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MATN1 gene variant (rs1065755) and malocclusion risk: Evidence from Romanian population analysis

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Abstract. Malocclusion, characterized by its diverse phenotypic expression, significantly impacts patients' quality of life. Over recent years, extensive attention has been directed towards the genetic basis of this condition, particularly focusing on various polymorphisms of the *MATN1* gene. Among these, the rs1065755 polymorphism has emerged as particularly relevant, associated with an elevated risk of mandibular prognathism. In this study, employing DNA sequencing, we investigated the extent of association between the rs1065755 SNP and malocclusion risk within the Romanian population. Our approach concentrated on assessing continuous phenotypic variation through four cephalometric measurements, aiming for a comprehensive understanding beyond categorical phenotypes. The findings shed light on the relationship between the *MATN1* rs1065755 SNP and the investigated dentofacial disorder, revealing a positive association between TT homozygous individuals and Class II skeletal malocclusion.

However, further investigations employing larger sample sizes are necessary to validate these findings conclusively.

Keywords: malocclusion, *MATN1*, rs1065755, cephalometric measurements.

Introduction

Malocclusion represents a multifaceted oro-facial anomaly, exhibiting complexity both in its phenotypic expression and genetic underpinnings. It manifests as a disharmony in growth between the maxillary and mandibular structures, resulting in an improper relationship between the two dental arches (Nishio and Huynh, 2016, Weaver *et al.*, 2017). The growth and development of the mandible are influenced by a combination of environmental factors and genetically predetermined intrinsic factors. According to Angle's classification system, based on the relative position of the Maxillary First Molar, malocclusion is categorized into three classes: Class I, Class II, and Class III (Yadav *et al.*, 2014).

Class I malocclusions represent one of the most common conditions in the daily clinical practice, being more common than normal occlusion. Individuals exhibiting Class I malocclusion typically demonstrate normal molar relationships, yet their teeth are misaligned within the occlusal line due to malpositioned teeth, rotations, spacing, overbites, open bites, posterior crossbites, or anterior crossbites (Buschang, 2014). When the patient exhibits a phenotype characterized by a maxilla protruding relative to the mandible (or a mandible retruded), accompanied by a convex facial profile, the condition is classified as Class II. Conversely, Class III malocclusion is characterized by a protruded mandible relative to the maxilla (or a maxilla retruded), resulting in a concave facial profile. Class III encompasses a wide spectrum of phenotypic variations, with mandibular prognathism being the most well-known (Liu *et al.*, 2009, Li *et al.*, 2010, Hardy *et al.*, 2012, Doraczynska-Kowalik *et al.*, 2017).

These latter two types of malocclusions (II and III) are frequently encountered among orthodontic patients and significantly impact both their masticatory functions and aesthetic appearance, as well as their mental well-being, leading to a diminished quality of life (Graber *et al.*, 2017, Ma *et al.*, 2019, Liu *et al.*, 2009). Hence, a comprehensive understanding of the genetic factors underlying this complex trait is imperative to facilitate accurate diagnosis and effective treatment by orthodontists (Zabrina *et al.*, 2021, Weaver *et al.*, 2017).

Among the candidate genes implicated in malocclusion, the *MATN1* (*matrilin-1*) gene situated on chromosome 1p35.2 (GRCh38.p14; NCBI accession number: NC_000001.11) is of particular interest in this study. *MATN1* encodes a cartilage extracellular matrix protein pivotal in enhancing and sustaining the chondrogenesis process upon stimulation by *TGFb1* (Moreno Uribe and Miller, 2015, Pei *et al.*, 2008). Notably, *MATN1* is markedly upregulated during chondrogenesis (Stokes *et al.*, 2002). Given the correlation of multiple single nucleotide polymorphisms (SNPs) with malocclusion, this paper focuses on the rs1065755 polymorphism (8572 C>T), which has been associated with an elevated risk of mandibular prognathism in Korean population (Jang *et al.*, 2010). Other studies address the potential genetic predisposition linked to the *MATN1* gene in various dental conditions across populations primarily from India (Rathod *et al.*, 2023, Balkhande *et al.*, 2018), Korea (Yamaguchi *et al.*, 2005), and Indonesia (Laviana *et al.*, 2021), leaving the European space a less explored territory.

