Two novel SNPs in genes involved in immune response and their association with mandibular residual ridge resorption

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Original article

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Abstract

“Residual ridge resorption” (RRR) is a multifactorial condition involving bone resorption of the residual ridge. We investigated 10 single nucleotide polymorphisms (SNPs) in seven genes with the aim of identifying the genetic factors associated with RRR susceptibility. The study group included 96 RRR patients and 96 controls. Age at first edentulism, duration of edentulism, and bone height were recorded. Saliva was collected from the subjects for DNA extraction. Genotype analysis was performed on the ‘SequenomMassARRAYiPLEX’. The genotype and allele frequencies calculated in patients and controls were compared. We found that rs1800896 in the IL10 gene and rs5743289 in NOD2 gene showed significant association with RRR. Within the RRR group, genotypes for each SNP were separated, and we observed that the age at first edentulism and bone height showed variations in the different genotypes of the ten studied SNPs. This study demonstrated an association between SNPs in IL10 and NOD2 genes. It also revealed that the genotypes of the different SNPs influence bone resorption and health. Additionally, age at first edentulism and bone height were much lower in some genotypes. This study demonstrates the need for larger multicenter trials to confirm these findings. Finally, we suggest that the results of this study may be utilized for developing novel genetic diagnostic tests and for identifying Saudi individuals who may be more susceptible to RRR development following dental extraction.

1. Introduction

“Residual ridge resorption” (RRR) is a multifactorial condition involving bone resorption of the residual ridge. Following tooth extraction, wound healing is normally uneventful, with bone formation occurring in the tooth socket and bone resorption at the external surface of the alveolar bone, forming a saddle-shaped ‘residual ridge’ (Lam 1960; Pietrokovski et al., 2003). However, a number of studies have shown that this process is not entirely uneventful. There is resorption of the residual ridge in most patients and the extent of ridge loss (volume and height) differs significantly among patients (Lam 1960; Jahangiri et al., 1998; Bartee 2001). In most patients, even after wound healing, active bone resorption persists and some of the jaw structure is removed due to excessive jawbone atrophy. This condition is referred to as residual ridge resorption (RRR). Residual ridge resorption is believed to have a multifactorial etiology, with the adaptive immune response influencing the local osseous. In this respect, it has been documented that cytokines may be implicated in bone resorption (Singh, Kaur et al. 2016).

Several factors have been implicated in the pathophysiology of RRR, including osteoclast activating factor, endotoxins from dental plaque, prostaglandins, human gingival bone resorption stimulating factor, physical activity, heredity, factors playing a role in age-related bone loss, such as diet, race, lower secretion of estrogens, and those affecting gene expression of specific proteins (Atwood 1971; Hausmann 1974; Atwood 2001; Singh, Kaur et al. 2016). The differences observed in the
occurrence, severity, and complications resulting from RRR are believed to have a genetic basis. However, in the literature, there is a lack of studies on the genetic factors involved in RRR. In an attempt to unveil the role of genetic factors in the development of RRR, some studies have explored single nucleotide polymorphisms (SNPs) in different genes, including cytokine and growth factor genes, genes of matrix metalloproteinases (MMPs), FGFRI, and HIF-1α (Jahanegiri et al., 1998; Suwanwela et al., 2011; Kim et al., 2012; Song and Lee, 2014; Paek et al., 2015; Sundar et al., 2015; Singh et al., 2016), and have highlighted significant associations between some polymorphisms and RRR.

These findings led to our interest in studying the possible genetic factors for RRR susceptibility, and we investigated SNPs in cytokine and cytokine receptor genes in the Saudi population, which had shown several interesting features of RRR in an earlier study (Al AlSheikh et al., 2019).

2. Methods and Materials

2.1. Sampling

The Research Ethics Committee at King Saud University, (KSU) Riyadh, evaluated and approved this study, and the Institutional Review Board (IRB) approval was also obtained (IRB Ref No: 17/0224/IRB). Signed informed consent was obtained from the participants before their inclusion in this study.

