Original Article

Comparative Analysis of FGFR2 Exon 8 and Exon 10 Sequences in Retrognathic Mandible Patients: A Case-Control Study

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Abstract

Objective: Class II malocclusion is associated with the gene FGFR2. Genotyping involved conducting genome linkage scans to identify mutations in various mandibular genes and loci associated with Class II malocclusion. The present study aimed to improve the current understanding of genetic factors involved in the development of a retrognathic mandible and to correlate genetic variations with phenotypic characteristics.

Methods: Two hundred patients with class II jaw relation have been examined; twenty patients with a retrognathic mandible and another twenty with normal mandibular size and position have been selected from the population by analyzing their lateral cephalometric radiographs. DNA was extracted from saliva samples collected from 40 individuals. FGFR2-8 and FGFR2-10 genes were amplified using the genomic DNA of patients' saliva by PCR. The results of sequenced samples were analyzed using a phylogenetic tree.

Results: Cephalometric readings indicated that patients with class II had a retrognathic mandible, while their maxilla was normally positioned. Genetically, when comparing FGFR2 exon 8 and exon 10, exon 10 is more promising for detecting class I and class II, because it mimics the results of clinical examination by cephalometric radiographs. In FGFR2-10 the controls were in one group of the phylogenetic tree.

Conclusions: This study concludes that FGFR2-10 may be promising for detecting class II malocclusion, while FGFR2-8 was not very specific. All found mutations were point mutations and can be considered new SNPs (Single Nucleotide Polymorphisms). FGFR2-10 showed clearer grouping patterns between cases and controls in the phylogenetic tree; these findings may serve as a diagnostic aid and require further validation.

Keywords: *FGFR2-8, FGFR2-10, Genetic Analysis, Retrognathic Mandible, Point Mutation.*

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Introduction

Skeletal Class II malocclusion results from maxillary protrusion or mandibular retrognathism (hypoplasia)[1], characterized by decreased SNB angle (Sella-Nasion-B point angle), everted lower lip, reduced chin projection, and abnormal gonial angles. Cephalometrically, it demonstrates an increased mandibular plane angle, greater lower facial height, and an altered facial axis, all of which are correlated with mandibular length deficiency. Multiple factors, including heredity, environmental influences, and epigenetic modifications, impact how the craniofacial skeleton develops in humans. There are many different approaches to studying the diverse genetic components in a population. As genetic studies and facilities advanced quickly in recent years, a hereditary predisposition to a skeletal-facial profile was identified[2].

By providing a wide range of genetic markers for constructing genetic maps, advanced molecular techniques have supported the discovery of DNA mutations. This has allowed us to study the hereditary predisposition of diseases. Mutations in the nucleic acid sequence can be detected using DNA sequencing. To better anticipate the outcome of subsequent development or therapy, it can assist orthodontists in identifying and addressing the hereditary component in a particular malocclusion[3].

Class II malocclusion is associated with the genes FGFR2. Genotyping involved conducting genome linkage scans to identify mutations in various mandibular genes and loci associated with Class II malocclusion. PAX5, SNAI3, MYO1H, TWIST1, and PAX7 are linked to craniofacial skeletal variance in patients with malocclusion, whereas FGFR2, MSX1, MATN1, MYOH1, ACTN3, GHR, KAT6B, HDAC4, and AJUBA genes are connected with mandibular skeletal malocclusion[4].

Many cell types, including osteoblastic cells, are controlled in migration and proliferation by fibroblast growth factor (FGF). By activating tyrosine kinase receptors (FGFRs) on the surface of target cells, FGFs exert their effects. On the other hand, their precise action mechanism is still unclear[5]. During craniofacial development, FGFR2 is prominently expressed in the mesenchyme of the developing maxilla and mandible, serving a crucial function in osteogenesis and sutural homeostasis[6]. FGFR2 has been identified as a skeletal malocclusion risk gene, and FGFR2 polymorphisms regulate its transcriptional expression and then osteogenic differentiation[7]. Exons 10 and 8 of the FGFR2 gene encode a segment of the immunoglobulin-like domain III of the receptor, which is critical for ligand binding specificity. Mutations in exon10, particularly missense mutations such as S252W and P253R, are commonly associated with Apert syndrome. These mutations cause constitutive stimulation of FGFR2 signaling, resulting in modified osteogenic differentiation and premature suture fusion[8,9]. Mutations in exon 8, including C342Y and C342R, are frequently linked to Crouzon and Pfeiffer syndromes[10].

This research aims to further the understanding of FGFR2-8 and FGFR2-10 in the formation of retrognathic mandibles and to correlate genetic variants with phenotypic traits.

Patients and Methods

Study design

This study was designed as an unmatched case-control study, conducted at the postgraduate clinic at the College of Dentistry, University of Sulaimani, and laboratories at the College of Medicine, University of Sulaimani. The Ethical Committee at the College of Dentistry, University of Sulaimani, approved the research project with Code No. (COD-EC-25-0089) on August 11, 2025.

Participants

The purpose, procedures, potential risks, and benefits of the study were fully explained to all participants. Participant confidentiality and data anonymity were maintained throughout the study.

The datasets used/or analyzed during the current study are available from the corresponding author upon reasonable request.

Sample Size

During the research period, 200 individuals with class II jaw relations seeking orthodontic treatment were recruited for this study. Regarding ethnic variations, the presence of true mandibular retrognathism is not a common condition in the examined society[11]. G*Power sample size justification was applied; 20 individuals were classified and chosen according to the inclusion criteria for classes II, and another 20 individuals with normal mandibular size and position were selected from the population. Because the diagnosis of mandibular retrognathism was made early during the growth spurt, which starts at 10-11 years old, the participants' ages ranged from 11 to 32 years old. Patients with previous orthodontic treatment or orthognathic surgery, a history of mandibular trauma, or systemic disease, and retrognathic mandible patients belonging to the same family were excluded.

