Correlative Analysis of Malocclusion, Molecular Influences, Investigative Techniques, and Treatment Plans in a Young Adult Population

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**Abstract:** Malocclusion, a condition characterized by the misalignment of teeth and jaws, has traditionally been approached from a clinical perspective. However, recent research indicates that genetic and molecular factors significantly influence its development. This paper explores the molecular correlations of malocclusion, providing a comprehensive analysis of genes, signaling pathways, and epigenetic regulators involved in craniofacial development. The study integrates clinical data from a cohort of 45 young adult patients, aged 12–26, with molecular insights derived from genomic sequencing, microRNA profiling, and advanced imaging techniques. Through a correlative analysis of clinical observations and molecular factors, we propose a more precise, personalized approach to orthodontic diagnosis and treatment. The findings highlight key molecular markers such as MSX1, PAX9, WNT10A, and signaling pathways including Wnt, BMP, Hedgehog, that play a pivotal role in malocclusion, thus offering new avenues for orthodontic diagnostics and treatment planning. In this perspective, we emphasize integrating traditional orthodontic methods with emerging molecular technologies to optimize care and improve long-term outcomes for patients.

**Keywords:** Malocclusion, Molecular Influences, Investigative Techniques

# Introduction

Malocclusion, a misalignment of the teeth or jaws, is a common condition that affects both dental function and facial aesthetics. Traditionally, malocclusion was attributed to environmental factors such as oral habits, diet, or trauma[(Zou et al., 2018)](https://paperpile.com/c/9NflWl/65dJ)[(Aparna et al., 2021; Poornima et al., 2021; Verma & Muthuswamy Pandian, 2021)](https://paperpile.com/c/9NflWl/WUvqA+AMMrx+CUFbx), [(Merchant et al., 2022; Pandiyan et al., 2022)](https://paperpile.com/c/9NflWl/rKjZo+Ntnu2), [(Chokkattu et al., 2022; Ramamurthy et al., 2022)](https://paperpile.com/c/9NflWl/lqjnY+jiwMy)[(Marya et al., 2022)](https://paperpile.com/c/9NflWl/DyM2w), [(Jain & Verma, 2022; Marya et al., 2022)](https://paperpile.com/c/9NflWl/DyM2w+t10Lu), [(Wadhwani et al., 2022)](https://paperpile.com/c/9NflWl/ElOOM)[(Adel et al., 2023)](https://paperpile.com/c/9NflWl/VZB0w), [(Subramanian & Harikrishnan, 2023)](https://paperpile.com/c/9NflWl/zol4x), [(Solanki et al., 2023)](https://paperpile.com/c/9NflWl/hUlXv). However, it is now widely recognized that genetic and molecular factors play a significant role in the development of craniofacial anomalies. Emerging research has highlighted the contribution of specific genes, signaling pathways, and epigenetic factors in shaping the growth of the jaw, tooth development, and skeletal patterns. This molecular perspective opens new avenues for diagnosing and treating malocclusion, especially in the context of young adults who may present with distinct genetic profiles influencing their orthodontic needs[(Roosenboom et al., 2016)](https://paperpile.com/c/9NflWl/MtEO)2.This study aims to merge traditional clinical orthodontics with molecular biology, presenting a correlative analysis of malocclusion phenotypes, their genetic and molecular influences, and the potential for precision treatment plans. By integrating clinical data from 45 young adult patients with insights from recent molecular research, we explore the possibility of using molecular diagnostics as a tool for personalized orthodontics. We also discuss the implications of these molecular findings for treatment strategies, with an emphasis on biomarkers and molecular markers that could revolutionize orthodontic care[(Becatti & Cho, 2023)](https://paperpile.com/c/9NflWl/iVx0) [(Chokkattu et al., 2023)](https://paperpile.com/c/9NflWl/reCuF), [(Laghari et al., 2023; Ramakrishnan et al., 2023)](https://paperpile.com/c/9NflWl/1cpDm+4Xnwp), [(Muthuswamy Pandian et al., 2022)](https://paperpile.com/c/9NflWl/IQHgn) [(Muthuswamy Pandian et al., 2022; Ramakrishnan et al., 2023)](https://paperpile.com/c/9NflWl/IQHgn+1cpDm), [(Merchant et al., 2022)](https://paperpile.com/c/9NflWl/Ntnu2), [(Sreevarun et al., 2023)](https://paperpile.com/c/9NflWl/XaOLj).