The study included 192 Saudi individuals (96 patients suffering from RRR; and 96 controls). All patients were being treated at the clinic (outpatient) at the College of Dentistry, KSU, Riyadh, Saudi Arabia in the period from May to November 2017. Healthy individuals not suffering from RRR, were recruited as controls.

Complete and partial mandibular edentulous cases were included, while all others were excluded. In the patients with partial edentulism, the position of the mandibular posterior teeth, either unilaterally or bilaterally, was recorded. All individuals (patients and controls) were interviewed to obtain information about their age, clinical history, age at first edentulism, duration of edentulism, and any other relevant data, such as dental hygiene habits. The digital panoramic dental radiograph (OPG), less than one year-old, of each patient, was examined and assigned an anonymous identification number. The bone height, i.e., the distance between superior and inferior borders of the mandible, as described in the American College of Prosthodontists (ACP) classification (McGarry et al., 2001), of all patients was recorded by two trained prosthodontists conducting duplicate readings. The mean of these readings was recorded.

The patients and control individuals were asked to refrain from eating at least 30 min before sample collection, and 2 ml saliva was collected in centrifuge tubes (Falcon, Corning Life Sciences, NY, USA) and stored at –80 °C until required. The DNA was extracted using the QiaGen kit (Qiagen, Hilden, Germany), following the manufacturer’s instructions. The concentration and purity of the extracted DNA were estimated using NanoDropND-1000 spectrophotometer (NanoDrop™ 2000, Thermo Fisher Scientific).

2.2. Genotyping

A literature search was carried out, and SNPs were selected for genotyping. The SNPs, including TNF-α (rs1800629), IL10 (rs1800872, rs1800896), IL1RN (rs419598), TNFRSF11B (rs11573847), TNFRSF11A (rs4485469), NOD2 (rs5743289), and MMP1 (rs1799750, rs554499, rs5854) were genotyped. The SNPs studied were also verified on NCBI dbSNP websites and are listed in Table 1. The MassARRAY Designer software version 4.0 (Agena Biosciences, CA, USA) was used to design PCR and primers for MassEXTEND multiplexed assays automatically. The PCR and extension primers designed for this study are presented in Table 2.

The genotyping analysis was performed using the reagents included in the iPLEX Gold SNP genotyping kit (Sequenom, CA, USA) on the ‘SequenomMassARRAYiPLEX’, and using the software and equipment provided with the MassARRAY platform (Sequenom, CA, USA), following the recommendations of the manufacturer. The PCR reaction (containing PCR buffer, 0.1 M PCR primer, 2 mM MgCl2, 500 M deoxynucleoside triphosphates (dNTPs), 0.5 U HotStarTaq enzyme, and genomic DNA) was carried out as described by AL-Eitan et al (AL-Eitan et al., 2019).

2.3. Statistical analysis

Genotype and allele frequencies were calculated manually in the patients and control groups, and the results were compared using odds ratio (OR) with 95% confidence intervals (CI). The χ² and p-values were obtained, and a p-value < 0.05 was considered statistically significant. All patients were grouped according to the different genotypes of each SNP they were carrying and the results of the clinical parameters, i.e. age, age at first diagnosis, and bone height, were separately calculated for each genotype. The analysis was conducted using IBM SPSS program version 22 software. Results were correlated to the clinical data, and demographic data and Pearson’s correlation coefficient (r) were obtained.

3. Results

In total, 96 patients and 96 controls were enrolled in this study. The mean age of the patients was 49.85 ± 13.14 years (minimum: 21, maximum 80); mean age at start of edentulism was 40.2 ± 13.60 years (minimum: 12, maximum 70); and mean mandibular bone height was 22.9 ± 3.80 mm (minimum: 13, maximum: 34.8). The genotype and allele frequencies of the parameters studied are presented in Table 3.

