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Genetic Influence of ACTN3 Gene Polymorphism rs1815739 on Skeletal Class II Malocclusions with Mandibular Retrognathism

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KEYWORDS

Class II malocclusion, Mandibular retrognathism, *ACTN3*, Gene polymorphism, Genotyping

ABSTRACT:

Introduction: Skeletal Class II malocclusion with mandibular retrognathism is a prevalent dentofacial anomaly influenced by both genetic and environmental factors. The *ACTN3* gene, which plays a critical role in skeletal muscle structure and function, has been proposed to affect craniofacial growth.

Objectives: This study evaluated the association between the *ACTN3* gene polymorphism rs1815739 (C>T) and skeletal Class II malocclusion with mandibular retrognathism in an Indian population.

Methods: A case-control study was conducted involving 90 subjects aged 20 ± 1.5 years, comprising 45 individuals with skeletal Class II malocclusion (cases) and 45 with normal mandibular development (controls). Mandibular retrognathism was assessed using the SNB angle on lateral cephalograms. Genomic DNA was extracted from peripheral blood samples, and genotyping for rs1815739 was performed using Restriction Fragment Length Polymorphism-Polymerase Chain Reaction (RFLP-PCR). Statistical analyses included Chi-square test, odds ratio calculation, and Hardy-Weinberg equilibrium assessment.

Results: Genotype distribution in the control group was CC (22%), CT (46.7%), and TT (31.1%), whereas the case group showed CC (11.1%), CT (64.5%), and TT (24.4%). Allele frequencies for the C and T alleles were 0.45 and 0.55 in controls and 0.43 and 0.57 in cases, respectively. No statistically significant association was found between the rs1815739 polymorphism and skeletal Class II malocclusion ($p > 0.05$).

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Conclusion: The findings indicated that no statistically significant association between the *ACTN3* gene SNP rs1815739 and the skeletal Class II malocclusion with mandibular retrognathism, suggesting that rs1815739 is unlikely to be a major contributing factor in its etiology in the Indian population.

1. Introduction

Malocclusion is the third-most common oral health issue, generally classified into Class I, Class II, and Class III categories in orthodontics. The prevalence and characteristics of malocclusions can vary across different regions and ethnic groups worldwide [1]. Among these, skeletal Class II malocclusions represent more than one-third of all malocclusions observed globally, with Caucasians being particularly affected more than any other population in the world [2]. The prevalence of Class II malocclusion in the Indian population has been reported to vary from 8% to 29% [3].

Skeletal malocclusions cause a complex craniofacial growth and developmental problems. The most frequent problems associated with these conditions include altered facial appearance, limited masticatory function, temporomandibular joint (TMJ) dysfunction, an increased risk of dental trauma, and compromised quality of life [4].

The etiology of malocclusion is multifactorial, involving both genetic and environmental factors that influence various components of the craniofacial complex, including bones, teeth, and muscles. Research, particularly from family and twin studies, has shown that genetic factors play a significant role in the development of skeletal Class II malocclusions [5]. As the genetic contribution to malocclusion increases, the success rate of orthodontic and orthopedic treatments tends to decrease. Class II and Class III malocclusions are generally considered more complex than Class I malocclusions, which makes their treatment more challenging. However, genetic studies focusing on Class II and Class I malocclusions are relatively scarce [6]. Gaining a deeper understanding of the etiological factors behind dentofacial variations is essential for developing more effective and patient specific treatment strategies. Current literature suggested several genes such as *FGFR2, ACTN3, MSX1, MATN1, MYOH1, BMP2, ADAMTS9, AJUBA, GHR, KAT6B,* and *HDAC4* are positively associated in the genetic etiology skeletal class II malocclusion [7].

The *ACTN3* (Alpha-Actinin-3) gene encodes an actin-binding protein that is specifically expressed in skeletal muscle fibers and is located on human chromosome 11 at position 11q13.2. The protein has a molecular mass of approximately 103 kD and features an N-terminal actin-binding domain comprising about 250 amino acids. *ACTN3* is localized to the Z-line of muscle fibers, where it plays a crucial role in organizing the structural framework of muscle cells and contributes to the efficiency of muscle contraction [8]. *ACTN3* influences elite athletic sprinting muscle performance and fiber type proportions. It plays a key role in muscle contraction, particularly in sprinting and jumping [9].

