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Significant association of a single nucleotide polymorphism in the upstream region of FGFR1OP2/wit3.0 gene with residual ridge resorption of mandible in Saudis

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Abstract: Residual ridge resorption (RRR) is the decrease in the jaw structure that follows tooth extraction. It is a multifactorial disorder, but reports on the associated genetic factors are scarce, particularly amongst the Saudis. This study aimed to investigate the role of single nucleotide polymorphisms (SNPs) in fibroblast growth factor receptor 1 oncogene partner 2 (FGFR1OP2) in RRR development in Saudis. The study included 192 individuals (RRR = 96; controls = 96) attending outpatient clinics at the College of Dentistry, King Saud University. Demographic and clinical data were collected, the digital panoramic dental radiograph was obtained, and mandibular residual ridge height was measured. DNA was extracted from saliva and genotyping was conducted on "Sequenom MassARRAY iPLEX". Genotype and allele frequencies of three SNPs were calculated and compared. The age at first diagnosis and bone height were compared in the three genotypes of each SNP. The age of the patients, age at first edentulism, and bone height ranged 21-80 years, 12-70 years, and 13-34.6 mm, respectively. All three genotypes of the studied SNPs (rs2279351, rs78054962 and rs2306852) were identified. SNP rs2279351 associated significantly with RRR, and the mutant C allele was highly predisposing. No association was observed for the other two SNPs. The genotypes of all SNPs had an influence on age at first edentulism and bone height, but the results were not statistically different. Since FGFR1OP2 plays a role in the process of rapid wound healing in the oral cavity, it may be playing a role in the development of RRR by influencing the rate of resorption of the jawbone. SNP rs2279351 may alter its expression and hence RRR development. This study is limited due to small a sample size, and further large-scale studies are required to confirm this association and to consider rs2279351 as a possible marker of RRR development.

Introduction

Tooth extraction is immediately followed by activation of a cascade of inflammatory reactions that lead to the temporary closure of the extraction socket by clotting of blood. Within the first week, the disrupted tissue integrity is restored, active bone formation is initiated, and newly formed bone progressively fills the socket in around six months. However, catabolic remodeling of the residual ridge alveolar bone occurs and is most rapid in the first six months but continues at a slower rate throughout life (Jahangiri *et al*., 1998; Bartee, 2001). The jaw structure slowly decreases, leading to what is known as "residual ridge resorption (RRR)" (Thompson, 1946). Thompson (1946), Atwood (1971), and Tallgren (1957) were among the earlier researchers to report the occurrence of RRR, and later several studies showed that both the quantity and architecture of the jaw bone is affected (Hansson and Halldin, 2012; Devlin and Ferguson, 1991; Singh *et al*., 2016). It has been also shown that different individuals differ in the rate and site of remodeling of the bone (Devlin and Ferguson, 1991). Several investigations have explored the possible causes leading to RRR, and functional, anatomic, prosthetic, metabolic, and genetic factors, have been implicated in the development of RRR (Atwood, 1979). A search through literature highlighted that very few studies have explored the genetic factors that may be implicated in the inter-individual variations in developing RRR.

We hypothesized that because single nucleotide polymorphisms (SNPs) play a significant role in producing variations between individuals, these may be involved in

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the differences seen in the extent of bone resorption. We selected the study of polymorphic variations in fibroblast growth factor receptor 1 oncogene partner 2 (FGFR1OP2), which encodes for wound-inducible transcript-3.0 (wit3.0), a factor implicated in the process of rapid wound healing that is known to occur in the oral cavity (Atwood, 1979). We conducted this study on Saudi RRR patients and selected three SNPs that occur in the promoter region of FGFR1OP2, to investigate the association, if any, with RRR.

Materials and Methods

Ethical approval
The study proposal was submitted to the Research Ethics Committee at King Saud University, Riyadh, and Institutional Review Board (IRB) approval was obtained. Each individual who voluntarily participated in this study was required to sign an informed consent prior to inclusion in this study.

Study population
Only Saudi patients were recruited in this study, after the purpose and objective of the research was explained to them, and informed consent was signed. The sample collection was carried out during the period from May to November 2017. The patients recruited in this study were attending the outpatient clinics at the College of Dentistry, King Saud University, Riyadh, Saudi Arabia. Healthy individuals, not suffering from RRR, and attending clinics for minor ailments, were recruited as controls from the same hospital, after signing of informed consent. A total of 192 individuals (RRR patients = 96; controls = 96) were included in the study.

