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Original Article

Presence of Single Nucleotide Polymorphisms in Transforming Growth Factor β and Insulin-Like Growth Factor 1 in Class II Malocclusions due to Retrognathic Mandible

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Abstract

Aim: The aim of this study was to evaluate specific single nucleotide polymorphisms (SNP) of transforming growth factor-beta (TGF-β) (rs1800469) and insulin-like growth factor-1 (IGF-1) (rs17032362) genes in Class II individuals with a normal maxilla and retrognathic (short) mandible.

Materials and methods: The study had 25 participants: 5 were assigned to the control group, which had a normal maxilla and mandible, and 20 to the experimental group, which had a structurally retrognathic mandible and a normal maxilla. The polymerase chain reaction was used with preselected primers after which Sanger sequencing was used to identify individual mutations.

Results: SNP at rs1800469 (TGF-β) in the study and control groups showed significant difference (p=0.009). The Odds Ratio of 5.28 signified that the individuals with SNP at rs1800469 were at 5.28 times higher risk of developing mandibular retrognathism. The IGF SNP showed its presence in experimental group but was not statistically significant.

Conclusion: Our study reports for the first time on the association between TGF-β SNP and mandibular retrognathism. Other SNP also showed its presence in the study group and its complete absence from control group directs us for further research.

Keywords

insulin-like growth factor-1, retrognathic mandible, single nucleotide polymorphisms, transforming growth factor-β

INTRODUCTION

Advanced molecular techniques have assisted us in determining DNA alterations by providing an infinite variety of genetic markers for the creation of genetic maps, allowing us to study a disease's genetic predilection. DNA sequencing can be used for detecting genetic variations in the nucleic acid sequence, known as single nucleotide polymorphisms. It can help orthodontists to determine the genetic component in a specific malocclusion so as to better predict the end result of further growth or treatment.

Mandibular condyle performs a crucial function in the development of orofacial structures by providing endochondral ossification. Therefore, any disturbance in the development of condyle can lead to mandibular asymmetries or retrognathism.

Mandibular condylar cartilage is designated as secondary cartilage as it shows differences in histological organiza-

tion when compared to primary skeletal cartilage. However, it is considered to be a part of the primary cartilaginous skeleton as it develops into permanent cartilage unlike other secondary cartilages which are mostly transient in nature.[1] The growth of cartilage is influenced by both inherent genetic factors and the broader category of epigenetic factors, which encompasses genetic elements susceptible to external influences or other modifying factors.[1-6]

The role of TGF-β and IGF in enhancing the growth of mandibular condylar cartilage (MCC) and their downstream events have been well documented by our team. They both have a synergistic role in the mandibular cartilage synthesis and remodeling.[2,3,5,6] Studies on the skeletal Class III malocclusion have identified SNPs and various genetic makers contributing to a prognathic mandible[7-10], whereas the studies concerning a retrognathic mandible or a skeletal Class II are scarce.

AIM

Our aim was to assess the genetic markers, specifically the SNPs of TGF-β (rs1800469) and IGF-1 (rs17032362), in relation to a structurally retrognathic mandible associated with a skeletal Class II malocclusion. By focusing on key genetic factors, including SNPs of TGF-β (rs1800469) and IGF-1 (rs17032362), our objective was to elucidate the genetic underpinnings of mandibular growth and condylar cartilage development in individuals with a Class II malocclusion. This exploration is crucial for enhancing our understanding of the complex interplay between genetic variations and craniofacial development, ultimately providing valuable insights that may contribute to improved predictions and treatment strategies for individuals with such malocclusions.

MATERIALS AND METHODS

Adult subjects of both sexes with a mean age of 26±3 years were included in the study. The experimental group consisted of 20 subjects with orthognathic maxilla and retrognathic mandible i.e., SNA=82°±2°, SNB≤78°, effective mandibular length (Co-Gn: Co condylium is the most posterior point of the condyle, and Gn is the lowest point of the lower jaw) ≤118 mm, mandibular length (Go-Me: Go is the most posterior point of the lower jaw, Me is the contact point of the corticalis of the mandibula and the symphysis) ≤76 mm. The control group consisted of 5 subjects with orthognathic maxilla and mandible i.e., SNA=82°±2°, SNB=80°±2° (Skeletal Class I), effective mandibular length =122±4 mm (Co-Gn: Co condylium is the most posterior point of the condyle, and Gn is the lowest point of the lower jaw), mandibular length =79±2 mm (Go-Me: Go is the most posterior point of the lower jaw, Me is the contact point of the corticalis of the mandibula and the symphysis).