Studies suggest that genetic variants of the *ACTN3* gene may influence craniofacial development, impacting both the skeletal and muscular components involved in malocclusion. Genetic research has indicated that *ACTN3* is expressed in individuals with skeletal Class II malocclusion, pointing to a potential biological role in bone growth and development. This suggests that *ACTN3* may contribute to the underlying genetic mechanisms influencing craniofacial structure, particularly during critical growth periods [10-12].

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2. Objectives

Current literature revealed that the genetic studies related skeletal class II malocclusions are very few within the Indian population. Hence, in the present study, we tested for the possible association between *ACTN3* gene Single nucleotide polymorphisms (SNP) rs1815739 located in the 11q13.2 region and skeletal class II malocclusions with mandibular retrognathism.

3. Methods

Research design and Ethical approval

The Institutional Review Board (IRB No. 23/Vol-1/2023) approved this case-control study, and it was performed as per Helsinki guidelines on medical research and ethics. Written informed consent was obtained from all adult participants. For minors, consent was provided by their parents or legal guardians. Lateral cephalograms were acquired for all study participants. Cephalometric tracings and measurements, (angle between sella-nasion-B point [SNB]) were made using the OneCeph digital cephalometric tracing software (version beta 1.1, NXS, Hyderabad, India).

Study participants, inclusion, and exclusion criteria

A total of 90 subjects of both genders, aged 20 ±1.5years, were included in the study. The sample comprised 45 subjects with Class II malocclusion and mandibular retrognathism (cases), and 45 subjects with normal mandibular development (controls). Patients with a retrognathic mandible (angle between sella-nasion B point [SNB] <78°) were included as the cases, and controls were selected based on a normal SNB angle of 80 ± 2°. Patients with abnormal maxilla, growth and development disturbances, craniofacial syndromes, orofacial clefts, any missing teeth and trauma were excluded from the study.

DNA isolation and SNP genotyping

Four milliliters of peripheral venous blood were collected in the Ethylene Diamine Tetra Acetic acid (EDTA) coated tubes from each subject. Genomic Deoxyribonucleic Acid (DNA) was isolated from blood lymphocytes using a Qiagen DNA Mini kit (Qiagen GmbH, Hilden, Germany) following the manufacturer's protocol. The isolated DNA was then amplified using polymerase chain reaction (PCR).

Amplification of the *ACTN3* gene SNP rs1815739 was performed using the following primers: forward primer 5′-CTGTTGCCTGTGGTAAGTGGG-3′ and reverse primer 5′-TGGTCACAGTATGCAGGAGGG-3′. The PCR amplification was performed under the following standard conditions: an initial denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 45 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 1 minute. A final extension step was carried out at 72°C for 10 minutes. The PCR products were then analyzed by electrophoresis on a 2% agarose gel and visualized under ultraviolet (UV) light using a gel documentation system. Genotyping of the amplified products was conducted using Restriction Fragment Length Polymorphism-Polymerase Chain Reaction (RFLP-PCR).

Statistical analyses

The genomic data were analyzed using MedCalc statistical software (https://www.medcalc.org) The Hardy-Weinberg equilibrium (HWE) for the *ACTN3* gene polymorphism (SNP rs1815739) was assessed in both cases and controls using the Chi-square test**.** The genotype and allele distribution of the *ACTN3* gene SNP rs1815739 in both cases and controls were statistically evaluated. The Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between genotypes and

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case-controls. A p-value < 0.05 was considered statistically significant.

4. Results

A total of 90 patients were evaluated, with 45 individuals in each of the case and control groups. Figure 1 shows the agarose gel template with different genotypes of the *ACTN3* gene (rs1815739).