Inclusion and exclusion criteria
Mandibular edentulous cases with both complete and partial edentulism were included in the study, while patients were excluded if they were suffering from any chronic and systemic diseases that could affect bone conditions (e.g., osteoporosis, pituitary disease, or other metabolic bone diseases; patients undergoing prosthetic surgical procedures like sulcus deepening or ridge augmentation; patients with history of bone transplantation and patients with mandibular defects).

Demographic, clinical and radiographic examinations
All patients and controls were interviewed, and information related to clinical history, age, age at first edentulism and its duration were recorded on specially designed forms and entered on excel sheets. For each patient, the digital panoramic dental radiograph (OPG), less than one-year-old, was examined and was assigned an anonymous identification number.

Measurement of mandibular residual ridge height
For each patient, the bone height-defined as the "distance between superior and inferior borders of the mandible"-was measured according to the recommendation of the American College of Prosthodontists (McGarry *et al.*, 1999). Two trained prosthodontists (examiners) measured the mandibular bone height. Duplicate readings were made for each patient. All radiographs were re-assessed to elevate intra-examiner reliability, and some of the radiographs, examined by one examiner, were re-measured by the other one. The mean of the readings was calculated and recorded.

Collection of saliva and genomic DNA extraction
On the day of saliva sample collection, the patients and controls were asked to refrain from eating at least 30 min before sample collection. Two mL of saliva was collected in Falcon tubes without stabilization solution and stored at -80°C until required for DNA extraction. The DNA was extracted using Qiagen kits, according to the procedure recommended by the manufacturer. NanoDropND-1000 spectrophotometer (NanoDrop™ 2000, Thermo Fisher Scientific, Waltham, MA USA) was used to determine the concentration and purity of the DNA extracted from each individual. An OD_{260}/OD_{280} ratio closer to 1.8 indicated a relatively pure DNA sample.

SNP selection and genotyping
The three SNPs selected for this study are presented in Tab. 1. The SNPs were checked on the NCBI dbSNP [https://www.ncbi.nlm.nih.gov/snp] websites. The selection of SNPs was based on their location in the upstream promoter region (Kim *et al.*, 2012) of the FGFR1OP2 gene.

The MassARRAY Designer software version 4.0 was utilized to design the primers for the PCR reactions, and the MassEXTEND primers program was used for designing the primers for multiplexed assays. The sequences of the designed primers used in this study are presented in Tab. 2.

The "Sequenom MassARRAY iPLEX" was employed to perform the genotyping analysis, using the reagents provided in the iPLEX Gold SNP genotyping kit (Sequenom, San Diego, CA, USA), and following the recommendations of the manufacturer. The Sequenom also provided the software and equipment required for the genotyping. The PCR reaction consisted of PCR buffer, 0.1 M each of the forward and backward PCR primers, 500 mM deoxynucleoside triphosphates (dNTPs), 2 mM $MgCl_2$, 0.5 U of HotStarTaq enzyme, and genomic DNA. The conditions applied for the PCR were as follows: initial denaturation at 95°C for 2 min, followed by 45 cycles of denaturation at 95°C for 30 s, then "annealing" at 56°C for

TABLE 1

Genetic variants in the upstream region of FGFR1OP2/wit3.0 gene studied in the Saudi RRR patients and controls

SNP number FGFR1OP2	SNP Position	Allele	Frequency in NCBI SNP database
rs2279351	chr12:26937617	A/C	A:C = 0.8598:0.1402
rs78054962	chr12:26938171	C/T	T:C = 0.9904:0.0096
rs2306852	chr12:27089540	A/G	A:G = 0.9936:0.0064

30 s, and finally "extension" at 72°C for 1 min.

TABLE 2

The sequence of the PCR primers and extension primers used for the studied SNPs

SNP ID	PCR primer 1	PCR primer 2	Extension primer
	ACGTTGGATGACATTCGAAAAG	ACGTTGGATGAGGTGAAAATAGC	GGGGCGCAAAGCCAAAG
rs2279351	CACATGGC	TGGATCG	TGTTA
	ACGTTGGATGCTCCACCCCTCG	ACGTTGGATGTGGTTGGTACTTCG	
rs78054962	AGATTTTC	CTGTTG	TTTTCCACCCGCTAATTT
	ACGTTGGATGTGTACTTCACAC	ACGTTGGATGATTGTGGACTTGCT	ATCTTCCATGGAATATTG
rs2306852	TCACCAGC	CAGTAG	TAGAATAA