In this frame, this research work aims to identify the connection between mutation in gene encoding *MATRILIN-1* (rs1065755) and the risk of various malocclusion types in the Romanian population, with specific consideration to continuous phenotypic variation as demonstrated by four different cephalometric measurements.

Materials and methods

The experimental sample comprises a total of 78 Romanian patients of both genders (50 females and 28 males) with an average age of 21.8 years. The sample set originated from the records of a private clinic and were included in this study only after an informed consent was obtained from the patients who volunteered for the study. Exclusion criteria involved instances of growth disturbances, syndromes, cleft lip and palate, missing teeth, inadequate quality of radiographic records, unsigned consent forms, and trauma. The patients were categorized into study (skeletal class II and III) and control groups based on the cephalometric morphology. The studied cephalometric measurements included ANB (Point A-Nasion-Point B), SNA (Sella-Nasion-Point A), SNB (Sella-Nasion-Point B) angles, as well as the Wits appraisal (AoBo). The SNA angle denotes the maxillary position, where values exceeding the mean (82°) indicate maxillary prognathism, while values below the mean suggest maxillary retrognathism. The SNB angle assesses mandibular position relative to the cranial base, with values surpassing the mean (80°) indicating mandibular prognathism and values lower than the mean suggesting mandibular retrognathism.

Jaw disparity is evaluated through ANB (mean of 0-2°) and AoBo (mean of 0-2 mm) angles. Elevated values relative to the mean signify a Class II tendency, while values below the mean indicate a Class III trend (Ghergie *et al.*, 2013a). Based on these parameters, the analyzed sample set consists of 37 patients classified under class II anomalies, 25 categorized with class III malocclusion, and 16 belonging to the control group.

Buccal swabs were obtained from all patients for molecular investigations and promptly transported on ice to the genetic laboratory for DNA isolations and amplification. Genomic DNA was extracted from oral mucosa cells using the Animal and Fungi DNA Preparation (Jena Bioscience, Germany) following the manufacturer's guidelines. After the quality and quantity of genomic DNA was evaluated using NanoDrop 1000 Spectrophotometer (ThermoFischer Scientific, US), the gene fragment containing the target SNP (rs1065755) was amplified. A 330 bp segment of *MATN1* gene was amplified using the forward 5'-CACCTTCTGGTTCTGCCAACT-3' and reverse 5'-CATCCCCATGTCCAGCCTTAC-3' primers (Jang *et al.*, 2010). The PCR reaction was optimized and consistent results were obtained when using the following reaction mixture: 1x Reaction Buffer, 2.5 mM $MgCl_2$, 0.2 mM each dNTP, 0.5 μM of each primer, 1.25 units/ reaction of MangoTaq polymerase (Bioline, Meridian Bioscience, USA), and 1 μl of DNA template. The standard amplification conditions were initial denaturation at 95°C for 5 minutes, followed by 35 cycles of 95°C for 30 seconds (denaturation), 62°C for 30 seconds (annealing), 72°C for 30 seconds (extension), and a final extension of 72°C for 5 minutes. The PCR products were visualized on a 1.5% agarose electrophoresis gel (Cleaver Scientific Ltd, Warwickshire, United Kingdom). The expected amplicons were purified from the agarose gel using FavorPrep GEL/ PCR Purification Kit (Favorgen Biotech Corp., Pingtung, Taiwan), and subjected to Sanger sequencing at Macrogen Europe (The Netherlands). To screen for the rs1065755 C>T *MATN1* polymorphism the obtained sequences were aligned in BioEdit Sequence Alignment Editor v. 7.2.5.0 (Hall, 1999) along with the reference sequence deposited in NCBI (NC_000001.11).