Data collection

Cephalometric Analysis

Lateral cephalometric radiographs were taken for every 40 individuals using the Vatech Computed Tomography X-ray System (model: PHT-30LFO). Radiographs were

taken with the head in a neutral position, the teeth in centric occlusion, and the lips relaxed. A head and neck radiologist took all radiographs, following standardized protocols to ensure consistency and minimize distortion. The subjects were positioned using ear rods and a nasion support to stabilize the head and maintain a constant distance between the X-ray source, the patient, and the detector. Exposure parameters were standardized for all images: 83 kVp, 10.0 mA, scan time 12.3 sec, and DAP 20.17 mGy*cm². All radiographs were assessed for quality and clarity. WebCeph™ performed cephalometric tracing and analysis **(**AI-powered cloud-based cephalometric analysis software). This software automatically identified anatomical landmarks, and all landmark positions were manually verified and adjusted where necessary to ensure accuracy. Standard cephalometric parameters, including SNA (Sella-Nasion-A point angle), SNB (Sella-Nasion-B point angle), and ANB (A point-Nasion-B point angle), were assessed based on Steiner analysis[12]. Repeated tracing of 20% of samples was conducted by a professional orthodontist and all clinical and cephalometric radiographs were double-checked. Inter-examiner reliability was assessed between the AI and manual analyses using Cohen's kappa coefficient. The kappa value was 0.84, indicating almost perfect agreement between examiners ($p < 0.001$).

Saliva Sample Collection

To prevent contamination and changes in salivary flow, participants were instructed to refrain from eating, drinking (apart from water), smoking, chewing gum, and engaging in oral hygiene practices (such as brushing their teeth) for at least 1 hour before saliva sample collection. Before collection, participants relaxed for 5 minutes and rinsed their mouths with distilled water to remove food particles. Next, participants were asked to sit comfortably and allow saliva to pool in the mouth. They passively drooled into a pre-weighed, sterile polypropylene tube for 5–10 minutes until a minimum volume of 2 mL was obtained. Finally, samples were transported on ice and stored at –20°C, and kept for 2 weeks to prevent degradation[13].

Genetic Analysis

DNA Extraction

For genomic DNA extraction, the Presto™ DNA Kit (100 Preps) (Geneaid, Taiwan) was used according to the manufacturer's instructions.

Agarose Gel Electrophoresis

According to Sambrook and Russell's instructions[14]. The agarose gel was prepared by dissolving two tablets of agarose powder (0.5g each) in 100 ml of 1X TBE to prepare 1% agarose. Next, 10 µL (10 mg/ml) of Ethidium bromide was added to the prepared agarose. The gel runs at 90 volts and 70 mA for 60 minutes. All 40 DNA samples were checked for DNA availability using a Nanodrop (Jenway Genova Nano, UK), then subjected to gel electrophoresis, and the PCR products were subjected to electrophoresis. The bands of extracted genomic DNA were detected using a UV Transilluminator (Major Science, Taiwan).

PCR for Confirming Genes

For gene detection, PCR was used to amplify FGFR2-8 and FGFR2-10 genes. The forward and reverse primers, along with the PCR programs for the genes, are shown in Table 1. B codes for FGFR2-8 PCR products and C codes for FGFR2-10 PCR products. The numbers before letters B and C indicate the number of patients. (10CFGFR2-10CI) and (C1 10-1 10 F) represent the positive control (class I), and other samples represent (class II). (10CFGFR2-10CI) and (C1 10-1 10 F) represent the positive control (class I), and other samples represent (class II)

Sequencing of Genes

PCR products were sent to Macrogen (Seoul, South Korea) for Sanger sequencing.

Statistical Analysis

Patient demographic data, along with cephalometric measurements, have been tabulated in Microsoft Excel© for patients with a normal and a retrognathic mandible. The data was subjected to statistical analysis using the IBM SPSS statistical package version 29, and the DATAtab Team (2025). DATAtab: Online Statistics Calculator. DATAtab, e.U. Graz, Austria. For each cephalometric angle, a t-test was used to assess differences between normal and retruded-mandible patients. P-value set at < 0.001 to be considered significant.

For Genetic comparison measurements, BioEdit, Mega 11, and NCBI BLAST were used for molecular analysis. For blasting, each sequence was added to confirm identity (normal and retrognathic patients). After confirmation, we used BioEdit and Mega 11 to align the sequences of patients and normal individuals for FGFR2-8 and FGFR2-10 to build phylogenetic trees for both genes.

Table 1: presents the forward and reverse primers, along with the PCR programs, for the FGFR2-8 and FGFR2-10 genes.

Gene	Forward primer			Reverse primer		
FGFR2-8	5'GGTCTCTCATTCTCCCATCCC3'			5' CCAACAGGAAATCAAAGAACC 3'		
FGFR2-10	5' CCTCCACAATCATTCCTGTGTC 3'			5' ATAGCAGTCAACCAAGAAAAGGG 3'		
PCR program	Initial temp	Denaturation	Annealing	extension	No. of cycles	Final extension
FGFR2-8 FGFR2-10	94°C-5 min	94°C-45 sec	61°C-40 sec	72ºC-45sec	40	72°C-10 min

Results

Cephalometric analysis

The sample comprises 40 participants, 50% of whom have a Class I skeletal relationship and 50% have a Class II skeletal relationship. The cephalometric analysis data have been subjected to a normality test. The Shapiro-Wilk test result indicated that none of the measurement parameters deviated significantly from normality (p-value > 0.001). The p-values are as follows for SNA, SNB, and ANB (0.781, 0.061, and 0.124); accordingly, parametric tests were applied.