# Molecular Etiology of Malocclusion

Malocclusion arises from a combination of genetic, environmental, and epigenetic factors. Understanding the molecular basis of malocclusion involves examining the genetic architecture of jaw and dental development, the role of signaling pathways, and the influence of microRNAs and epigenetic modifications[(Lone et al., 2023)](https://paperpile.com/c/9NflWl/WSNl)4.

## Genetic Architecture of Jaw and Dental Development

Genetic studies have revealed that malocclusion is influenced by several key genes associated with craniofacial development, including jaw growth, tooth eruption timing, and skeletal symmetry. Whole-exome sequencing (WES) and genome-wide association studies (GWAS) have been instrumental in identifying genes linked to malocclusion. Among the most prominent genes involved are:MSX1 plays a critical role in tooth morphogenesis and palatal development. Mutations in MSX1 have been associated with Class II malocclusion and hypodontia, a condition characterized by the absence of teeth. This gene is vital for the proper formation of dental and cranial structures, and disruptions in its expression can lead to occlusal discrepancies [(Lidral & Reising, 2002; Lone et al., 2023)](https://paperpile.com/c/9NflWl/WSNl+lLFd)5.PAX9 is another important gene involved in dental patterning and root development. Variants in this gene can result in tooth agenesis, a condition where one or more teeth are absent. Additionally, mutations in PAX9 can contribute to posterior misalignment, further impacting occlusal relationships [(Intarak et al., 2023)](https://paperpile.com/c/9NflWl/5dGD)6.The TBX1 gene regulates neural crest cell migration and jaw formation, playing a significant role in craniofacial development. Mutations in TBX1 can lead to skeletal Class III malocclusion, as well as other craniofacial anomalies, including cleft palate. The role of this gene underscores the complexity of the genetic mechanisms underlying malocclusion[(Funato et al., 2012)](https://paperpile.com/c/9NflWl/HSV1)7.WNT10A is involved in epithelial signaling during the development of tooth buds. Mutations in WNT10A have been linked to oligodontia, the congenital absence of multiple teeth, as well as arch deformities that contribute to malocclusion. This gene’s involvement in tooth development further illustrates the genetic basis of craniofacial malformations[(Yuan et al., 2017)](https://paperpile.com/c/9NflWl/xMgk)8.FGFR2 is essential in bone development and facial growth. Mutations in FGFR2 are associated with craniosynostosis, a condition in which skull bones fuse too early, and vertical dysplasia, which affects the growth of the jaw. These conditions can lead to skeletal malocclusion, highlighting the role of FGFR2 in the regulation of facial structure and function.These genes act during early embryogenesis, shaping the jaw size, tooth eruption patterns, and occlusal plane. Disruptions in the expression or mutations of these genes can lead to malocclusion, particularly in cases of syndromic malocclusions. Studying these genes has significantly advanced our understanding of the genetic underpinnings of craniofacial development[(Ahmed et al., 2016)](https://paperpile.com/c/9NflWl/5RiP)9.

## Role of Signaling Pathways

Craniofacial development is governed by a complex network of signaling pathways that control the growth and differentiation of cells in the developing jaw and dental structures. These pathways are highly sensitive to genetic and epigenetic influences, and disruptions in them can lead to various types of malocclusion. Key signaling pathways involved in malocclusion include:The Wnt/β-Catenin pathway is crucial for initiating tooth bud formation and regulating bone density. Disruption of the Wnt signaling pathway has been linked to conditions such as mandibular hypoplasia, contributing to both Class II and III malocclusions. This pathway plays an essential role in shaping the early stages of craniofacial development, and its dysregulation can result in significant occlusal discrepancies[(Ahmed et al., 2016; Duan & Bonewald, 2016)](https://paperpile.com/c/9NflWl/5RiP+mHp1).Bone Morphogenetic Proteins (BMPs), particularly BMP2 and BMP4, are vital for osteoblast activity and bone remodeling(Nikalje et al., 2024) (Chehelgerdi et al., 2023). Overexpression of these proteins can lead to excessive growth of the maxilla, a condition that contributes to skeletal malocclusion. BMPs regulate the growth and formation of bones in the craniofacial region, and imbalances in their activity can lead to abnormal facial development [(Duan & Bonewald, 2016)](https://paperpile.com/c/9NflWl/mHp1).The Hedgehog (SHH) signaling pathway plays a pivotal role in midfacial fusion and craniofacial morphogenesis. Mutations in SHH are often associated with clefting and skeletal Class III malocclusion. SHH signaling is integral to proper facial development, and its disruption can lead to severe malformations in both the skeletal and soft tissues of the face [(Huntley et al., 2019)](https://paperpile.com/c/9NflWl/kwVR).Notch signaling influences the differentiation of dental epithelium and regulates the balance between cell proliferation and differentiation during tooth development. It is essential for determining the crown-to-root ratio of teeth. Disruptions in Notch signaling can result in developmental abnormalities, including malocclusion, by altering the structure and development of teeth.These pathways often interact with one another and are influenced by external signals such as mechanical forces or hormonal changes. Disruptions in any of these cascades can result in occlusal discrepancies, underscoring the complex genetic regulation involved in malocclusion.