The results of the present study showed that rs1800896 (−1082 T > C) in the promoter region of the gene and a transversion mutation are significantly associated with RRR. The

| No. | SNP ID     | Gene       | Chromosomal Location | Ancestral Allele |
|-----|------------|------------|----------------------|------------------|
| 1   | rs1800629  | TNF-α      | 6:31575254           | G                |
| 2   | rs1800872  | IL10       | 1:206773062          | C                |
| 3   | rs1800896  | IL10       | 1:206773552          | A                |
| 4   | rs419598   | IL1RN      | 2:11329630           | T                |
| 5   | rs11573847 | TNFRSF11B  | 8:118944538          | T                |
| 6   | rs4485469  | TNFRSF11A  | 18:62332340          | A                |
| 7   | rs5743289  | NOD2       | 16:50722863          | T                |
| 8   | rs1799750  | MMP1       | 11:102799765         | T                |
| 9   | rs554499   | MMP1       | 11:102790807         | T                |
| 10  | rs5854     | MMP1       | 11:102790143         | C                |
Table 2
PCR primers and Extension primers for the studied SNPs designed using MassARRAY Designer software.

| SNP ID   | PCR primer 1                      | PCR primer 2                      | Extension primer |
|----------|-----------------------------------|-----------------------------------|------------------|
| rs1800629| ACGTTGGATGCCATTTGAGGACAGCTTAC    | ACGTTGGATGCCATTTGAGGACAGCTTAC    | AGGCTGAACCCGCCCTC |
| rs1800872| ACGTTGGATGCCATTTGAGGACAGCTTAC    | ACGTTGGATGCCATTTGAGGACAGCTTAC    | ATCTCTGAGGCCCTTCTG |
| rs1800896| ACGTTGGATGCCATTTGAGGACAGCTTAC    | ACGTTGGATGCCATTTGAGGACAGCTTAC    | GTTGTTTTTATCTGAGCC |
| rs419598 | ACGTTGGATGCCATTTGAGGACAGCTTAC    | ACGTTGGATGCCATTTGAGGACAGCTTAC    | GCTCTCTCTCTCTCTCTCT |
| rs11573847| ACGTTGGATGCCATTTGAGGACAGCTTAC   | ACGTTGGATGCCATTTGAGGACAGCTTAC   | AGAGAGAGAGAGAGAGAG |
| rs4485469 | ACGTTGGATGCCATTTGAGGACAGCTTAC   | ACGTTGGATGCCATTTGAGGACAGCTTAC   | ACGAGAGAGAGAGAGAGAG |
| rs5743289 | ACGTTGGATGCCATTTGAGGACAGCTTAC   | ACGTTGGATGCCATTTGAGGACAGCTTAC   | TTTGTTTTTATCTGAGCC |
| rs1799750 | ACGTTGGATGCCATTTGAGGACAGCTTAC   | ACGTTGGATGCCATTTGAGGACAGCTTAC   | GAGAGAGAGAGAGAGAGAG |
| rs554499  | ACGTTGGATGCCATTTGAGGACAGCTTAC   | ACGTTGGATGCCATTTGAGGACAGCTTAC   | GAGAGAGAGAGAGAGAGAG |
| rs5854   | ACGTTGGATGCCATTTGAGGACAGCTTAC   | ACGTTGGATGCCATTTGAGGACAGCTTAC   | GAGAGAGAGAGAGAGAGAG |

Table 3
The genotype and allele frequencies of RRR patients and controls.

| SNP        | Prevalence (%) | Statistic s |
|------------|----------------|-------------|
| Control    | Cases          | OR          | CI  | χ² | P value |
| rs1800629  | 60.9           | 59.5        | Ref |     |         |
|            |                |             |     | 0.386–2.36 | 0.01 | 0.919   |
|            | 0.02           |             |     | 0.02–0.02   | 0.01 | 0.919   |
|            | 0.02           |             |     | 0.02–0.02   | 0.01 | 0.919   |
| rs1800872  | 58.8           | 55.4        | Ref |     |         |
|            |                |             |     | 0.179–0.83  | 0.03 | 0.863   |
|            |                |             |     | 0.14–0.74   | 0.01 | 0.919   |
|            |                |             |     | 0.02–0.14   | 0.01 | 0.919   |
| rs1800896  | 31.4           | 56          | Ref |     |         |
|            |                |             |     | 0.179–0.83  | 0.03 | 0.863   |
|            |                |             |     | 0.14–0.74   | 0.01 | 0.919   |
| rs419598   | 31.4           | 56          | Ref |     |         |
|            |                |             |     | 0.179–0.83  | 0.03 | 0.863   |
|            |                |             |     | 0.14–0.74   | 0.01 | 0.919   |
| rs11573847 | 31.4           | 56          | Ref |     |         |
|            |                |             |     | 0.179–0.83  | 0.03 | 0.863   |
|            |                |             |     | 0.14–0.74   | 0.01 | 0.919   |