The demographic distribution of the data is summarized by patients' jaw relationships: 20 patients with class I and 20 with class II (Table 2). No missing data has been reported.

Table 3 presents the cephalometric readings and the two-sided independent samples t-test results. The mean value of the SNA angle for class I patients is within the normal limit (81.02 ± 3.57), as well as for the class II patients (80.92 ± 2.23), which indicates that the class II patients showed no statistical difference from class I patients (p-value = 0.918); in other words, their maxilla is normally positioned. While the value of the SNB angle for class I patients was (77.95 ± 3.6) and (74.55 ± 2.09) for class II patients, the t-test showed a significant difference between them (p-value < 0.001). The same result has been reported for the ANB angle; the mean value for class I patients was (3.11 ± 1.16) and (6.38 ± 1.85) for class II patients, the t-test also showed a significant statistical difference between the two groups (p-value < 0.001) in the measurements of SNA and SNB angles that reflect the skeletal relationships, with significant differences between retrognathic mandible patients and normal individuals confirming that patients are true class II.

The extracted DNA from 40 saliva samples was checked by nanodrop; the nanodrop gave a concentration of 20 ng to 100 ng/ml. After that, they were run by gel electrophoresis, and then PCR was used to detect FGFR2-8 and FGFR2-10. The PCR results for the two genes were confirmed by gel electrophoresis. Figure 1 shows a sample for PCR product gel electrophoresis. All sequences were analyzed using Mega 11 to produce a phylogenetic tree. For FGFR2-8 sequences, all cases were compared against the NCBI database for exon 8. The result was that all cases were similar in sequence except for 9B, 8-2B, and 8-1B. In 9B and 8-2B, there are multiple mutations in different locations. In 8-1B, this case has a mutation at 166 bp of the gene: guanine has converted to Adenine. Figure 2 shows the alignment of the current study sequences compared to the USA exon 8 FGFR2 gene sequence in NCBI. For FGFR2-10 sequences, all cases were compared against the NCBI database for exon 10. The result was that all cases were similar in sequence, except that 6C had a mutation in position 119 bp of the gene, Adenine nucleotide has converted to Cytosine nucleotide. It may be a point mutation. Figure 3 shows the alignment of the current study sequences compared to the USA exon 10 FGFR2 gene sequence in NCBI. All found mutations were point mutations and can be considered new SNPs (Single Nucleotide Polymorphisms).

All sequences were analyzed using Mega 11 to produce a phylogenetic tree as shown in Figures 4 and 5. Figure 4 shows the phylogenetic tree for the FGFR2-8 gene. This phylogenetic tree demonstrates that the samples are divided into three main groups: the first group contains one class I individual and three class II patients, the second group contains one class I individual and two class II patients, and the third group contains five class II patients, which are genetically closer to the second

group than the first group. Figure 5 shows the phylogenetic tree for the FGFR2-10 gene. This phylogenetic tree demonstrates that the samples are divided into four groups. The first group contains two class I individuals and two class II patients that are genetically closest to class I.

The second group contains three class II patients; these eight patients are genetically further from the first group's class II. The third group contains two class II patients, who are the same distance from the class I cases. The last group consists of three class II patients, who are the furthest from group one.

Table 2: Demographic distribution of the data according to the sex of participants.

Sex	Class	Frequency	Minimum	Maximum	Mean ± Std.
Female	Class I	11	11	32	20 ± 6.56
	Class II	10	15	26	21.6 ± 2.88
Male	Class I	9	11	32	20.44 ± 7.37
	Class II	10	11	18	14.9 ± 2.47

Table 3: Cephalometric measurements.

		Frequency	Minimum	Maximum	Mean ± Std.	p-value
SNA	Class I	20	75.62	87.55	81.02 ± 3.57	0.918
	Class II	20	76.56	84.38	80.92 ± 2.23	
SNB	Class I	20	72.44	83.39	77.95 ± 3.6	>0.001
	Class II	20	69.67	78.36	74.55 ± 2.09	
ANB	Class I	20	0.6	4.81	3.11 ± 1.16	>0.001
	Class II	20	3.37	10.03	6.38 ± 1.85	

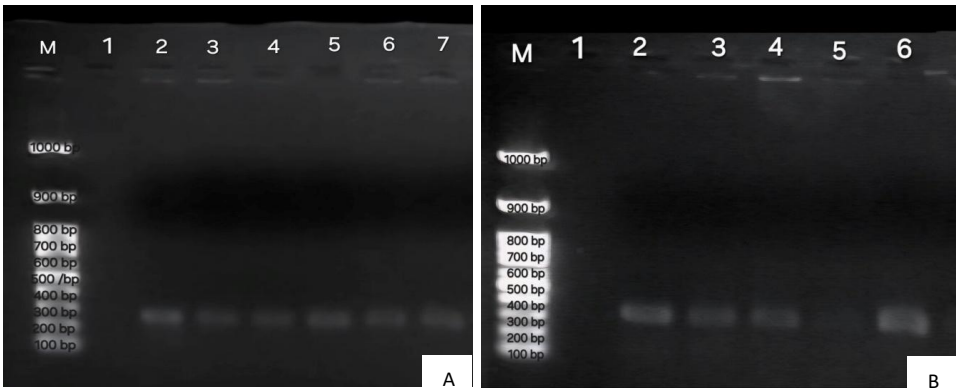

Figure 1: Shows the FGFR2-8 and FGFR2-10. (A): Lane M represent the DNA ladder (Marker 100-1000 bp), Lane 1 is negative control, Lane 2-7 represent DNA bands size 257 bp of FGFR2-10. (B): Lane M represent the DNA ladder (Marker 100-1000 bp), Lane 1 is negative control, Lane 2-6 represent DNA bands size 325 bp of FGFR2-8.