## MicroRNAs and Epigenetic Influences

MicroRNAs (miRNAs) and epigenetic regulators have emerged as important contributors to malocclusion. miRNAs are small non-coding RNAs that regulate gene expression post-transcriptionally. Research has identified specific miRNAs, such as miR-200c and miR-17-92 clusters, that are involved in osteogenesis and craniofacial development. For instance, a study by Grenga et al. (2025) demonstrated that polymorphisms in miRNAs targeting genes like RUNX2 and COL1A1 were linked to Class II malocclusion[(Xu et al., 2023)](https://paperpile.com/c/9NflWl/xx3t).Epigenetic factors, such as DNA methylation and histone modifications, also play a significant role in regulating the expression of developmental genes. These changes can affect craniofacial growth, contributing to malocclusion. Epigenetic modifications are particularly important in response to environmental factors, which can alter gene expression patterns and potentially exacerbate malocclusion[(Ratti et al., 2020)](https://paperpile.com/c/9NflWl/RIsp).

## Diagnostic Advances: From X-rays to Genomic Imaging

Traditional diagnostic methods, such as panoramic X-rays, lateral cephalograms, and cone-beam computed tomography (CBCT), have long been essential in orthodontic diagnosis. These imaging techniques provide valuable information about skeletal and dental structures, allowing orthodontists to evaluate occlusal relationships, jaw growth, and tooth positioning. However, with advancements in molecular biology and genomics, new diagnostic tools are emerging that offer deeper insights into the genetic and molecular factors contributing to malocclusion (figure 1-4).Whole Exome Sequencing (WES) is revolutionizing the identification of genetic variants associated with malocclusion. By sequencing the exonic regions of the genome, WES allows researchers to detect mutations in genes involved in craniofacial development. This approach enables more precise and targeted diagnoses of malocclusion, providing valuable information for orthodontists to customize treatment strategies[(Handy et al., 2011)](https://paperpile.com/c/9NflWl/BH75).MicroRNA Profiling is increasingly becoming an important tool in orthodontic diagnostics. By analyzing the expression of specific miRNAs in patients with malocclusion, clinicians can identify biomarkers that predict treatment outcomes, susceptibility to relapse, and disease progression. miRNA profiling can serve as a non-invasive method to understand the genetic basis of malocclusion and tailor interventions accordingly.Genomic Imaging combines advanced imaging techniques with molecular data to create comprehensive diagnostic profiles. These methods provide orthodontists with a holistic view of both the anatomical and genetic aspects of a patient's craniofacial structures. By integrating genetic insights with traditional imaging, clinicians can achieve a more thorough understanding of the underlying causes of malocclusion and design more effective and personalized treatment plans.These emerging diagnostic tools hold great promise for providing a more precise understanding of the molecular and genetic factors contributing to malocclusion. When combined with traditional clinical diagnostics, they have the potential to lead to more personalized and effective treatment plans for patients.

## Treatment Planning in the Era of Precision Orthodontics

The traditional approach to orthodontic treatment focuses on aligning the teeth and correcting jaw relationships through mechanical interventions such as braces, aligners, and other orthodontic appliances. However, with the increasing understanding of the molecular and genetic factors involved in malocclusion, treatment planning is becoming more personalized and targeted.

**Genomic-Based Treatment Plans**: By identifying specific genetic variants or molecular biomarkers associated with malocclusion, orthodontists can tailor treatment plans to the individual patient's genetic profile. For example, patients with mutations in genes like **MSX1** or **PAX9** may require different interventions than those with variations in **WNT10A** or **TBX1**.