Genotype prevalence (%):
GG 60.9 59.5 Ref 0.386–2.36 0.01 0.919
GA 17.4 16.2 0.955 0.386–2.36 0.01 0.919
AA 21.7 24.3 1.145 0.51–2.56 0.11 0.740
GA + AA 39.1 40.5 1.061 0.54–2.07 0.03 0.863
GA + GG 78.3 75.7 0.864 0.39–1.88 0.13 0.713
Allele Frequency
G 0.696 0.676 0.911 0.55–1.50 0.13 0.716
A 0.304 0.324 1.097 0.67–1.80 0.13 0.716

Genotype prevalence (%):
GG 58.8 55.4 Ref 0.179–0.83 0.03 0.863
GT 26.5 25.7 1.030 0.47–2.24 0.01 0.941
TT 14.7 18.9 1.366 0.54–3.43 0.44 0.506
GT + TT 41.1 48.5 1.150 0.59–2.23 0.17 0.681
GT + GG 85.3 88.2 0.739 0.30–1.79 0.45 0.503
Allele Frequency
G 0.721 0.682 0.911 0.55–1.50 0.13 0.716
A 0.279 0.324 1.097 0.67–1.80 0.13 0.716

Genotype prevalence (%):
TT 75 74.6 Ref 0.45–3.34 0.16 0.68
TC 37.1 25.6 0.386 0.179–0.83 0.03 0.863
CC 31.4 18.2 0.326 0.14–0.74 0.21 0.64
TC + CC 0.686 0.419 0.359 0.18–0.69 0.21 0.64
TC + TT 0.686 0.817 2.047 0.96–4.35 3.54 0.059
Allele Frequency
T 0.50 0.689 2.216 1.38–3.53 11.26 0.0007
C 0.50 0.311 0.451 0.28–0.72 0.21 0.64

Genotype prevalence (%):
AA 95.7 87.5 Ref 0.83–11.92 3.09 0.078
AG 4.3 12.5 3.143 0.83–11.92 3.09 0.078
GA + AA 100 100 1.158 0.02–59.14 0.02–59.14 0.02–59.14
Allele Frequency
A 0.022 0.062 3.00 0.81–11.13 2.95 0.007
G 0.978 0.938 0.333 0.09–1.23 2.95 0.007

Genotype prevalence (%):
AA 51.5 41.1 Ref 0.61–3.14 0.61 0.43
AG 26.5 29.4 1.200 0.67–1.80 0.13 0.716

wild-type allele T was >four times predisposed to RRR compared to the mutant C allele (OR = 0.451; p = 0.0007). The two alleles behaved in a co-dominant manner as the presence of the homozygous phenotypes influenced the relative risk accordingly (TC + CC: OR = 0.359; and TC + TT: RR = 2.047).

The patients were grouped according to the genotypes of each SNP and the value of the clinical parameters, i.e. age at first diagnosis and bone height were separately calculated in each genotype. The results are presented in Figs. 1 and 2.

The SNPs, including TNF-α (rs1800629), IL10 (rs1800872, rs1800896), IL1RN (rs419598), TNFRSF11B (rs11573847), TNFRSF11A (rs4485469), NOD2 (rs5743289), and MMP1 (rs1799750, rs554499, rs55854) were genotyped in RRR patients and healthy controls (Table 2). The genotype distribution frequency for SNPs (rs1800629, rs1800872, rs419598, rs11573847, rs4485469, rs1799750, rs554499, and rs5854) showed no statistical difference between RRR patients and healthy controls. For the rs5743289 located in the gene NOD2, the frequencies of genotype TC, TT, and TC + CC were 10.0%, 1.4%, and 97.1%, respectively in RRR patients, whereas in controls it was 0%, 10.9%, and 89%, respectively. The GG genotype of RRR patients was associated with a 13.8 fold increased risk when compared with that of TC genotype (odds ratio, 13.8; 95% CI, 0.77–24; P = 0.01). The relationship between genotype and clinical characteristics of RRR patients was evaluated, but no association could be determined (data not shown).