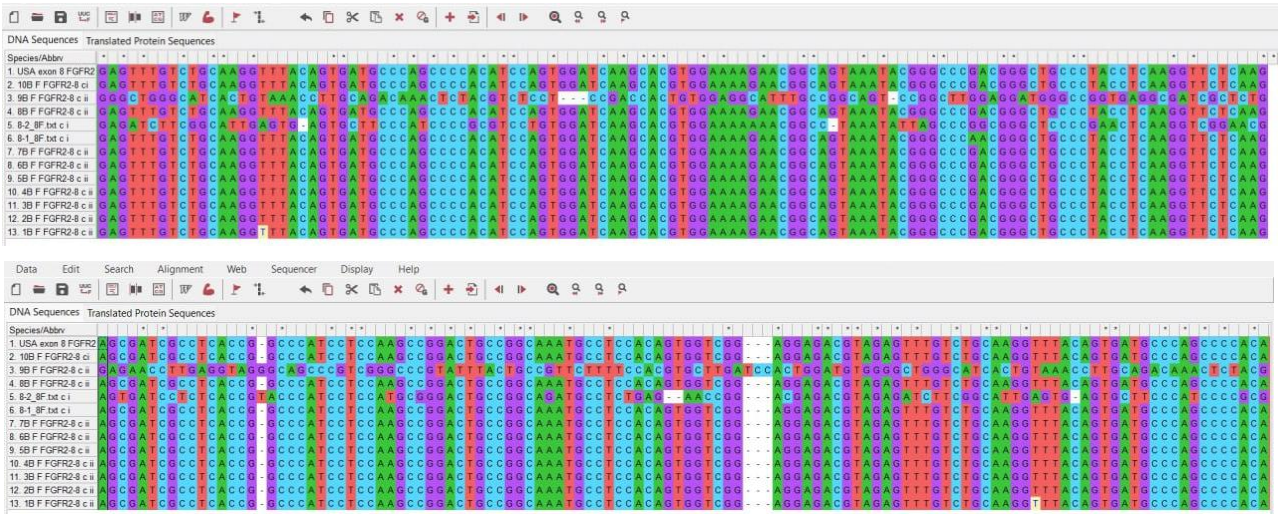

Figure 2: Shows the alignment of the current study sequences compared to USA exon 8 FGFR2 gene sequence in NCBI. Acc.No. Y17131.1.

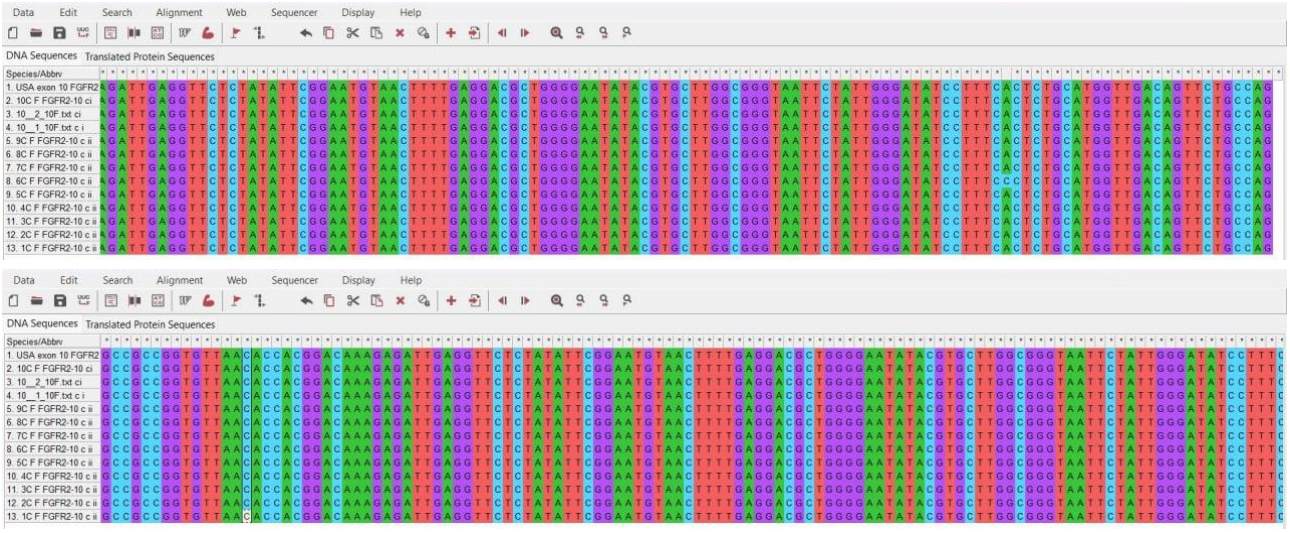

Figure 3: Shows the alignment of the current study sequences compared to USA exon 10 FGFR2 gene sequence in NCBI, Acc.No. AF169399.