The patient selection criteria for the experimental group of 20 individuals included specification regarding their feeding history. It is imperative to note that, as part of this criterion, individuals in the experimental group were exclusively those who were fed naturally during infancy. This consideration is essential due to the inherent compensatory nature of embryonic mandibular retrognathism up to 6 months, a process facilitated through natural nutrition.

Participants with harmful habits, such as mouth breathing and finger sucking, were deliberately excluded from the study. This exclusion was implemented to mitigate potential external factors known to contribute to a distal bite, with finger sucking additionally linked to the risk of a shortened lower jaw due to obstruction.

The study was approved by the Institutional Ethics Committee. A written informed consent, in adherence to their diagnostic and involvement in the results for scientific review without revealing their identity, was obtained from all the participants. Tracings of the lateral cephalograms, taken for every participant were done manually on acetate matte tracing paper.

Angular and linear parameters, including SNA (Sella-Nasion-A point) and SNB (Sella-Nasion-B point) within angular measurement, as well as mandibular length and effective mandibular length within linear measurement, were assessed in the tracings of both subjects and controls.

For detecting the presence of selected SNPs, 2 ml of blood sample was withdrawn from the cubital fossa of each subject and stored in an EDTA vacutainer at 4°C in a refrigerator. Testing of DNA amplicons on 0.8% agarose gel, found the quality of DNA samples to be satisfactory **(Fig. 1)** for further procedures described below. Further tests were conducted, where the DNA was isolated with the help of Xcelgen Blood DNA isolation kit.

The protocol was as follows:

1. 200 µl of human blood sample was taken and transferred to a sterile 1.5 ml Eppendorf tube.
2. One volume of red blood cell lysis buffer was added to the tube and inverted back and forth 5 times for proper mixing. Centrifugation was done at 10,000 rpm for 1 minute.
3. One volume of phosphate buffered saline was added to the tube and inverted back and forth 5 times to mix well. Centrifugation was done at 10,000 rpm for 1 minute.
4. 10 µl of proteinase K was added to the Eppendorf tube.
5. One volume of buffer lysate, e.g., 200 µl of buffer to 200 µl of blood sample, was added.
6. Incubation was done at 55°C for 20-30 minutes on thermomixer.
7. After incubation, 200 µl of ethanol (96%-100%) and 200 µl of DNA wash buffer was added to the lysate. Mixing of the entire lysate was done by pipetting.
8. Entire lysate was transferred to the DNA spin column and centrifuged at 10,000 rpm for 1 minute.
9. The column was placed into the same collection tube. 500 µl of DNA wash buffer II was added and centrifuged at 10000 rpm for 1 minute.

Primers for each restriction site are listed in **Table 1**. Polymerase chain reaction (PCR) was performed using