The final step for the extension of the PCR product was carried out at 72°C for 5 min. The PCR products obtained during this reaction was then used in an iPLEX reaction, where extension primers were bound immediately adjacent to target SNP sites and extended by a single nucleotide base into the SNP site using mass-modified dideoxynucleotides. The assay process was composed of the initial locus-specific PCR reaction, which was followed by single base extension using the dideoxynucleotide terminators of an oligonucleotide primer which anneals immediately upstream of the polymorphic site of interest. The distinctive mass of the extended primer identifies the SNP allele using the MALDI-TOF mass spectrometry. Desalting of the products was achieved using SpectroCLEAN resin. The cleaned extension products, so obtained, were then dispensed onto a 96 SpectroCHIP array using an RS1000 Nanodispenser. In the last and final step, the array was placed into a MassARRAY Compact 96 mass spectrometer and the generated spectra were acquired using SpectroAcquire software. The automated allele calling and data analysis were achieved through the MassARRAY Typer, software version 4.0.5. The differentiation between allele was based on the differences in their masses on the MALDI-TOF mass spectrometer.

Statistical analysis

For each sample and each SNP, genotypes were recorded on an Excel spreadsheet. Genotype and allele frequencies were calculated manually in the patients and control groups, and the results were compared using the Odds ratio (OR), 95% confidence intervals (CI) [http://ihg.gsf.de/cgi-bin/hw/hwa1.pl]. Chi-square (χ^2) and p-values were obtained, and $p < 0.05$ was considered statistically significant. Based on the three genotypes of each SNP, the patients were grouped into three groups, and the results of the clinical parameters, i.e., age at first diagnosis and bone height, were calculated in each genotype and values were compared using "Student's t-test". IBM SPSS program version 22 software was used for statistical analysis.

Results

Tab. 3 presents the age, age at first edentulism, and the bone height in the Saudi patients suffering from RRR. The age of the patients ranged from 21 to 80 years, where the youngest patients had their first edentulism when they were only 12 years old. Age at first edentulism showed a marked variation from 12 to 70 years with a mean of 40.2 years and SEM of 1.26 years. The bone height showed a marked variation in the different patients and ranged from 13 to 34.6 mm.

TABLE 3

The value of age, bone height, years of edentulism and "age at first edentulism" of the RRR patients

Parameter	Mean	Median	SEM	Minimum	Maximum
Age (years)	47.85	50.00	1.22	21	80
Years of edentulism (years)	7.38	5.00	0.834	0	50
Age at first edentulism (years)	40.18	40.50	1.26	12.00	70.00
Bone Height (mm)	22.86	23.00	0.380	13.00	34.60

SEM, Standard error of the mean.

TABLE 4

Genotype and allele frequencies of rs2279351, rs78054962 and rs2306852 in Saudi patients suffering from RRR and normal controls

Variation rs2279351	**Control %**	**Cases %**	**OR**	**CI**	**X2**	***p*-value**
Genotype Frequency						
AA	85.2	65.2	Ref			
AC	8.1	15.9	2.542	0.821-7.869	2.75	0.097
CC	6.5	18.8	3.756	1.143-12.34	5.24	0.022
AC+CC	14.7	34.7	3.081	1.299-7.310	6.86	0.009
AC+AA	93.4	81.1	0.302	0.093-0.984	4.30	0.038
Allele Frequency						
A	89.3	73	0.326	0.164-0.647	10.88	0.001
C	10.6	27	3.072	1.545-6.108		
Variation rs78054962	**Control %**	**Cases %**	**OR**	**CI**	**X2**	***p*-value**
Genotype frequency						
TT	91.0	87.0	Ref			
TC	2.0	7.0	4.250	0.459-39.3	1.89	0.169
CC	7.0	5.0	0.797	0.169-3.75	0.08	0.773
TC+CC	8.9	12.7	1.488	0.442-5.01	0.42	0.519
TC+TT	92.8	94.5	1.333	0.284-6.25	0.13	0.714
Allele Frequency						
T	91.0	91.0	0.874	0.341-2.24	0.08	0.778
C	8.0	9.0	1.144	0.446-2.94		
Variation rs2306852	**Control %**	**Cases %**	**OR**	**CI**	**X2**	***p*-value**
Genotype frequency						
AA	87.2	90.7	Ref			
AG	1.8	5.5	2.939	0.295-29.25	0.92	0.336
GG	10.9	3.7	0.327	0.063-1.699	1.93	0.165
AG+GG	12.7	9.2	0.700	0.208-2.358	0.33	0.563
AG+AA	89.0	96.2	3.184	0.61-16.531	2.08	0.149
Allele Frequency						
A	88	93.5	1.934	0.740-5.051	1.86	0.123
G	11	6.4	0.517	0.198-1.351		