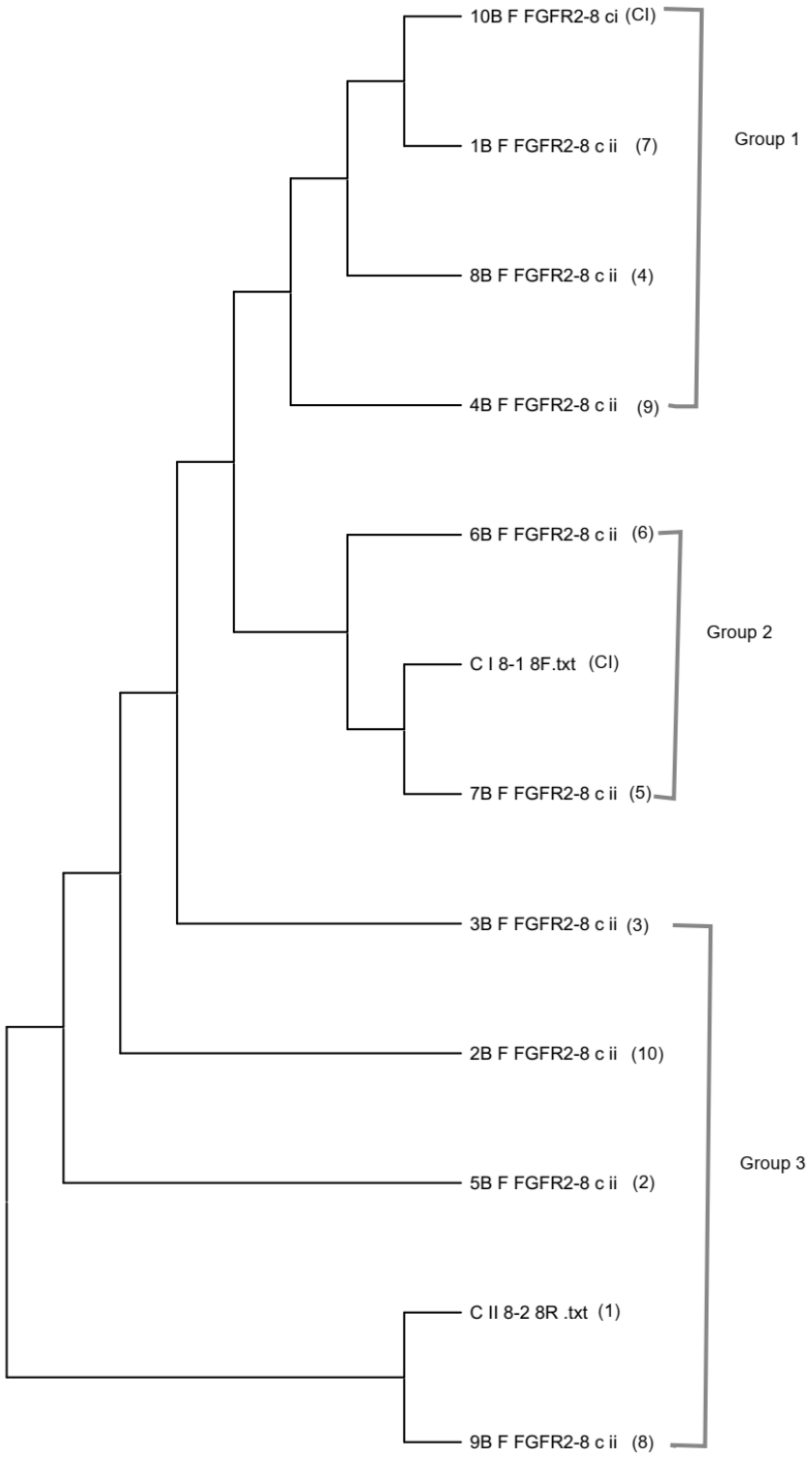

Figure 4: Phylogenetic tree for the FGFR2-8 gene. Compared with (10BFGFR2-8CI) and (C18-18F), which represent the positive control (class I), the other samples represent (class II). The phylogenetic tree shows three main groups: group (1), group (2), and group (3). group (1) includes (1) class I and (3) class II, group (2) includes (1) class I and (2) class II, and group (3) includes (5) class II. The brackets on the right side of the sample codes contain numbers indicating clinical severity as assessed by cephalometric radiography. Number (1) indicates the least severe, while 10 indicates the most severe.

