need for invasive treatments such as orthognathic surgery in adulthood. This approach supports Sustainable Development Goal (SDG) 3 (Good Health and Well-Being) by improving oral health outcomes and reducing long-term healthcare costs.

From an economic perspective, understanding genetic predispositions to malocclusion could optimize resource allocation in orthodontic treatment, minimizing unnecessary procedures and focusing on high-risk patients. This efficiency aligns with SDG 12 (Responsible Consumption and Production) by promoting cost-effective healthcare strategies.

Additionally, this research fosters scientific sustainability by providing a foundation for future studies on craniofacial genetics, encouraging interdisciplinary collaboration between genetics, orthodontics, and public health, thus aligning with SDG 17 (Partnerships for the Goals).

By integrating genetic screening into early orthodontic assessments, this work supports SDG 4 (Quality Education) by advancing knowledge in precision dentistry.

Ultimately, this project emphasizes ethical responsibility in healthcare innovation, ensuring that genetic research translates into equitable, accessible, and sustainable orthodontic solutions for diverse populations.

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## FIGURES

All figures presented in this thesis were created by the author.