The LD proxy analysis of rs1800896 showed that it is very closely associated with five other SNPs (R² = 1) located in IL10 and IL19 genes. These 5 SNPs are rs3024500, rs3024496, rs1878672, rs3024491, and rs2222202 (Supplementary Fig. 1).

4. Discussion

This paper reports polymorphism in genes involved in immune response and antibacterial actions, and their association with RRR in Saudi population. Of the ten polymorphic sites investigated in seven genes (TNF-α; IL-10, IN1RN, TNFRSF11A and B, NOD2, and MMP1), we identified two sites that are significantly associated with RRR, confirming that genetics plays a role in the etiology of
RRR. In this study, we report our findings and show that identify two SNPs associated with RRR in Saudi patients.

In TNF-α gene, an upstream variant 308G > A (rs1800629) was investigated, but no association was seen with RRR. The TNF-α was selected as it is a pro-inflammatory cytokine, which, along with IL-1β, plays a crucial role in inflammatory response. Additionally, it is a differentiation factor for osteoclasts and has a vital role in local osteolysis in chronic inflammatory diseases (Azuma et al., 2000). It has also been shown that TNFα, in collaboration with IL1 and regulated by the expression of RANK1 and OPG, has an essential role in decreasing bone density. Interestingly, the frequency of the minor A allele was 0.304 in the healthy controls, which is significantly higher compared to that reported in the 1000 Genome Project.

Two SNPs were investigated in IL-10, an anti-inflammatory and highly pleiotropic cytokine produced by a variety of cell types. It has also been implicated in inflammatory response, autoimmune diseases and cancer (Mannino et al., 2015). We investigated two SNPs in the IL10 gene, rs1800872 (–592G/T) and rs1800896 (–1082 T > C). Both these SNPs have been extensively investigated and some studies have reported the association of one or both SNPs with various pathologies (Sun et al., 2013; Zhang et al., 2017). The results of the present study showed that rs1800896 (–1082 T > C) in the promoter region of the gene and a transversion mutation are significantly associated with RRR. The wild-type allele T was >four times predisposed to RRR than the mutant C allele (OR = 0.451; p = 0.0007). The two alleles behaved in a co-dominant manner, as the presence of the homozygous phenotypes influenced the relative risk accordingly (TC + CC: OR = 0.359; and TC + TT: RR = 2.047). However, the rs1800872 (–592G/T), which occurs in the promoter region of the IL10 gene, did not exhibit any association with RRR. Compared to the results of the 1000 Genome Project, the frequency of the minor allele was significantly lower in healthy controls (1000 Genome: 0.4349; healthy controls: 0.279).

Two genes belonging to the soluble TNF receptor superfamily, 11A and 11B, were investigated. The TNFRSF11B gene encodes osteoprotegerin (OPG), which functions as an osteoclastogenesis inhibitory factor, i.e., as a negative regulator of bone resorption (Komatsu et al., 2008; Fu et al., 2013; Mesa et al., 2017). We investigated the SNPs rs4485469 and rs11573847 in TNFRSF11A and TNFRSF11B, respectively. The rs4485469 is an A > G transition, with a minor allele (G) frequency of 0.35 in the control group of individuals, although a higher frequency of 0.475 was reported in the 1000 Genome Project. No association of rs4485469 was detected with RRR in this study, and neither could we find any other studies for comparison of our results. The SNP rs11573847 is an A to G transition, where the minor allele G has been reported at a frequency of 0.0605 (1000 Genome Project). This SNP is involved in osteolysis susceptibility, as shown in a study including meta-analysis. No association of rs11573847 was identified with the RRR patients during our investigation. Additionally, in the control group, the frequency of occurrence of the minor G allele was very low (0.022), and no homozygous GG cases were detected in the patients or controls (Table 3).