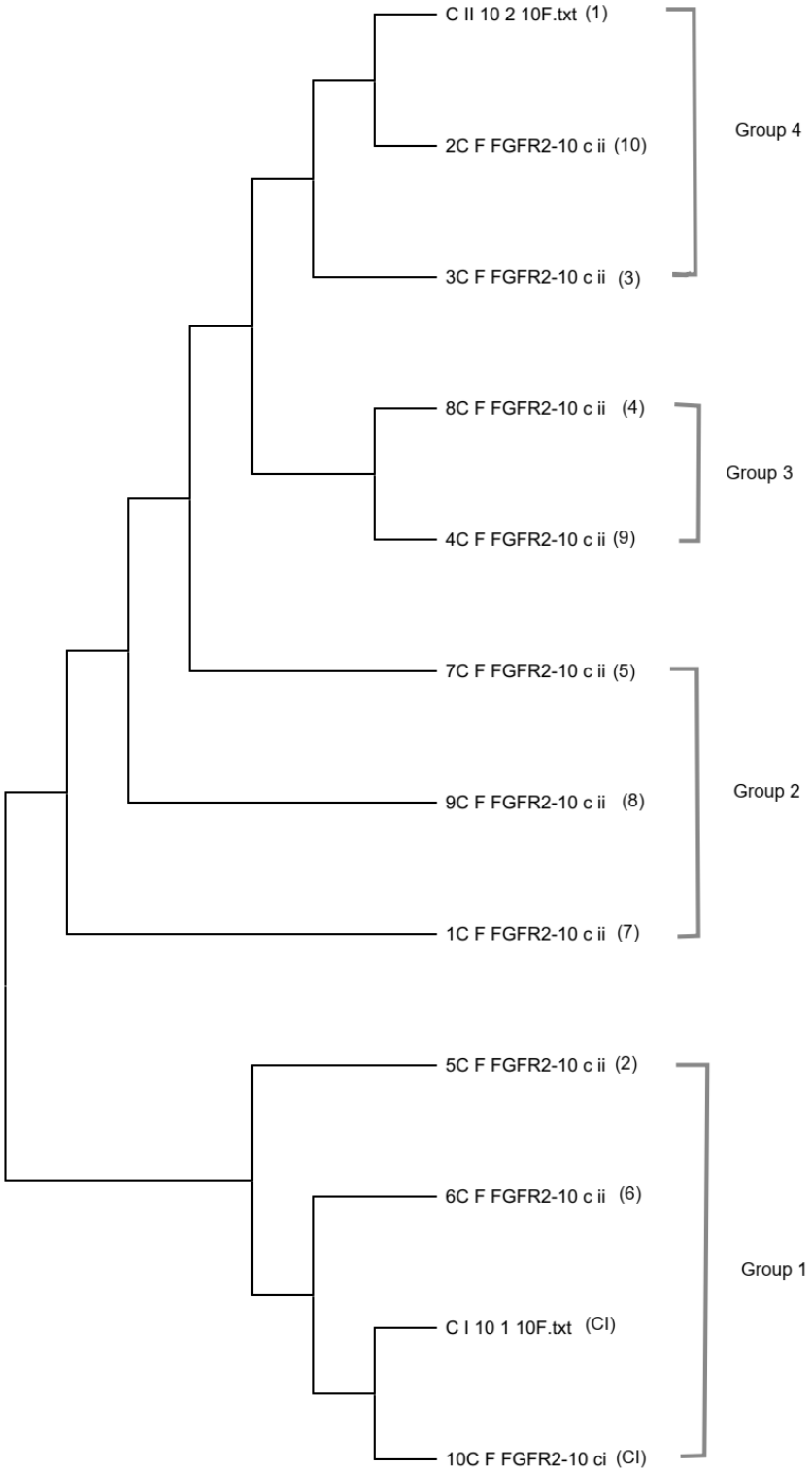

Figure 5: Phylogenetic tree for the FGFR2-10 gene. Compared with (10CFGFR2-10CI) and (C1 10-1 10 F), which represent the positive control (class I), the other samples represent (class II). The phylogenetic tree shows four main groups: group (1), group (2), group (3), and group (4). Group (1) includes (2) class I and (2) class II; group (2) includes class II, group (3) includes (2) class II, and group (4) includes (3) class II. The brackets on the right side of the sample codes contain numbers indicating clinical severity as assessed by cephalometric radiography. Number (1) indicates the least severe, while (10) indicates the most severe.

Discussion

According to the phylogenetic tree, this study found that the selected genes (FGFR2-10 and FGFR2-8) exhibit sequence variation between retrognathic mandibles and normal individuals. Thus, this result rejects the null hypothesis that there are no differences in the order of the selected genes between retrognathic mandibles and normal individuals. Also, it answers the question, "Is it possible to predict mandibular retrognathism by genetic analysis?" The results reveal that yes, it is possible. This research is a novel genetic study of the selected genes (FGFR2-10 and FGFR2-8) in patients with retrognathic mandibles of Kurdish nationality in the Kurdistan region of Iraq. It is hoped that this variation in the sequence of these genes could be used to detect mandibular retrognathism early, enabling interceptive orthodontic therapy or preparation for orthognathic surgery to shorten treatment time and achieve more stable results.

All sequences were analyzed using Mega 11 to produce a phylogenetic tree. For FGFR2-8 sequences, all cases were compared against the NCBI database for exon 8. All cases were similar in sequence except for 9B, 8-2B, and 8-1B. In 9B and 8-2B, multiple mutations occur at different locations. In 8-1B, this case has a mutation at 166 bp of the gene: guanine has converted to Adenine. Figure 2 shows the alignment of the current study sequences with the USA exon 8 FGFR2 gene sequence from NCBI. For FGFR2-10 sequences, all cases were compared against the NCBI database for exon 10. The result was that all cases were similar in sequence, except that 6C had a mutation in position 119 bp of the gene, Adenine nucleotide has converted to Cytosine nucleotide. It may be a point mutation. Figure 3 shows the alignment of the current study sequences with the USA exon 10 FGFR2 gene sequence from NCBI. All found mutations were point mutations and can be considered new SNPs (Single Nucleotide Polymorphisms).