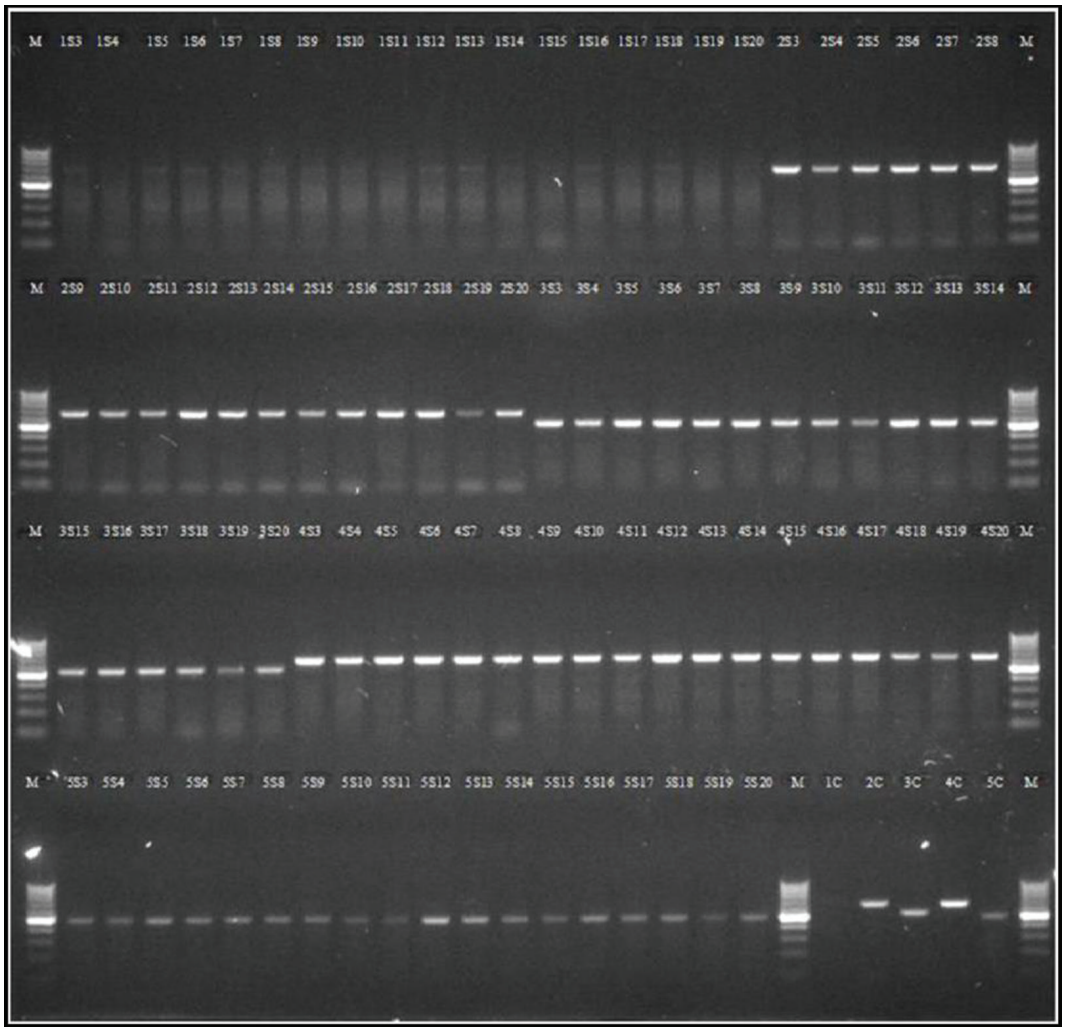

Figure 1. Quality check of the DNA on 0.8% agarose gel.

synthesized primer sets using isolated DNA as template. Briefly, 20 ng of DNA was used to carry out PCR amplification in final reaction volume of 25 µl. Composition of reaction mixture is given in **Table 2** and the PCR conditions used are provided in **Table 3**.

All PCR products were sequenced by the ABI sequencer, 3730xl (Sanger Sequencing). The amplicons were then purified and automated DNA sequencing was carried out on ABI 3730xl Genetic Analyzer (Applied Biosystems, USA). The BigDye Terminator v. 3.1. Cycle Sequencing Kit was used for sequencing as per manufacturer's protocol, where sequencing cycle was set with the thermal ramp rate of 1°C per second for 30 cycles.

Statistical analysis

Statistical analyses were performed using Student's *t*-test and *p*-values were calculated to evaluate the distribution

Table 1. Restriction sites selected with respect to the corresponding gene

Sr. No	Gene	Restriction site
1.	Transforming growth factor β	rs1800469
2.	Insulin-like growth factor 1	rs17032362
3.	Myosin 1H	rs11611277

Table 2. Components of reaction mixture for PCR

	Components	Quantity
1.	Nuclease free water	10.5-X µl
2.	Template DNA	X* µl
3.	Forward primer (10 pmole/µl)	1.0 µl
4.	Reverse primer (10 pmole/µl)	1.0 µl
5.	2XPCR master mix	12.5 µl
	Total volume	25 µl

*X represents variable volume of genomic DNA.

Table 3. PCR conditions

Initial denaturation	Denaturation extension	Annealing (X35)		Final extension	Hold
95°C	94°C	66°C	72°C	72°C	4°C
5 min	30 sec	45 sec	45 sec	10 min	15 min

*X represents the number of cycles

of each SNP across all samples. Additionally, odds ratios were computed to determine the precise risk. These analyses were conducted utilizing Sigmaplot (v. 13) software package.