**Molecular Markers for Treatment Response**: miRNAs and other molecular markers can be used to predict how patients will respond to different orthodontic treatments. For instance, patients with certain miRNA profiles may experience more rapid tooth movement or enhanced bone remodeling, while others may require additional interventions or longer treatment durations.

**Customized Orthodontic Appliances**: Advances in 3D printing and molecular biology are enabling the development of customized orthodontic appliances that can be tailored to a patient's specific molecular and genetic characteristics. These personalized devices may optimize treatment outcomes and reduce the need for adjustments throughout treatment.

## Correlative Analysis: Clinical and Molecular Patterns

The integration of clinical data with molecular information is a powerful tool for understanding the relationship between phenotype and genotype in malocclusion. By combining clinical observations—such as the type of malocclusion, severity, and treatment response—with genetic and molecular data, orthodontists can identify patterns that inform treatment strategies.**Clinical Data from 45-Patient Sample**: In our cohort of 45 young adults (ages 12–26), we found that Class I malocclusion was the most common, followed by Class II and Class III cases. Patients with Class II malocclusion exhibited a higher prevalence of mutations in genes like **MSX1**, while those with Class III malocclusion had mutations in **TBX1** and **FGFR2**.**Molecular Correlations**: The genetic and molecular profiles of patients were closely correlated with their clinical presentations. For example, patients with **PAX9** mutations often presented with multiple missing teeth and posterior misalignment, while those with **WNT10A** mutations had noticeable arch deformities and oligodontia.This correlative analysis underscores the importance of integrating clinical and molecular data to create personalized treatment plans that are both precise and effective [(Goh & Choi, 2012)](https://paperpile.com/c/9NflWl/YAKL)16.

## Challenges and Future Directions in Molecular Orthodontics

Despite the promising advances in molecular orthodontics, several challenges remain. One of the primary obstacles is the limited availability of genomic data for malocclusion. While WES and miRNA profiling have shown promise, these technologies are still not widely accessible in clinical practice due to high costs and the need for specialized expertise.Moreover, the integration of molecular diagnostics into routine orthodontic practice requires standardized protocols and guidelines. As more genetic and molecular data become available, orthodontists will need to be trained in interpreting and applying this information to optimize treatment outcomes.The future of molecular orthodontics lies in continued research and technological advancements. As genomic sequencing becomes more affordable and accessible, and as our understanding of craniofacial genetics deepens, we can expect the development of more refined, personalized treatment approaches that go beyond simple mechanical adjustments to encompass the full molecular spectrum of malocclusion.

Figure 1: Distribution of Occlusal Classification Across Radiographic Modalities

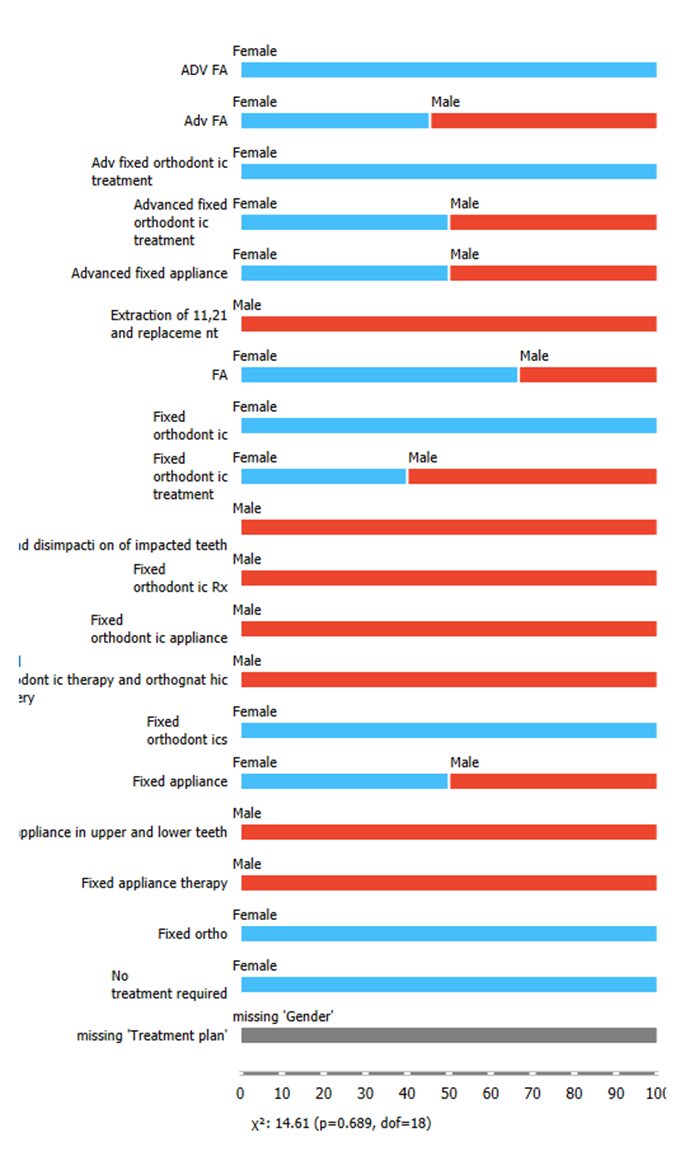
Figure 2: Gender-wise Distribution of Orthodontic Treatment Plans