As shown in Figure 4, the phylogenetic tree of FGFR2-8 divides the samples into three groups: group (1), group (2), and group (3). Numbers on the right side indicate clinical severity, which is assessed using cephalometric radiographs; number (1) is the least severe, and number (10) is the most severe class II. The first group contains four clades: one class I and three class II. 10B has been proven to be genetically and clinically class I, with an ANB of 1.4°. 1B is proved to be genetically and in cephalometric analysis class II, with ANB of 5.47° and SNB of 74.650°; it has a level (7) of severity. 1B genetically is the closest class II case as compared to 10B, which is class I of this group. 8B, which is class II genetically and clinically, with ANB 7.75 and SNA 74.57°, has level (4) of severity. 4B is proven to be class II clinically and genetically, with an ANB of 8.14 and SNB of 76.03°, and it has a level (9) of severity. Genetically, 8B is positioned further away than both 1B and 10B, while 4B is the most distant class II in this group. The second group consists of three clades: one class I and two class II. The lateral cephalometric radiograph indicates that (C1 8-1) is class I with an ANB of 4.0°, which agrees with the genetic result, as confirmed by the phylogenetic tree. 7B is proved to be class II both genetically and clinically, with ANB 3.82° and SNB 72.75°; it has a level (5) of severity. It is the closest class II of this group to (C1 8-1), which is class I of this group. 6B is proved to be class II both genetically and clinically, with an ANB of 7.72° and SNB of 76.63°; it has a level (6) of severity; it is further classified as more class II than 7B. The third group consists of five clades of class II. 3B is the closest sample of the third group to the second group; it is genetically and clinically class II, with an ANB of 5.31° and SNB of 78.36°, and it has a level (3) of severity. 2B is further than 3B, which is also genetically and clinically class II, with an ANB of 10.03° and an SNA of 74.34°; it has a level (10) of severity. 5B is at a further distance than 3B; 5B is class II genetically and clinically, with an ANB of 6.26° and with SNB of 80.95°, it has level (2) of severity. (C II 8-2) and 9B are both at the same distance, the furthest samples of the third group, and are both proven to be class II genetically and clinically. (C II 8-2), with ANB of 3.37° and SNB of 78.24°, has a severity level (1). 9B, with ANB of 3.45° and SNB of 73.94°, has a level (8) of severity.

As shown in Figure 5, when the FGFR2-10 gene sequences of class II patients are compared with those of class I individuals, four groups (1-4) are identified. Numbers on the left indicate clinical severity, assessed on a cephalometric radiograph; number 1 is the least severe, and number 10 is the most severe class II. In group (1), there are four clades, two of which indicate class I; the furthest clade is 5C, and the nearest is 6C. In the first group, the lateral cephalometric radiograph shows a class I (C1 10 1) with ANB 4.0°, which agrees with the genetic result, as confirmed by the phylogenetic tree. Based on the lateral cephalometric radiograph, 10C was class I with an ANB of 1.4°, which also agreed with the genetic result, as confirmed by the phylogenetic tree. These two normal samples are in the same clade. 6C is a class II, shown genetically to be closest to the class I clade, but clinical results from cephalometric radiographs showed an ANB of 7.72° and an SNB of 76.63°; it has a level (6) of severity. The 5C is class II genetically and clinically, with an ANB of 6.26° and

with SNB of 80.95°; it has a level (2) of severity and is further from class I individuals in comparison to 6C. The following three samples are grouped into group (2) genetically according to the phylogenetic tree of Figure 3. 1C has proven to be class II both genetically and clinically, with ANB of 5.47° and SNB of 74.65°; it has a level (7) of severity. 9C is proven to be class II both genetically and clinically, with ANB of 3.45° and SNB of 73.94°; it has a level (8) of severity. 7C has been proven to be class II both genetically and clinically, with ANB 3.82° and SNB 72.75°, and it has a level (5) of severity. 1C is the nearest clade to group 1, while 7C is the furthest clade of this group. The third group is formed by two cases: 4C, which is proven to be class II both genetically and clinically, with ANB of 8.14° and SNB of 76.03°, has level (9) of severity, and 8C, which is class II both genetically and clinically, with ANB of 7.75° and SNA 74.57°, has level (4) of severity; they are genetically closest to each other and the same distance from group 1. The fourth group consists of three samples. 3C is genetically class II with ANB of 5.31° and SNB of 78.36°; it has a level (3) of severity. 3C is the closest one to group 1. 2C and (C II 10 2) are genetically at the same distance, and they are the furthest samples from group 1 samples, with 2C having an ANB of 10.03° and SNA of 74.34°; it has a level (10) of severity, which is the most severe class II case clinically. (C II 10 2) has an ANB of 3.37° with SNB of 78.24° and level (1) of severity, which means it is the least severe class II case clinically.

Many studies have been done on FGFR2 in Iraq[15], Iran[16], Turkey[17], and Saudi Arabia[18]. These studies examined the contribution of FGFR2 to breast cancer and Craniosynostosis, but no study has examined the use of these genes for detecting class I, class II, and class III in this area. Other researchers who have studied skeletal class I, class II, and class III have found SNPs in FGFR2[19]. A systematic review has stated that, through reviewing and reanalyzing available human studies, 19 genes were found to be associated with skeletal class II malocclusion, FGFR2 being one of these genes[20]. However, the existing literature predominantly reports associations involving intronic regions of the FGFR2 gene.

Finally, when comparing FGFR2 exon 8 and exon 10, exon 10 is more promising for detecting class I and class II, because the controls of FGFR2-10 were in the same group on the phylogenetic tree, while controls of FGFR2-8 formed two different groups, so it is recommended to conduct further study on FGFR2-8 to inspect its specificity. None of the genes were specific for detecting the severity of class II cases compared to clinical and radiographic analysis. According to the results of this study, exon 10 of the FGFR2 gene can serve as a biomarker to identify patients with retrognathic mandibles.

The primary outcome of this study was the genetic comparison between class I and class II individuals; the secondary outcome was the relationship between lateral cephalometric radiographs and genetic results. This study found that FGFR2-10 is a diagnostic marker for class II patients, which strengthens this study's findings.