RESULTS

Table 4 proves the homogeneity of study and control groups. The mean cephalometric parameters like ∠SNA 81.0, ∠SNB 73.65, effective mandibular length 102.6 mm and mandibular length 65.1 mm in the study group confirms that it included cases with true mandibular retrognathism, whereas cephalometric parameters like ∠SNA of 81.4, ∠SNB of 80.2, effective mandibular length 119 mm and mandibular length 79.2 mm confirms that the control group included skeletal class I individuals.

The distribution of SNP at rs1800469 in cases and controls showed significant difference as shown in **Table 5** with *p*-value of 0.009. The percentage of samples showing mutations in the study group was 65%, as compared to 0% in the control group. The Odds Ratio of 5.28 signifies that the individuals with SNPs at rs1800469 were at 5.28 times higher risk of developing mandibular retrognathism than those without mutation.

The distribution of SNP at rs17032362 in cases and controls showed a non-significant difference indicated by a *p*-value of 0.356 as shown in **Table 6**. The percentage of

Table 4. Comparison of measurements between study group and control group

	Groups	n	Mean	Standard deviation	t-test value	*p* value
SNA	Study	20	81.0	0.91	−0.925	p=0.365
	Control	5	81.4	0.54		
SNB	Study	20	73.65	1.30	−10.87	p<0.001
	Control	5	80.2	0.44		
Effective mandibular length	Study	20	102.6	5.67	−6.324	p<0.001
	Control	5	119.0	1.22		
Mandibular length	Study	20	65.1	6.41	−4.834	p<0.001
	Control	5	79.2	0.44		

*p<0.05: significant difference; **p<0.001: highly significant difference

Table 5. Association of presence of SNP at rs1800469 between study and control group

rs1800469	Study n (%)	Control n (%)	Odds Ratio (95% CI)	t test	*p* value
Present	13 (65%)	0 (0%)	5.28 (3.46-7.81)	6.771	p = 0.009 highly significant
Absent	7 (35%)	5 (100%)			

p<0.05: significant difference; p<0.001: highly significant difference

Table 6. Association of presence of SNP at rs17032362 between study and control group

rs170323662	Study n (%)	Control n (%)	Odds Ratio (95% CI)	t test	*p* value
Present	3 (15%)	0 (0%)	3.17 (1.97-4.86)	0.852	p=0.356, no significant difference
Absent	17 (85%)	5 (100%)			

p<0.05: significant difference; p<0.001: highly significant difference

samples showing mutation in the study group was 15% as compared to 0% in the control group. The Odds Ratio of 0.852 signifies that the individuals with SNP at rs17032362 were at a 0.852 times higher risk of developing mandibular retrognathism than those without mutation.

In restriction site 1800469, C allele was over-presented in the control group subjects (p=0.006). In restriction site 17032362, G allele was over-presented in the mandibular retrognathism subjects (p=0.47) **(Table 7)**.

DISCUSSION

Human gene mapping studies of maxilla and mandible (normal or retrognathic position and size) are scarce; they have focused majorly on the skeletal Class III malocclusion.[18,19,21] Previous studies have found correlation between mandibular prognathism and genes EPB-41, GHR, LTBP-2, MATRILIN-1, TGF-β3, and MYO-1H indicating that molecular mechanisms involved in bone (TGF-β3, LTBP) and cartilage (MATRILIN-1, GHR) growth influence mandibular size discrepancies.[7-9,11-13] Skeletal Class II malocclusion is always considered to be of a multifactorial etiology with various permutations and combinations related to length and position of both the maxilla and the mandible.[20,22-26] Thus, we attempted to focus on skeletal Class II malocclusion with a normal maxilla and retrognathic mandible.

In our previous studies[2,3,5,6], TGF-β and IGF-1 have proven to be important and synergistic factors in development and growth of the mandible. The role undertaken by TGF-β in repair of cartilage is well explained. Administration of growth factors like TGF-β and IGF-1 in our animal study also proved to have a positive correlation with the growth of MCC.[6] As the growth of MCC with administration of these factors increased, it urged us to investigate its role in a Class II individual with normal maxilla and a retrognathic mandible.

TGF-β has proven to be an important factor in MCC growth and differentiation.[2,5,14] It has a role in the differentiation of chondrocytes and also prevents the growth of any other cells. TGF-β also maintains the surrounding microenvironment by increasing the deposition of extra cellular matrix and maintaining vascularity by promoting angiogenesis. In our present study, we found a significant role of TGF-β SNP (rs1800469) in producing a phenotype with a retrognathic mandible leading to a skeletal Class II malocclusion. The Odds Ratio of 5.28 signifies the higher risk of a skeletal Class II with the respective SNP.