Genotype and allele frequencies were calculated for the studied SNPs, and the results in the RRR patients were compared to the results in the controls and are presented in Tab. 4. All three genotypes of rs2279351 (AA, AC and CC), rs78054962 (TT, TC and CC), and rs2306852 (AA, AG and GG) were identified in the normal Saudi individuals and RRR patients. For rs2279351 the wild-type A allele was significantly protective against the development of RRR (OR = 0.266; $p = 0.022$). The mutant C is significantly predisposing with a dominant influence. The two other studied SNPs, i.e., rs78054962 and rs2306852, did not show a significant influence on the development of RRR.

Tab. 5 compares the Minor Allele Frequencies (MAF) of the three studied SNPs in Saudis (normal and RRR) with those reported for different populations in the 1000 genome project [https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes], and in Koreans (Kim *et al.* 2012).

The three genotypes of each SNP were separated, and the age at first diagnosis and bone height were separately calculated in each genotype. The results are presented in Tab. 6 and Fig. 1. As can be seen, there were differences in both parameters in the different genotypes of each SNP, but the differences were not significant. In the genotypes of rs2279351 and rs78054962, the mutant CC genotype had higher bone height than the other two genotypes, and patients with this genotype had a higher age at first edentulism. While for rs2306862, the age at first diagnosis was higher in the mutant GG genotype, but the bone height was lower.

TABLE 5

Minor Allele Frequencies (MAF) of the three studied SNPs in Saudis (normal and RRR) and different populations as reported in the 1000 genome project*, and in a study from Korea (Kim et al., 2012)

Population		Minor Allele Frequency (MAF) in SNP		
	Group	**rs2279351 (C)**	**rs78054962 (C)**	**rs2306852 (G)**
Saudis (this study)	Healthy	0.106*	0.08	0.11
	RRR	0.270*	0.09	0.064
Koreans (Kim *et al.*, 2012)	RRR	0.083	0.038	0.003
1000 genome from https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/				
African Carribbeans in Barbados	Healthy	0.128	0.0000	0.0052
Americans of African ancestry in SW USA	Healthy	0.049	0.0000	0.0000
Bengali from Bengladesh	Healthy	0.145	0.0116	0.0116
Chinese Dai in Xishuangbanna, China	Healthy	0.145	0.0000	0.0000
Utah Residents (CEPH) European ancestry	Healthy	0.161	0.0000	0.0101
Han Chinese in Beijing, China	Healthy	0.039	0.0534	0.0049
Southern Han Chinese	Healthy	0.062	0.0143	0.0048
Colombians from Medellin, Colombia	Healthy	0.276	0.0106	0.0000
Esan in Nigeria	Healthy	0.141	0.0000	0.0000
Finnish in Finland	Healthy	0.086	0.0455	0.0202
British in England and Scotland	Healthy	0.154	0.0000	0.0110
Gujarati Indians from Houstan, Texas	Healthy	0.228	0.0000	0.0146
Gambian in Western Gambia	Healthy	0.075	0.0000	0.0000
Iberian Population in Spain	Healthy	0.149	0.0000	0.0047
Indian Telugu from the UK	Healthy	0.191	0.0000	0.0000
Japanese in Tokyo, Japan	Healthy	0.077	0.0385	0.0196
Kinh in Ho Chi Minh City, Vietnam	Healthy	0.040	0.0202	0.0096
Luhya in Webuye, Kenya	Healthy	0.056	0.0000	0.0000
Mende in Sierra Leone	Healthy	0.088	0.0000	0.0000
Mexican Ancestry from Los Angeles, USA	Healthy	0.390	0.0078	0.0000
Peruvians from Lima, Peru	Healthy	0.282	0.0353	0.0000
Punjabi from Lahore, Pakistan	Healthy	0.145	0.0052	0.0000
Puerto Ricans from Puerto Rico.	Healthy	0.211	0.0048	0.0000
Sri Lankan Tamil from the UK	Healthy	0.166	0.0000	0.0000
Toscani in Italia	Healthy	0.200	0.0000	0.0000
Yoruba in Ibadan, Nigeria	Healthy	0.153	0.0000	0.0000

Statistically significant difference between patients and controls.