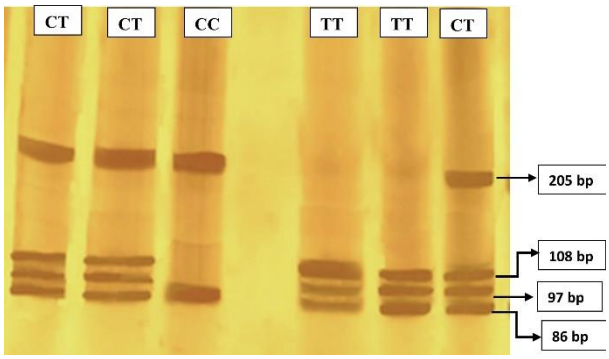

Figure 1. Agarose gel template showcasing different genotypes of the *ACTN3* gene (rs1815739), RFLP -PCR band pattern for different genotypes as follows: CC genotype (205 + 86bp bands), CT genotype (205 + 108 + 97+ 86bp bands) and TT genotype (108 + 97+ 86bp bands)

Genotype	Cases vs Controls OR (95% CI)	p-value
CC vs CT	2.76 (0.82 to 9.27)	0.10
CC vs TT	1.57 (0.41 to 5.95)	0.50
CC vs CT+TT	2.28 (0.71 to 7.33)	0.16
TT vs CC+CT	0.71 (0.28 to 1.81)	0.48
CT vs CC+TT	2.07 (0.88 to 4.82)	0.09
C	reference	reference
T	1.09 (0.60 to 1.97)	0.76

Table 1 presents the genotype and allele distribution of the *ACTN3* SNP rs1815739. In the control group, the genotype frequencies were: CC in 10 individuals (22%), CT in 21 individuals (46.7%), and TT in 14 individuals (31.1%). In the case group, the distribution was: CC in 5 individuals (11.1%), CT in 29 individuals (64.5%), and TT in 11 individuals (24.4%).

Table 1: Genotype and allele distribution of *ACTN3* gene SNP rs1815739 (C>T) in controls and cases

Genotype/ Alleles	Cases n=45 (%)	Controls n=45 (%)
CC	5 (11.1)	10 (22)
CT	29 (64.5)	21 (46.7)
TT	11 (24.4)	14 (31.1)
C	39 (0.43)	41 (0.45)
T	51 (0.57)	49 (0.55)

Abbreviations: C: Cytosine, T: Thymine

Table 2 provides a comprehensive summary of the risk assessment associated with the *ACTN3* variant rs1815739 polymorphism, using odds ratios to quantify the strength of association between different genotypes.

Table 2: Risk assessment by Odds Ratio (OR) for *ACTN3* gene SNP rs1815739 (genotype and allele)

Abbreviations: C: Cytosine, T: Thymine, OR: Odd's Ratio, CI: Confidence Interval

In this study, the *ACTN3* polymorphism (rs1815739:C>T) did not show a significant association with skeletal class II malocclusion. The allele frequency of the C allele was 0.45 in the control group and 0.43 in the case group, while the T allele frequencies were 0.55 in controls and 0.57

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in cases. Statistical analysis revealed no significant difference (P > 0.05) in the distribution of *ACTN3* genotypes between the two groups, suggesting that this polymorphism is not a contributing factor to the development of skeletal class II malocclusion.

5. Discussion

The etiology of malocclusion is multifactorial, involving genetic and environmental factors acting on the various components of the craniofacial complex, including bones, teeth, and muscles. Increasingly, genetic analyses are being employed to explore the underlying causes of different types of malocclusions [13]. With advancements in molecular genetics, genetic polymorphism identification in our population would be vital in identifying the biological mechanisms involved in causing these defects.

Advancements in gene identification studies have led to the discovery of several genes implicated in the genetic etiology of Class II malocclusion. Current literature suggests that genes such as *FGFR2, ACTN3, MSX1, MATN1, MYOH1, BMP2, AJUBA, ADAMTS9, GHR, KAT6B, PAX9* and *HDAC4* are positively associated with the development of skeletal Class II malocclusion [14-17]. Nakasima et al. analyzed lateral cephalometric radiographs of patients with mandibular retrognathism and their parents across multiple families. Their findings indicated a strong familial tendency in the development of Class II malocclusion, suggesting a significant genetic component in its etiology [18].

The *ACTN3* gene, encoding α-actinin-3, is a structural protein found in fast-twitch muscle fibers and has been widely studied in the context of muscle performance and athletic phenotypes [19]. Although *ACTN3*'s role in skeletal muscle physiology is well established, its involvement in craniofacial development remains unclear. A few studies have proposed that masticatory muscle strength and function, which are partially governed by genetic factors, may influence mandibular growth patterns, thereby affecting the development of malocclusions [20].