Frequencies of alleles and genotypes between malocclusion cases and control individuals were analyzed. To assess the associations between *MATN1* gene polymorphisms and mandibular prognathism, the Pearson Chi-square test was performed, and the standardized residuals were visualized using the *corrplot* package, available with R 4.1.1 (R Core, 2020). A p -value of less than 0.05 was considered statistically significant ($p < 0.05$). Furthermore, to evaluate the relationship between the cephalometric parameters and the genetic variability at the investigated locus a principal component analysis (PCA) was computed using the *prcomp* function of R and visualized in a two-dimensional space using *ggplot2 package.*

Results

Of the total number of selected individuals, the SNP of *MATN1* gene (rs1065755) was successfully genotyped in 75 instances. Overall, the wildtype allele (C) exhibited a frequency of 64.67%, while the alternate variant (T) appeared with a frequency of 35.33%. Remarkably, the observed allele frequencies within the Romanian population closely align with global frequencies, with a minor difference of 1.87. This discrepancy becomes even more negligible when comparing allele frequencies with those of the European population, reveled by the ALFA project (Phan *et al.*, 2020). The heterozygous were dominant (54.67%), followed by wildtype homozygous (37.33%), and a smaller proportion of homozygous for the mutant allele (8%).

While there is only a slight variation in terms of allelic frequency among the investigated categories (mandibular retrognathism, prognathism and controls having orthognathic mandible) (Fig. 1a), there is a sizeable difference exists in genotypic composition among malocclusion types (Fig. 1b). The highest frequency of mutant homozygous (TT) is observed in Class II individuals (11.76%), it decreases to 8.33% in Class III and it is completely absent from the control group, in which the T allele is exclusively present in heterozygous individuals, constituting the most frequent genotype (64.71%).

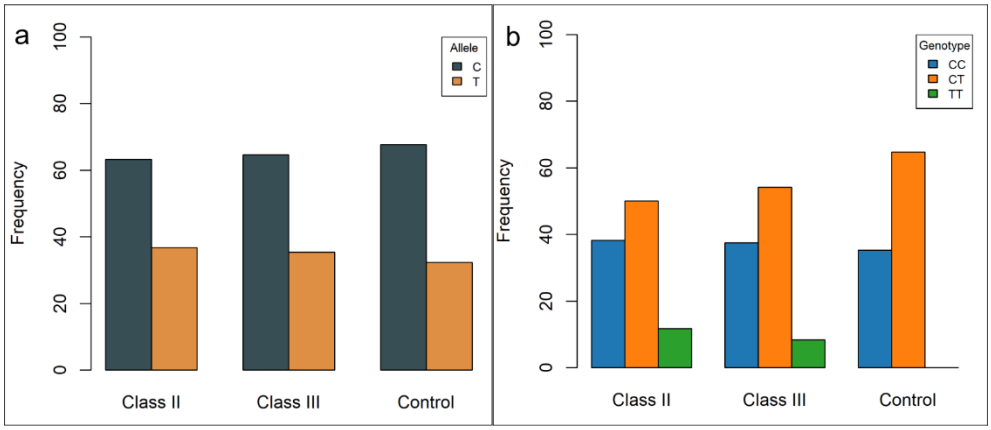

Figure 1. Allelic (**a**) and genotypic (**b**) frequencies in the investigated malocclusion types.

Moreover, the Pearson's Chi-squared test for each allele in a category of individuals (chi-squared = 0.45, p-value = 0.7984) indicated that there is not enough evidence to suggest an association between allele type and a class of orthodontic deformity. On the other hand, the correlation plot for the Pearson's

chi squared test residuals for each genotype in a class (chi-squared = 13.056, p-value = 0.01082) showed a positive association between TT homozygotes and Class II malocclusion, as well as a negative correlation between this genotype and the control group (Fig. 2). At the same time, the heterozygotes show an opposite pattern.

