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Association between TaqI polymorphism of vitamin D receptor gene and vertical growth of the mandible: A cross-sectional study

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Objective: To determine whether the gonial angle on digital panoramic radiographs is associated with vitamin D receptor (*VDR*) TaqI polymorphism. **Methods:** Genomic DNA samples were collected from the buccal mucosa of patients aged 26–43 years. TaqMan assay for single nucleotide polymorphism genotyping was used to detect the genotype of TaqI polymorphism. The gonial angle was measured bilaterally on panoramic radiography. The normal gonial angle was fixed as 121.8°, and it represented the cutoff value for the high gonial angle (HGA) and low gonial angle (LGA) groups. Various genetic models were analyzed, namely dominant (homozygous [AA] vs. heterozygous [AG] + polymorphic [GG]), recessive (AA + AG vs. GG), and additive (AA + GG vs. AG), using the chi-squared test. **Results:** The reliability of the gonial angle measurement was analyzed using a random sample (26%) of the tests, with the intra-examiner correlation showing an intra-class correlation coefficient of 0.99. The frequencies of the AA, AG, and GG genotypes of rs731236 polymorphism were 40.5%, 41.9%, and 17.6% in the HGA group and 21.8%, 51.0%, and 27.2% in the LGA group, respectively (P = 0.042). A statistically significant difference was observed in the allele frequencies between the two groups (P = 0.011). Moreover, a significant correlation was observed in the dominant genetic model. **Conclusions:** TaqI polymorphism in the *VDR* gene plays a critical role in the vertical growth of the mandible and decreased gonial angle.

Key words: Genetics, Growth evaluation, Bone biology

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INTRODUCTION

Skeletal malocclusions result from craniofacial growth and developmental problems.[1] Studies on families and twins have demonstrated that genetic components play a pivotal role in the etiology of dental malocclusions.[2] One study reported that genetic backgrounds were responsible for 40% of malocclusion cases, and hereditary factors were more influential in skeletal patterns than in dental patterns.[3] Vertical malocclusions occur due to several etiological variables during the growth period, such as functions of the lips and tongue, eruption of teeth, bad habits, airway obstruction, and genetics.[4,5]

The angle between a hypothetical tangential line running along the inferior border of the mandibular corpus and another along the posterior border of the mandibular ramus is called the gonial angle.[6] It serves as a useful indicator for determining the developmental process of the craniomaxillary complex and mandibular rotation.[7] The gonial angle increases with the clockwise rotation of the mandible, resulting in a high-angle profile, whereas it decreases with the counter-clockwise rotation of the mandible, resulting in a low-angle profile. Therefore, it is an important angular value to be considered when planning the treatment for patients with orthodontic problems.[8] The gonial angle determined on panoramic radiography is as accurate as that on lateral cephalography.[9]

Vitamin D, a fat-soluble secosteroid, plays a fundamental role in maintaining skeletal homeostasis in the body.[10] Vitamin D undergoes a sequential transformation process, wherein it is initially metabolized to 25-hydroxyvitamin D_3 ($25(OH)D_3$) or calcifediol, followed by its conversion to 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), which represents the biologically active state of vitamin D and is commonly called calcitriol.[11] Although the vitamin D receptor (VDR) is a nuclear biological macromolecule, it mediates the biological effects of vitamin D.[12]

Vitamin D receptor TaqI polymorphism occurs in the genomic region spanning intron 8 and exon 9 of the *VDR* gene. This particular genetic variant is associated with various pathological conditions.[13] A clinical study reported that *VDR* TaqI polymorphism is associated with external apical root resorption during orthodontic therapy.[14] An anthropometric study showed that although FokI polymorphism was associated with a larger head size, TaqI polymorphism was not associated with any anthropometric findings evaluated in the study.[15] Xiong et al.[16] found a strong association between adult height and TaqI polymorphism. Küchler et al.[17] suggested that single nucleotide polymorphism (SNP) in genes related to the maintenance of vitamin D levels is associated with mandibular retrognathism in humans. However, literature findings regarding the effect of *VDR* TaqI polymorphism on the gonial angle and lower facial proportions are lacking. TaqI polymorphism (rs731236), characterized by an adenine (A) > guanine (G) alteration, is located within the 3' untranslated region of the *VDR* gene. This alteration is considered synonymous, as it does not change the amino acid sequence. However, it may affect the messenger RNA stability, as evidenced by a discernible variation at position + 352 of exon 9.[18] The allele frequency is an essential metric in statistical genomic research. Many evolutionary processes can alter allele frequencies. Thus, minor allele frequencies (MAFs) in SNPs can be used to determine the demographic history of a population.[19] Among the countries investigated for TaqI polymorphism, the highest MAF was reported in Europe (0.47%).[20] In a study conducted in our country, Turkey, the MAF value was 0.63%;[21] hence, we chose this SNP for this study because the MAF of TaqI polymorphism may be high in our country.