The current study investigated the association between the *ACTN3* gene polymorphism (rs1815739: C>T) and skeletal Class II malocclusion with mandibular retrognathism in a cohort of 90 subjects (45 cases and 45 controls). Our analysis demonstrated no significant association between the rs1815739 genotype and class II skeletal malocclusion. The allele frequencies were comparable between cases (C: 0.45, T: 0.55) and controls (C: 0.42, T: 0.58), and odds ratio analysis under both dominant and recessive models did not reveal a statistically significant (P > 0.05) risk conferred by any specific genotype. Despite previous evidence suggesting a potential link between *ACTN3* and craniofacial development, our findings did not reveal a statistically significant association between the rs1815739 polymorphism and the occurrence of skeletal Class II malocclusion.

Previous research has suggested a potential link between *ACTN3* polymorphisms and craniofacial morphology. Zebrick et al., reported a significant overrepresentation of the 577XX (TT) genotype in individuals with skeletal Class II malocclusion, indicating a potential role of *ACTN3* in the horizontal growth dimension of the facial skeleton [10]. In contrast, our findings do not support a similar association within the Indian population, suggesting that population-specific genetic backgrounds or differing environmental interactions may influence craniofacial development outcomes.

A study by Cunha et al., evaluated the association of genetic variant *ACTN3* with craniofacial skeletal patterns in Brazilian populations. Significant associations were found between these genetic variant and sagittal and

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vertical craniofacial patterns, indicating that *ACTN3* may influence craniofacial morphology [21]. Izaddin Alalim et al., analyzed the *ACTN3* rs1815739 polymorphism in relation to various craniofacial skeletal patterns in a Turkish cohort. While no significant differences were found concerning vertical or sagittal facial patterns, associations were observed between this polymorphism and the maxillary anteroposterior position and incisor inclination, suggesting a role in specific craniofacial features [22].

Yaylacı et al., found no overall significant association between *ACTN3* rs1815739 and open bite malocclusion, although a trend was observed toward increased severity in individuals with the XX genotype [23]. This supports our study observation that while differences in genotype frequencies exist between malocclusion and control groups, these are not statistically robust. The current findings reinforce the notion that *ACTN3* may not act as a major independent determinant but could contribute to phenotypic variability in combination with other genetic or environmental factors. These discrepancies across studies may arise from differences in sample size, ethnicity, age groups, phenotyping criteria, or gene-environment interactions.

Collectively, these studies suggest that *ACTN3* genetic variants may influence craniofacial development, affecting both skeletal and muscular components of malocclusion. Our findings support the growing body of evidence indicating that the genetic basis of malocclusion is complex and likely polygenic. Several genes, including *FGFR2, MSX1, MATN1, MYOH1, BMP2, PAX9, ADAMTS9, AJUBA, TNF-a, KAT6B,* and *HDAC4* [24, 25], are more directly linked to craniofacial development and susceptibility to malocclusion. It is likely that interactions between multiple genetic variants across these genes contribute to the phenotypes of malocclusion. However, further research is necessary to fully elucidate these genetic influences and their clinical implications.

The present preliminary study contributes to the limited body of literature on the genetic etiology of skeletal Class II malocclusion within the Indian population. It also highlights the need for population-specific genetic studies, as findings in one ethnic group may not be generalizable to others due to genetic diversity.

6. Conclusion

The present study investigated the association between the *ACTN3* gene polymorphism rs1815739 (C>T) and skeletal Class II malocclusion with mandibular retrognathism in an Indian population. The results demonstrated no statistically significant association between this genetic variant and the condition, suggesting that rs1815739 is unlikely to be a major contributing factor in its etiology. This highlights the complexity of genetic markers, as a variant identified as a risk factor in one ethnicity, population, or familial group may not exhibit the same association in another. Variability in results may be attributed to the multifactorial nature of malocclusion, epigenetic influences, and gene–gene interactions.

Conflict of interest

The authors declare no conflict of interest in this paper.

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