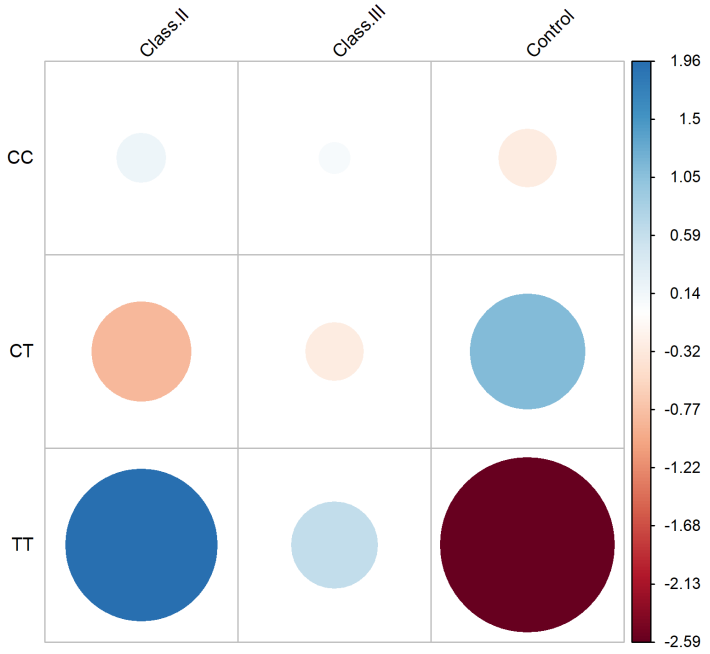

Figure 2. Correlation plot for the Pearson's chi squared test residuals for each genotype in a class (*p-value* = 0.01082).

The PCA performed based on four cephalometric measurements (Fig. 3) shows a clear division between the Class II malocclusion and Class III cases along the PC1 and PC2 components, capturing 80.57% of the variance is displayed. Samples from the control group are dispersed along a diagonal between these categories, except for one outlier (the farthest heterozygous on the PC1 component). However, there is no evident clustering of the samples based on the identified genotype. The PCA analysis was performed exclusively on individuals with complete records, encompassing a total of 47 samples with both genetic and cephalometric measurements available.

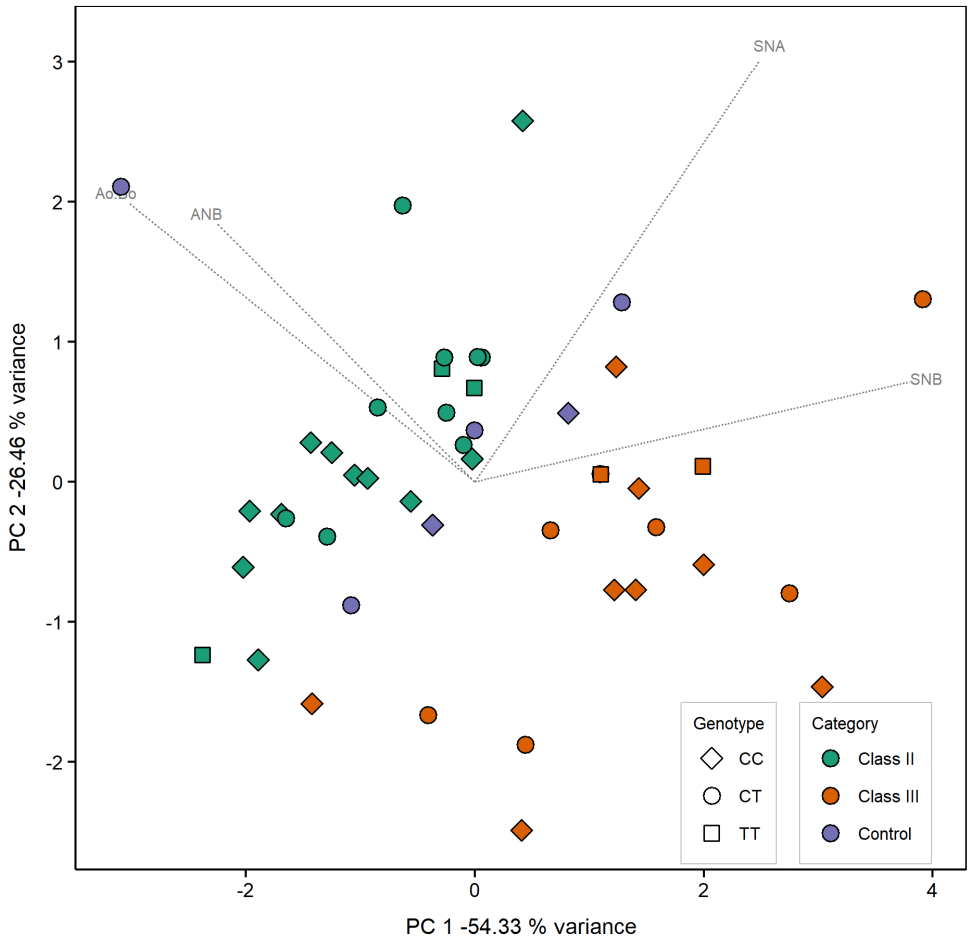

Figure 3. Principal Component Analysis (PCA) performed based on four cephalometric measurements.