This study had several limitations. First, regarding sample size, there were few cases of true retrognathic mandibles. In a study conducted by Nadir and Amin 2024 in Sulaimani city[11], the facial angle and Frankfort mandibular plane angle FMA showed a statistically significantly higher value in Class II patients than in Class I patients. Finding the perfect individual was difficult because our inclusion criteria required that all participants in this study have sought orthodontic treatment for a retruded mandible and decreased facial height. A second limitation of this study was the lack of laboratory standardization. Cost and time constraints, which limited the use of cutting-edge technology and the duration of data collection, may have affected the generalizability and comprehensiveness of the findings. Despite these limitations, the findings of this study provide valuable information and lay a base for future studies in the area.

Conclusion

This study indicates that FGFR2-10 may be specific for detecting class II malocclusion, whereas FGFR2-8 lacks specificity. The differences in the sequence of these genes are suggested for the early detection of mandibular retrognathism, enabling interceptive orthodontic therapy or preparation for orthognathic surgery to reduce treatment duration and enhance stability. In this study, a point mutation was identified in two patients; further studies are required to confirm that this mutation is an SNP.

References

1. Oueis R, Waite PD, Wang J, Kau CH. Orthodontic-Orthognathic Management of a patient with skeletal class II with bimaxillary protrusion, complicated by vertical maxillary excess: A multi-faceted case report of difficult treatment management issues. Int Orthod. 2020;18(1):178-90.
2. Nanci A. Ten Cate's Oral Histology-E-Book: Ten Cate's Oral Histology-E-Book. Elsevier Health

Sciences; 2024.
3. Sharma P, Patil A, Sharma S, Rout T, Hemgude P, Sabane A. Presence of single nucleotide polymorphisms in transforming growth factor β and insulin-like growth factor 1 in class II malocclusions due to retrognathic mandible. Folia Med (Plovdiv). 2024;66(2):243-9.
4. George AM, Felicita AS, Milling Tania SD, Priyadharsini JV. Systematic review on the genetic factors associated with skeletal Class II malocclusion. Indian J Dent Res. 2021;32(3):399-406.
5. Novais A, Chatzopoulou E, Chaussain C, Gorin C. The potential of FGF-2 in craniofacial bone tissue engineering: a review. Cells. 2021 Apr 17;10(4):932.
6. Zhao X, Erhardt S, Sung K, Wang J. FGF signaling in cranial suture development and related diseases. Front Cell Dev Biol. 2023;11:1112890.
7. Jiang Q, Mei L, Zou Y, Ding Q, Cannon RD, Chen H, et al. Genetic polymorphisms in FGFR2 underlie skeletal malocclusion. J Dent Res. 2019;98(12):1340-7.
8. Al-Namnam NM, Jayash SN, Hariri F, Rahman ZAA, Alshawsh MA. Insights and future directions of potential genetic therapy for Apert syndrome: A systematic review. Gene Ther. 2021;28(10-11):620-33.
9. Li F, Meyer AN, Peiris MN, Nelson KN, Donoghue DJ. Oncogenic fusion protein FGFR2-PPHLN1: Requirements for biological activation, and efficacy of inhibitors. Transl Oncol. 2020;13(12):100853.
10. Liu J, Nam HK, Wang E, Hatch NE. Further analysis of the Crouzon mouse: effects of the FGFR2(C342Y) mutation are cranial bone-dependent. Calcif Tissue Int. 2013;92(5):451-66.
11. Nadir HH, Amin AA. Cephalometric assessment of skeletal class II malocclusion in a sample of kurdish population in Sulaimani city (Retrospective Study). Sulaimani Dent J. 2025;11(1):18-26.
12. Mohammed SA, Ali TM, Rashid ZJ. Evaluation of Skeletal Jaw Relation by Different Cephalometric Angles for Sample of Kurdish Young Adults in Sulaimani City-A Cephalometric Study. Sulaimani Dent J. 2022;9(1):21-30.
13. Yu KM, Lee AM, Cho HS, Lee JW, Lim SK. Optimization of DNA extraction and sampling methods for successful forensic microbiome analyses of the skin and saliva. Int J Legal Med. 2023;137(1):63-77.
14. Wittmeier P, Hummel S. Agarose gel electrophoresis to assess PCR product yield: comparison with spectrophotometry, fluorometry and qPCR. Biotechniques. 2022;72(4):155–8.
15. Slman ZA, Umran MA, Alwachi HK. Polymorphism of FGFR2 gene in breast cancer of Iraqi patients. Onkologia I Radioterapia. 2023;17(11):1.
16. Hosseini Mojgan, Houshmand Massoud, Froozan Shima. Association of FGFR2 and TOX3 genetic variants with the risk of breast cancer in Iranian women. Arch Breast Cancer. 2018;5(3):118-21
17. Nur BG, Pehlivanoğlu S, Mıhçı E, Çalışkan M, Demir D, Alper ÖM, et al. Clinicogenetic study of turkish patients with syndromic craniosynostosis and literature review. Pediatr Neurol. 2014;50(5):482-90.
18. Alghamdi M, Alhumsi TR, Altweijri I, Alkhamis WH, Barasain O, Cardona-Londoño KJ, Ramakrishnan R, Guzmán-Vega FJ, Arold ST, Ali G, Adly N. Clinical and genetic characterization of craniosynostosis in Saudi Arabia. Frontiers in Pediatrics. 2021;9:582816.
19. Ardani IGAW, Budipramana M, Rachmawati E, Nugraha AP, Ardana IKKG, Budhy TI, et al. COL1A1 and FGFR2 single-nucleotide polymorphisms found in class II and class III skeletal malocclusions in Javanese population. Eur J Dent. 2023;17(1):183-90.
20. Gershater E, Li C, Ha P, Chung CH, Tanna N, Zou M, et al. Genes and pathways associated with skeletal sagittal malocclusions: a systematic review. Int J Mol Sci. 2021;22(23):13037.