Discussion

This is the first study reporting the genotype and allele frequencies of three SNPs of FGFR1OP2/wit3.0 in the Saudi population. All three SNPs are polymorphic in Saudis, and the three genotypes of each SNP were identified both in the control and patient group. When the allele frequencies in Saudis were compared to the allele frequencies in different populations, several differences were seen. It was seen that the minor allele (C) frequency of rs2279351 in healthy Saudis was similar to some populations but differed from others. In the RRR group, the frequency was significantly higher compared to the controls and was also significantly higher compared to the Korean RRR patients (Tab. 5). The minor alleles of rs78054962 (C) and rs2306852 (G), occurred at almost the same frequency in the Saudi controls and RRR patients. The frequency in healthy controls was higher in Saudis compared to all the populations reported in the literature, and the frequency in Saudi RRR was higher than in Korean RRR. Both these SNPs were not polymorphic in several populations where the minor allele frequency was zero (Tab. 5). Our results showed that, in Saudi RRR patients, only one of the studied polymorphic sites (rs2279351) in the upstream promoter region of FGFR1OP2/wit3.0 gene associated significantly with the development of RRR in the Saudi population while the other two (rs78054962 and rs2306852) did not. FGFR1OP2 is a factor implicated in the process of rapid wound healing that occurs in the oral cavity, and SNPs in the gene have been shown to associate with excessive atrophy of edentulous mandible (Suwanwela *et al.*, 2011). It is possible that FGFR1OP2 also has an influence on bone formation in the oral cavity, and changes in its level of activity have effects on wound healing and bone resorption. Since all the three studied SNPs lie in the promoter region of the gene, polymorphism or mutations in this region may have a strong influence on the expression of the gene, and hence the level of the gene product and this may influence the protein function. Further studies are necessary to confirm this suggestion.

TABLE 6

The age at first edentulism and bone height in different genotypes of the three studied SNPs

SNP	Genotype	No.	Bone Height (mm)	Age at first edentulism (years)
	AA	46	22.61 ± 4.05	39.12 ± 13.45
rs2279351	CA	10	22.21 ± 13.90	40.03 ± 13.90
	CC	13	23.98 ± 3.05	46.09 ± 12.28
	TT	50	22.52 ± 4.23	38.80 ± 12.89
rs78054962	TC	4	24.80 ± 3.81	45.25 ± 18.41
	CC	3	24.05 ± 8.69	46.33 ± 24.42
	AA	48	22.68 ± 4.36	40.04 ± 13.35
rs2306852	AG	3	20.83 ± 2.88	37.25 ± 12.20
	GG	2	19.45 ± 2.19	44.50 ± 13.43

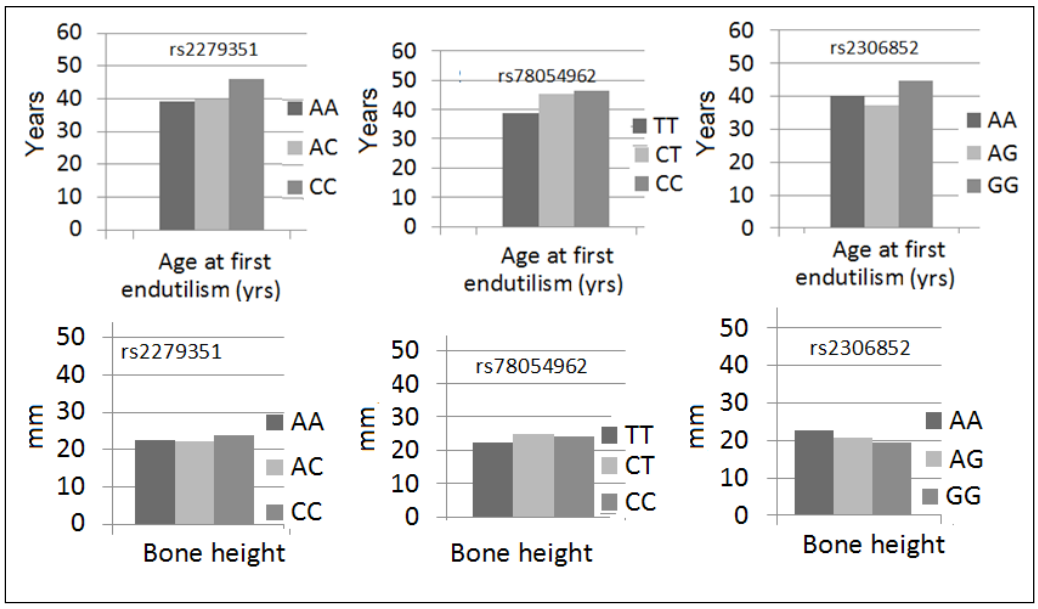

FIGURE 1. Schematic presentation of age at first edentulism and bone height in RRR patients with different genotypes of the studied SNPs.