IGF-1 plays a significant role in cartilage growth and differentiation by controlling cartilage homeostasis. It blocks the cytokine stimulated cartilage degradation.[5] In this study, presence of IGF-1 SNP (rs17032362) in the study group was about 15% and hence its complete absence in the control group validates some of its role in not producing a normal skeletal Class I phenotype.

The factors that influenced the development of a malocclusion may not be the only ones that will influence how the patient will respond to a given treatment.[15] Different patients respond differently to the same treatment as described by Carlson DS[16] and Hartsfield et al.[17] The normal patients have SNPs which respond to usual treatment whereas some patients may have SNPs (abnormal) which do not respond to normal treatment. The predictability of treatment outcome for a particular patient will thus be dependent on the identification of such SNPs.

Genomics and epigenomics are a duality i.e., no malocclusion can only be genetic or environmental in origin completely. They may be opposing but are interdependent on each other. This study for the first time has identified the role of TGF-β SNP (rs1800469) in a retrognathic mandible.

CONCLUSION

This study established an association between TGF-β SNP rs1800469 and mandibular retrognathism. The presence of IGF-1 SNP rs17032362 in the study group and its absence in the control group directs us for further research.

The strengths and limitations of the study should be considered when interpreting the results. The major strength is the standardization of participants with an average maxilla and exclusion of participants with a protruded maxilla. A relatively small sample size of the study conducted can be considered as a limitation, which may have influenced the relation between a retrognathic mandible and TGF-β gene polymorphisms. Even though previous studies have confirmed an association between TGF-β and incidence

Table 7. Comparison of each allele marker

Marker	Genotypes	Study	Control	Chi-square	*p* value
rs11611277	C	35 (87.5%)	10 (100%)	1.389	p=0.239
	A	5 (12.5%)	0 (0%)		
rs17032362	G	37 (92.5%)	10 (100%)	0.519	p=0.471
	A	3 (7.5%)	0 (0%)		
rs1800469	C	21 (52.5%)	10 (100%)	7.661	p=0.006
	T	19 (47.5%)	0 (0%)		

p<0.05: significant difference; p<0.001: highly significant difference

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of retruded mandible, the limited power of this study necessitates repetition with larger sample size. This study is a proof-of-concept study depicting the association of TGF-β with a retrognathic mandible or a skeletal Class II malocclusion due to retrognathic mandible.

Declarations of interest

None

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Conflict of interest

The authors report there are no competing interests to declare.

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Наличие однонуклеотидных полиморфизмов в трансформирующем факторе роста β и инсулиноподобном факторе роста 1 при аномалиях прикуса II класса, обусловленных ретрогнатической нижней челюстью

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Резюме

Цель: Целью данного исследования было оценить специфические однонуклеотидные полиморфизмы (SNP) генов трансформирующего фактора роста-бета (TGF-β) (rs1800469) и инсулиноподобного фактора роста-1 (IGF-1) (rs17032362) в классе II особей с нормальной верхней челюстью и ретрогнатической (короткой) нижней челюстью.

Материалы и методы: В исследовании приняли участие 25 участников: 5 были отнесены к контрольной группе с нормальной верхней и нижней челюстью, и 20 – к экспериментальной группе со структурно ретрогнатической нижней челюстью и нормальной верхней челюстью. Полимеразную цепную реакцию использовали с предварительно выбранными праймерами, после чего использовали секвенирование по Sanger для идентификации отдельных мутаций.

Результаты: SNP при rs1800469 (TGF-β) в основной и контрольной группах показал значительную разницу (p=0.009). Отношение коэффициентов от 5.28 означало, что у людей с SNP при rs1800469 риск развития нижнечелюстного ретрогнатизма был в 5.28 раза выше. SNP IGF показал своё присутствие в экспериментальной группе, но не был статистически значимым.

Заключение: В нашем исследовании впервые сообщается о связи между SNP TGF-β и нижнечелюстным ретрогнатизмом. Тот факт, что другой SNP также показал своё присутствие в основной группе, а его полное отсутствие в контрольной группе побуждает нас к дальнейшим исследованиям.

Ключевые слова

инсулиноподобный фактор роста-1, ретрогнатическая нижняя челюсть, однонуклеотидные полиморфизмы, трансформирующий фактор роста-β