This cross-sectional study aimed to determine whether the gonial angle on digital panoramic radiographs is associated with *VDR* TaqI polymorphism. We hypothesized that TaqI polymorphism in the *VDR* gene is associated with the gonial angle and vertical mandibular growth.

MATERIALS AND METHODS

The study complied with the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Recep Tayyip Erdogan University (Approval No: 2022/232). All the participants provided written informed consent and completed an assent form before their inclusion in the study. This study adhered to the Strengthening the Reporting of Genetic Association Study checklist for the preparation and reporting of the results.[22]

Power analysis was performed using G*Power software (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany), which revealed that at least 53 patients were required in each group, with a Type I error rate of $\alpha = 0.05$ and a Type II error rate of $\beta = 0.05$ for 80% power at an impact width of $d = 0.55$. In total, 200 individuals were screened for eligibility, of which 9 did not meet our inclusion criteria. Thus, this study included 191 patients aged 26–43 years, who visited the Faculty of Dentistry of Recep Tayyip Erdogan University. A flowchart of the study is presented in Figure 1.

We examined genomic DNA obtained from the saliva samples and panoramic radiographs of the participants. The same operator captured the panoramic radiographs for all participants using Orthopantomograph® Op300 Panoramic (Instrumentarium Dental, Tuusula, Finland). Patients with a history of orthodontic treatment, facial or mandibular surgery, or syndromes affecting the jaw or face were excluded from the study. The quality of the