Our investigation of rs419598 in interleukin 1 receptor antagonist (IL1RN) gene, also showed no association with RRR. This gene
encodes a protein that is an antagonist of the IL1 receptor, and hence, has modifying effects on the immune and inflammatory responses related to IL1. The rs419598, a synonymous mutation, is a +2018 T > C transition in the *IL1RN* that has been investigated in several studies and associated with reduced susceptibility to generalized periodontitis (Mesa et al., 2017). In a study on Japanese patients, individuals carrying the C allele had a significantly lower risk of developing chronic periodontitis (Komatsu et al., 2008). The rs419598 was also shown to be linked to orthodontically-induced external apical root resorption (Sharab et al., 2015; Iglesias-Linares et al., 2017), ankylosing spondylitis (Jin et al., 2013), knee osteoarthritis (Wu et al., 2013; Bastos et al., 2015), and the severity of knee and hip osteoarthritis (Kerkhof et al., 2011), although some studies have reported contradictory results (Bastos et al., 2015).

Nucleotide-binding oligomerization domain-containing protein 1 and 2 (NOD1 and NOD2) play a crucial role in innate immunity against certain bacterial infections. Our investigation of rs5743289 in *NOD2* gene exhibited its significant association with RRR, where the ancestral T allele is the minor allele in Saudis (confirming the results of previous studies: [https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=5743289]) and is highly protective against RRR development (T: OR = 0.55 and C: OR = 1.78). Its genotype frequencies in patients and controls were significantly different, while the allele frequencies were not. In the homozygous CC, the susceptibility to develop RRR was >seven times compared to that of the TT genotype. Additionally, the mutant C allele has a dominant effect, and the OR for CC + TC = 8.47. This is an exciting discovery, and requires further studies on larger populations and other SNPs in the *NOD2* gene. It is possible that the T allele of rs5743289 disrupts these responses and influences innate immunity, which in turn, is not able to detect the intracellular bacterial growth and leads to activation of mechanisms influencing bone resorption. The mechanisms by which bacterial infections influence RRR need further elucidation and clarification.

Three SNPs in matrix metalloproteinases (MMPs) were investigated, as these enzymes are involved in the breakdown of collagens I, II, and III, and may play a role in bone resorption. The MMPs are also pro-inflammatory mediators and have been implicated in the development of aseptic periprosthetic osteolysis, metastasis, invasiveness of cancers, and premature rupture of fetal membranes. The three SNPs in the *MMP1* genes investigated in this study did not show any association with RRR. The rs1799750 is a C > T transition at position /C01607 in the promoter region of the *MMP1* gene and is known to be involved in transcriptional upregulation (Titeux et al., 2008). It is suggested that the increased *MMP1* expression leads to increased collagen degradation, and hence, increase in disease severity. It was shown that rs554499 results in overexpression of *MMP1*, which may result in excessive degradation of collagen. The degradation products of collagen and matrix components are shown to be chemotactic for monocytes and may lead to the accumulation of macrophages in the periprosthetic connective tissues, causing further damage. We investigate rs5854, which results from a G to A transition at the 3’ end of the *MMP1* gene. The mutant “A” is reportedly associated with total hip arthroplasty failure. This study did not show a significant association between rs5854 and RRR. We suggest carrying

![Fig. 2. ‘Bone height’ (mm) in RRR in different genotypes of the SNPs studied during this investigation.](image-url)
out a detailed investigation on other SNPs in this gene in order to determine their possible associations with RRR.

Finally, an interesting observation made during this study was the effect of the genotypes of the SNPs on the age at first edentulism and bone height. The results show that some of the genotypes cause loss of teeth in patients at an early age, while others affect the bone resorption rate, where the bone loss is more than that in other genotypes. These results demonstrate the role of genetics in the development and progression of RRR. Our study also shows that both the age at first edentulism and bone height are affected by some of the genotypes of SNPs investigated. These results may be utilized for developing novel genetic diagnostic tests and for identifying individuals who may be more susceptible to RRR following dental extraction. We suggest further detailed investigations to identify the genetic markers of RRR and to confirm these findings.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to bias their work reported in this paper. Appendix A. Supplementary material

Supplementary data to this article can be found on line at https://doi.org/10.1016/j.sjbs.2020.01.016.

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