Discussion

Class II and III malocclusion are recognized as complex dentofacial anomalies, with varied prevalence across ethnic groups and geographic areas, and as such a comprehensive understanding of the genetic basis is crucial for the development of innovative, personalized therapies, as well as more effective preventive strategies (Dehesa-Santos *et al.*, 2021, Moreno Uribe and Miller, 2015). Research into hereditary factors as the root cause of mandibular deformities such as mandibular

prognathism and advancements in genetics highlight the quest for gene candidates associated with mandibular prognathism (Zohud *et al.*, 2023). It has been suggested that genetic investigations concerning Class II and I malocclusion are scarce and characterized by small sample sizes, uncertainty regarding the generalizability of findings to populations of diverse ancestries, and narrow trait definitions that overlook the intricate phenotypic spectrum of malocclusion (George *et al.*, 2021). Previous studies have identified several gene candidates as genetic contributors to skeletal malocclusion class II and III (some reviewed in: (Subono *et al.*, 2021, Doraczynska-Kowalik *et al.*, 2017, Mokhtar *et al.*, 2020)). Across various ethnicities, studies have suggested that genes correlated with mandibular prognathism are situated in different loci.

The *MATN1* gene, located on chromosome 1p35.2, is involved in the regulation of matrilin-1 synthesis in endochondral skeletal growth and has been identified as a candidate gene that could serve as a biological marker in mandibular prognathism (Jang *et al.*, 2010). The majority of studies examining the association between *matrilin-1* gene polymorphisms and craniofacial issues have concentrated on East Asian populations. This is likely due to the higher prevalence of dental malocclusion in this region compared to other ethnicities (Lone *et al.*, 2023). Through the examination of three *MATN1* polymorphisms (-158 T>C, 7987 G>A, 8572 C>T) in the Korean population, Jang *et al.* (2010) demonstrated that the 8572 C>T polymorphism is associated with an elevated risk of mandibular prognathism, whereas the 7987 G>A polymorphism exhibits a protective effect. Although demonstrating comparable minor allele frequencies of rs1065755 C>T between Koreans and Indians, the latter population did not exhibit a significant association with mandibular retrognathism at either the genotype or allele level (Balkhande *et al.*, 2018). In contrast, the frequencies observed in the Romanian population differ and the TT genotypes are positively correlated with Class II malocclusion (Fig. 2). In a different study (Kulkarni *et al.*, 2020), albeit somewhat constrained by a small sample size, rs20566 and frameshift variants at rs1065755 exhibited notably higher frequencies in 35 skeletal Class III patients with mandibular prognathism compared to 30 control individuals from an Indian population. By studying the *MATN1* gene's association with mandibular prognathism in the Deutero-Malay race in Indonesian subjects, Laviana *et al.* (2021) indicate that polymorphism of exon 5 regions of the *MATN1* gene, 354 T>C (rs20566) CC genotype, is the risk factor of such craniofacial disorder. In this case no CC genotype was identified in the control group. Similarly, our study reveals an absence of TT genotype at rs1065755 in the control group.

This preliminary study sheds light on the influence of *MATN1* polymorphism depicted by sequence variation at rs1065755 on skeletal malocclusion class II and III in Romanian population. For this ethnic group, only a limited number of

genes including *MYO1H* (Ghergie *et al.*, 2013a), *VDR* (Ghergie *et al.*, 2013b), and *COL1a1* (Topârcean *et al.*, 2021) have been investigated for their role in dental anomalies.

Conclusions

Overall, our study contributes to understanding the genetic basis of skeletal malocclusion Class II and III, particularly within the Romanian population. Our findings underscore the potential role of *MATN1* polymorphisms, specifically rs1065755, as a genetic marker for mandibular prognathism. However, further research with larger sample sizes is warranted to validate these findings and explore additional genetic factors contributing to malocclusion.

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