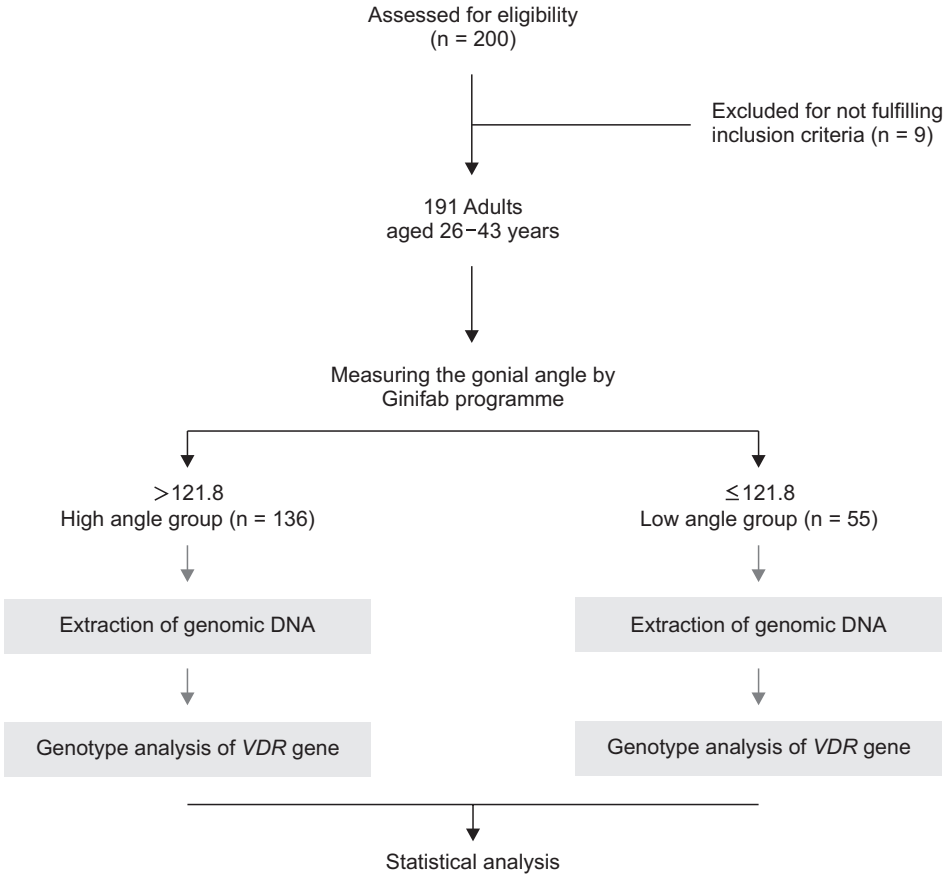

Figure 1. Schematic flowchart of the study.
VDR, vitamin D receptor.

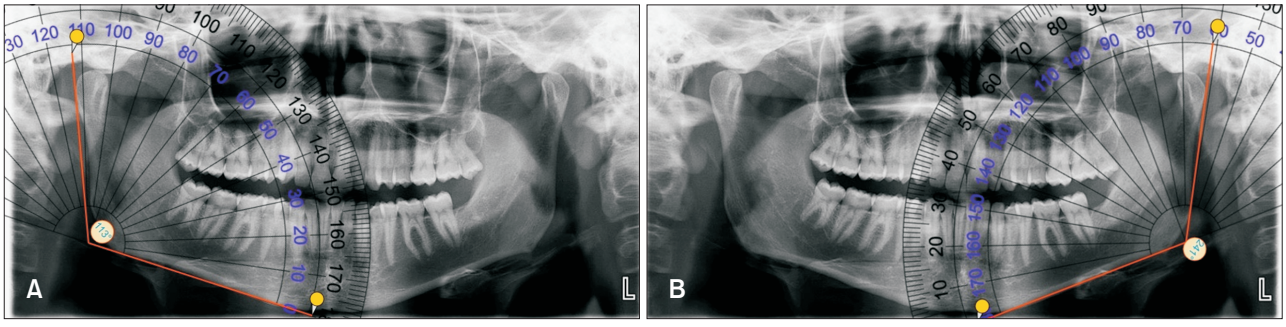

Figure 2. Gonial angle measurement. The angle between the tangent to the posterior edge of the ramus mandible and the tangent to the lower edge of the corpus mandible is measured on the right (**A**) and left (**B**) sides on panoramic radiography.

radiographs was checked, and diagnostically inadequate radiographs were excluded. The radiographic selection criteria were radiographs of high quality and sharpness, radiographs obtained using the same equipment, and default body posture during radiography.

Phenotypes definition

A calibrated orthodontist measured the gonial angle on the panoramic radiographs using the tangent from the posterior ramus mandible line between the articulare and gonion points and the tangent from the lower border of the corpus mandible between the gonion and menton points. For each participant, measurements were obtained on the right and left sides, and the average of the two values was calculated. To determine the intra-operator error, 50 radiographs were re-measured by the same operator after an interval of 1 month. The commercially available Ginifab program (Yiwu, China) was used to measure the gonial angle (Figure 2). The standard value for the gonial angle was set as 121.8°, which

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represented the cutoff value for the high gonial angle (HGA) group and low gonial angle (LGA) group.[23]

Extraction of genomic DNA

A single investigator performed the buccal swab to collect epithelial cells from the buccal mucosa of the participants using the Swab Collection and DNA Preservation System (Norgen Biotek Corp., Thorold, ON, Canada). The swab samples were stored at room temperature in a preservation reaction mixture to isolate the DNA molecules. The preservative solution not only inhibits the proliferation of both gram-negative and gram-positive bacteria and fungi effectively but also renders viruses inactive, thus enabling safe handling and transportation of non-infectious samples. Genomic DNA was extracted using DNA isolation kits (Norgen Biotek Corp.) according to the prescribed standards. DNA samples were analyzed using Denovix QFX Fluorometer (Denovix Inc., Wilmington, DE, USA), which specifically employs a fluorescent dye in the detection mechanism. After desiccation, the specimens were subsequently stored under freezing conditions at −20°C until further analysis.