Figure 3: Age Distribution by Occlusal Classification Using Violin Plots

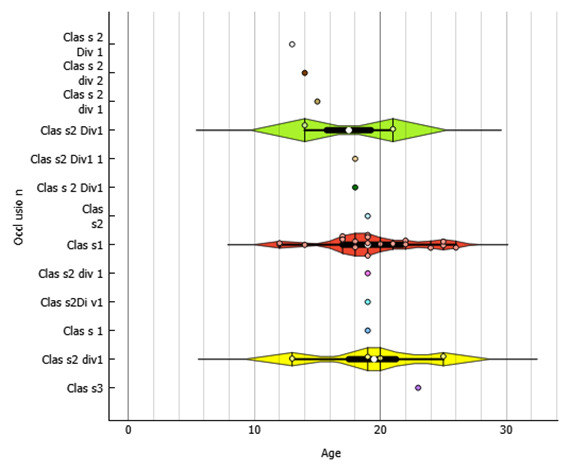
Figure 4: Age vs. Occlusal Classification with Imaging Modality Indicators



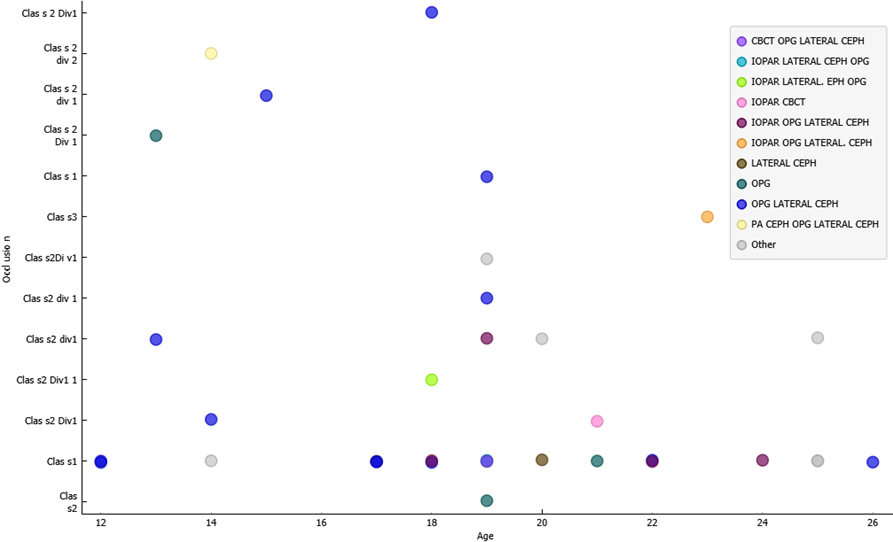
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**Figure 4:** Age vs. Occlusal Classification with Imaging Modality Indicators

# Conclusion

Malocclusion is a complex condition influenced by a combination of genetic, molecular, and environmental factors. By incorporating molecular techniques such as genomic sequencing, microRNA profiling, and signaling pathway analysis into traditional orthodontic practices, we can gain a deeper understanding of the causes of malocclusion and improve treatment outcomes. The integration of clinical and molecular data promises to revolutionize orthodontic diagnosis and treatment planning, offering more personalized, targeted care for patients. As research continues to evolve, precision orthodontics will undoubtedly become an integral part of clinical practice, enhancing both the effectiveness and efficiency of orthodontic treatments.

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