Residual ridge resorption is a normal process that occurs following teeth extraction and results in narrowing and shortening of the ridge and loss of a large amount of jaw structure. This is due to a life-long catabolic remodeling of the residual ridge (Jahangiri *et al.*, 1998). Studies have shown that there are extensive individual variations in the rate and extent of loss of the mandibular bone following the teeth extraction process in the edentulous patients (Sun *et al.*, 2013; Chappuis *et al.*, 2017; López-Roldán *et al.*, 2009; Reich *et al.*, 2010). Several factors have been implicated in the susceptibility to develop RRR, and these include both environmental and genetic factors. Thus, is a multifactorial disorder, which is polygenic, with minor contributions from many genes and other loci in the genome. This also suggests that genetic susceptibility in individuals in the presence of the environmental factors may be the reason for the extensive individual variability in extent and severity of RRR.

The knowledge related to the genetic factors in RRR development is scarce, and only a few studies have attempted to relate the rate and extent of severity of RRR to genetic variations (polymorphisms) and the rate of expression of some genes (Lin *et al.*, 2010; Kim *et al.*, 2012; Suwanwela *et al.*, 2011). Among the genetic variations that have so far been implicated in RRR development, are the single nucleotide polymorphisms in the FGFR1OP2/wit3.0 gene, the HIF-1α gene, collagen genes (*COL1A1 COL1A2),* other genes involved in bone remodeling, including estrogen receptor, vitamin D receptor, MMP-1, CD14, IL-1RA, TGF-β1, and TNF-α (Reich *et al.*, 2010; Nishimura and Garrett, 2004). A few studies have been reported from the USA, Korea, and India (Lin *et al.*, 2010; Kim *et al.*, 2012; Suwanwela *et al.*, 2011). Lin *et al.* (2010) showed, in an elegant study published in 2010, that FGFR1OP2/wit3.0 was overexpressed in the oral cavity and postulated that it may be involved in the regulation of the cell motility that is necessary to stimulate wound closure. It was also shown that wit3.0 is a cytoskeleton molecule that induces oral mucosa contraction after dental extraction and accelerates wound healing. It was also suggested that "FGFR1OP2/wit3.0 may possess therapeutic potential for management of wounds". A little later, a study reported genetic variations in patients suffering from long-term atrophy of edentulous mandible and showed that minor allele of an SNP rs840869 or rs859024 showed association with excessive atrophy of edentulous mandible (Suwanwela *et al.*, 2011). Though in the Korean population, it was reported that the patient with the minor allele of rs840869 showed no association with excessive atrophy of edentulous mandible, but the minor allele of ss518063493 did show an association (Kim *et al.*, 2012). A study from the USA published in 2011 showed that expression of the FGFR1OP2/wit3.0 gene was increased in the postoperative oral mucosa tissues (Suwanwela *et al.*, 2011). It also showed that the minor alleles of rs840869 or rs859024 in the FGFR1OP2/wit3.0 gene were associated with excessive atrophy of the edentulous mandible. A little later, a study on the Korean population investigated SNP in the FGFR1OP2/wit3.0 gene and reported that the SNPs: rs840689 and rs859024 may be associated with the severely resorbed edentulous mandible (Kim *et al.*, 2012). However, another study on the Korean population showed no association between rs840689 and RRR. In other studies, the correlation between osteoporosis and RRR development has been investigated, but a clear link has not been demonstrated. Very few population studies are available in the literature on the genetics of RRR, and this makes the comparison of the results with other population-based studies very difficult.

In conclusion, in this present study on Saudis, we have shown a strong association between rs2279351 and RRR. The minor C allele is highly predisposing to the development of RRR in the Saudis. This SNP lies in the 2 kb upstream region of the FGFR1OP2/wit3.0 gene and is believed to be in the promoter region of the gene (Kim *et al.*, 2012). We must point out that our present study has a limitation as it has investigated a small number of RRR patients, and further studies on a larger number of patients are required in Saudi Arabia and in other populations to confirm these results.

Declarations of Interest

None.

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