Genotype analysis

This study was designed to be genotype-blinded. The gonial angle was measured in 191 patients who visited the clinic. After these patients were grouped according to their measurement values, genotype and statistical analyses were performed. TaqMan Predesigned SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA) was used to genotype rs731236 polymorphism of the *VDR* gene. The total volume for each polymerase chain reaction (PCR) was 10 μL, which contained 10–30 ng DNA and 2X TaqMan. Real-time PCR was conducted using LightCycler® 480 II (Roche Diagnostics, Basel, Switzerland). The PCR had a reaction temperature of 95°C for 10 minutes, followed by 40 cycles at 92°C for 15 seconds and at 60°C for 1 minute.

Statistical analysis

The chi-squared test was used to assess the adequacy of the observed genotype frequencies in the given population against the expected frequencies according to the principles of the Hardy-Weinberg equilibrium model (https://wpcalc.com/en/equilibrium-hardy-weinberg/) (accessed on 06 April 2023). Data were analyzed using Statistical Product and Service Solutions, version 21.0 (IBM Corp., Armonk, NY, USA). The normality of the data was assessed using the Shapiro-Wilk test. Intra-class variation was studied using intra-class correlation coefficients (ICC) with 95% confidence intervals. The differences in the frequencies of the genotypes and alleles for a candidate gene were analyzed using the chi-square test; P values < 0.05 were considered statistically significant.

RESULTS

This study included 191 adults. Age and sex distributions according to the gonial angle groups are presented in Table 1. The results of the study revealed that 65% of the HGA group and 67% of the LGA group were female. The mean age was 33.7 years in the LGA group and 33.8 years in the HGA group.

This study aimed to investigate the reliability of the gonial angle measurements by analyzing a randomized sample (26%) of the administered tests. The intra-rater correlation analysis yielded an ICC of 0.99, indicating highly consistent and reliable results. This study presents an analysis of the *VDR* rs731236 gene in individuals classified according to their low or high gonial angles by using dominant, recessive, and additive genetic models. All participants were screened, and genotyping of all of the patients was performed successfully. The genotypes of the 191 patients with *VDR* TaqI polymorphism (rs731236) are shown in Table 2.

The frequency of the polymorphism did not deviate from the Hardy-Weinberg equilibrium ($P > 0.05$).

Table 2 summarizes the genotype distributions and allele frequencies of the *VDR* rs731236 gene polymorphism in the HGA and LGA groups. This study examined diverse genetic models, namely the dominant (homozygous [AA] vs. heterozygous [AG] + polymorphic [GG]), recessive (AA + AG vs. GG), and additive (AA + GG vs. AG) models. The chi-squared test was used for the analysis.

We recorded the allelic frequencies of rs731236 polymorphism in the HGA and LGA patients. The genotypic frequencies of AA, AG, and GG were 40.5%, 41.9%, and 17.6% in the HGA group and 21.8%, 51.0%, and 27.2% in the LGA group, respectively ($P = 0.042$). The statistical analysis revealed a significant difference in the allele frequencies between the two groups ($P = 0.011$). Additionally, a significant association was observed in the

Table 1. Age and sex distributions according to the gonial angle groups

	HGA > 121.8° (n = 136)	LGA ≤ 121.8° (n = 55)
Age	33.8 ± 11.2	33.7 ± 11.1
Sex		
Female	89 (65)	37 (67)
Male	47 (35)	18 (33)
Total	136 (100)	55 (100)

Values are presented as mean ± standard deviation or number (%).
HGA, high gonial angle; LGA, low gonial angle.

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Table 2. Analysis of vitamin D receptor rs731236 in low and high gonial angle groups using dominant, recessive, and additive models

Genotype/allele	HGA > 121.8° (n = 136)	LGA ≤ 121.8° (n = 55)	*P* value
Genotyping			0.042*
AA	55 (40.5)	12 (21.8)	
AG	57 (41.9)	28 (51.0)	
GG	24 (17.6)	15 (27.2)	
Recessive model			0.135
GG	24 (17.6)	15 (27.2)	
AA + AG	112 (82.4)	40 (72.8)	
Dominant model			0.014*
AA	55 (40.4)	12 (21.8)	
AG + GG	81 (59.6)	43 (78.2)	
Additive model			0.257
AG	57 (41.9)	28 (50.9)	
AA + GG	79 (58.1)	27 (49.1)	
Allele			0.011*
A	167 (61.3)	52 (47.2)	
G	105 (38.7)	58 (52.8)	

Values are presented as number (%).
HGA, high gonial angle; LGA, low gonial angle; AA, homozygous; AG, heterozygous; GG, polymorphic; A, normal allele; G, polymorphic allele.
*Chi-squared test, $P < 0.05$.

dominant genetic model; however, no difference was found in the recessive and additive models.

DISCUSSION

Skeletal malocclusion is a common problem affecting the dental and facial tissues.[24] Determining the growth pattern is crucial for formulating treatment plans within the domains of surgery and orthodontics. Consequently, the gonial angle has been identified as an indicator to identify growth patterns.[25] Many genetic studies in literature report the association of genes with orthodontic malocclusions and facial morphology.[26–28]

These genetic studies have mostly focused on skeletal Class III malocclusions.[29,30] Although the studies are limited, craniofacial phenotypes, including mandibular retrognathism and vertical growth patterns, have been evaluated.[31,32] SNPs are associated with common morphological changes, such as sagittal, transverse, and vertical growth patterns.[33] Human facial development is a complex process that involves numerous genes and protein translations. All these events have a specific period and are under hormonal control.[17] This study was designed to detect the potential relationship between the most frequently occurring SNPs in the *VDR* and the gonial angle. Vitamin D production occurs endogenously in the skin via sunlight activation or exogenous administration of supplements; it subsequently converts to the biologically active metabolite $1,25(OH)_2D_3$ and is catalyzed by the cytochrome P450 enzyme CYP27B1.[34] Thus, CYP24A1 regulates the concentration of the active form of vitamin D.[35]

Parathyroid glands contain CYP27B1 and CYP24A1 and play a vital role in the expression levels of these chemicals.[36] Therefore, SNPs in genes related to vitamin D metabolism are associated with mandibular morphology in humans.[37]

Similarly, our results suggest a positive correlation between *VDR* gene polymorphism and mandibular morphology. Few studies have reported associations between *VDR* polymorphism and morphological changes. Handoko et al.[15] genotyped four SNPs for the *VDR* gene (rs731236TaqI, rs10735810FokI, rs1544410BsmI, and rs7975232ApaI) and reported that only rs10735810 FokI polymorphism was associated with anthropometric measures.

Küchler et al.[37] posited that rs7975232ApaI polymorphism within the *VDR* seems to have a minimal impact on the manifestation of mandibular retrognathism. In our study, we evaluated TaqI polymorphism and found a statistically significant increase in the gonial angle with the AA genotype, indicating that rs731236TaqI polymorphism in the *VDR* gene is a susceptibility factor for decreased gonial angle and low angle growth pattern. The biological effects of vitamin D are facilitated by its interaction with a receptor encoded by the *VDR* gene.[38]

Based on these findings, a strong relationship between TaqI polymorphism of the *VDR* and mandibular morphology was expected.

This study has several limitations. It assessed only one SNP within the *VDR* gene, whereas ApaI, FokI, and BsmI have not yet been investigated. Additionally, only the gonial angle was evaluated on panoramic radiography, and no other vertical angular measurements were performed. Furthermore, serum vitamin D levels were not measured.

CONCLUSIONS

Our results suggest that TaqI polymorphism in the *VDR* gene plays a critical role in the vertical mandibular growth and decreased gonial angle. Clinicians should consider the patient's genetic polymorphisms when evaluating the gonial angle, which is an important parameter in treatment planning. Further studies are warranted to determine the effects of other *VDR* polymorphisms on the gonial angle.

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AUTHOR CONTRIBUTIONS

Conceptualization: BCT, GYT, FS. Data curation: BCT, GYT. Formal analysis: BCT, GYT, FS. Funding acquisition: GYT. Methodology: BCT, GYT, FS. Validation: BCT, GYT, FS. Writing–original draft: BCT, GYT, FS. Writing–review & editing: BCT, GYT.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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