Clinical and Genetic Analysis of Multiple Idiopathic Cervical Root Resorption

Yu Meng WANG¹, Wen Yan RUAN¹, Dan Dan CHI¹, Xiao Hong DUAN¹

Objectives: To explore the genetic background and clinical phenotypes of multiple idiopathic cervical root resorption (MICRR) in a Chinese family.

Methods: The proband and his three family members were clinically examined and had radiographs taken with a radiovisiography (RVG) system and CBCT to define the diagnosis of MICRR. Genomic DNA (gDNA) was extracted from peripheral blood samples of the patient, his father, mother and younger sister for whole exome sequencing (WES). The pathogenicity of rare variants with minor allele frequency (MAF) less than 0.005 were analysed following possible inheritance patterns, predicted results from 12 software programs, the American College of Medical Genetics (ACMG) 2015 criteria, and information from ClinVar, OMIM and HGMD databases as well as gene function.

Results: The proband presented the typical MICRR phenotypes such as thin cervical pulp wall and apple core–like lesions in radiographs. Following the recessive inheritance pattern, WES analysis identified SHROOM2, SYTL5, MAGED1 and FLNA with a higher chance of causing MICRR. Four genes with compound heterozygous variants and another 27 genes with de novo variants either in autosomal-dominant or autosomal-recessive pattern were also found to have the potential pathogenicity.

Conclusion: A total of 35 novel potential pathogenic genes were found to be associated with MICRR from a Chinese family through WES. The new genetic background of MICRR may be helpful for clinical and molecular diagnosis.

Keywords: de novo variants, multiple idiopathic cervical root resorption, pathogenic variant filtering, whole-exome sequencing


Root resorption is the loss of dentine, cementum and/or alveolar bone due to physiological or pathological reasons, which can occur anywhere in the tooth root. Physiological tooth absorption occurs in primary dentition and leads to exfoliation of permanent teeth; however, root resorption in permanent teeth is largely pathological. Tooth root resorption can be divided into internal resorption and external resorption, based on position and how they progress. The former involves resorption from the pulp cavity to the root surface, whereas the latter involves resorption from the root surface to the dentine and pulp cavity. External tooth root resorption can be further divided into root surface resorption, inflammatory resorption, external cervical root resorption (ECR), replacement resorption and transient apical resorption.¹

ECR is a rare and aggressive type of external root resorption, which is also known as aggressive root cervical resorption and invasive cervical external resorption. It usually occurs at the cementoenamel junction (CEJ) of the tooth neck, and gradually destroys the cementum, dentine and pulp tissue from the root surface. As resorption progresses, it further invades the coronal direction to damage the enamel and the
root direction to damage the tooth root. The aetiology of ECR is very complex, including local factors such as orthodontic treatment, trauma, apical or periodontal inflammation, internal bleeding, tooth replantation, periodontal surgery, tumours, cysts, bruxism and impacted teeth, and systematic factors such as Paget disease, Goltz syndrome, Papillon-Lefèvre syndrome, Turner syndrome, Stevens-Johnson syndrome, hyperparathyroidism, hypoparathyroidism, kidney disease, liver disease and bad eating habits. In the absence of an identifiable cause, ECR at the CEJ is termed idiopathic cervical tooth resorption (ICRR), and when more than three teeth are affected, ICRR is termed multiple idiopathic cervical tooth resorption (MICRR).

MICRR is an extremely rare and aggressive form of external root resorption, and current understanding of its aetiology is very limited due to the small number of cases. Possible causes of MICRR include viral infections such as pertussis, hepatitis B and feline viruses; hormone changes such as thyroid hormone and gestational hormone; and drug-related factors such as chemotherapy drugs and osteoporosis treatment drugs. Most researchers believe that the occurrence of MICRR is associated with enhanced activity of osteoclasts and odontoclasts. In 2010, Yu et al reported a case of MICRR involving 31 permanent teeth including an impacted third molar, which indicates oral exposure and microbial infection may not be causative factors of MICRR. In addition, clinicopathological analysis of affected teeth in MICRR has shown that connective tissue in areas of resorption contains fibroblasts and fibrocytes and osteoclast-like giant cells, but without the clear presence of inflammatory cells, which indicates MICRR may be a non-inflammatory disorder but involve osteoclast-related tooth resorption.

Family analysis of MICRR showed that three of the four affected family members had the heterozygous missense mutation (c.1219 G > A) in the IRF8 gene. Further functional studies suggest that this mutation may inhibit the expression of IRF8 and weaken IRF8 protein function, thereby inducing osteoclastogenesis at the transcription level and increasing the risk of root resorption. These studies add to the evidence that suggests abnormal osteoclast activity could lead to the occurrence of MICRR. Besides the above pedigree analysis, most other genetic analyses on MICRR were based on sporadic cases and the present authors found that most cases were sporadic except for IRF8 mutation related MICRR in the pedigree study. The disease-causing genes in these sporadic MICRR cases were lacked solid genetic evidence in other cases. Meanwhile, these reports did not disclose the details of the screening process of pathogenic genes, so it is difficult to determine the true harmfulness of these genes.

The present authors recruited a man with MICRR and with no other medical conditions from a Chinese family to explore possible pathogenic genes. We performed whole-exome sequencing (WES) in the pedigree, selected the genetic variants through strictly standardised steps and considered all the possible candidate pathogenic variants. Finally, we found that 35 novel variants of the proband may theoretically associate with MICRR. This study provides a new direction for the genetic aetiology of MICRR and the mechanism of its exploration.

Patients and methods

Clinical information

The proband was a 19-year-old man who was referred to the Clinic of Oral Rare Diseases and Genetic Diseases, School of Stomatology at the Fourth Military Medical University, Xi’an, China, with the chief complaint of tooth pain when chewing. He had undergone extraction of multiple teeth in his right maxilla in 2021 due to serious cervical tooth resorption that caused tooth crown fracture and tooth roots without restoration. In the 2 years before he presented to the clinic, the remaining teeth gradually developed similar symptom of cervical resorption, which resulted in tooth pain when chewing. The patient was examined and evaluated with radiographic detection, such as radiovisioigraphy (RVG) and 3D CBCT reconstruction, to evaluate the degree of resorption and the number of affected teeth. Professional oral clinical examinations were also performed on all members of the patient’s family. The study was approved by the Ethics Committee of the School of Stomatology, Fourth Military Medical University. Informed consent was obtained from each family member and from healthy controls.

WES

The proband and three unaffected members of his family (I-1, I-2, II-1, II-2) included in the study underwent clinical WES. Peripheral blood samples were collected from all family members. Genomic DNA (gDNA) was extracted using QIAamp DNA Blood Mini kit (Qiagen, Valencia, CA, USA) according to the manufacturer’s instructions. WES involving exome capture, high-throughput sequencing and common filtering was performed using Annoroad Gene Technology (Annoroad, Valencia, CA, USA).
Alignment of the sequence reads, indexing of the reference genome, variant calling and annotation were carried out using the SureSelect Human All Exon V6 system (Agilent, Santa Clara, CA, USA). Valid sequencing data of WES were mapped to the human reference genome using the Maq program. The number of the human genome reference assembly was hg19.

**Bioinformatic analysis**

Rare variants referred to those with an MAF less than 0.005\(^1\), which were chosen from the following databases: Exome Aggregation Consortium (http://exac.broadinstitute.org/), Exome Variant Server (http://evs.gs.washington.edu/EVS), 1000 Genomes Project (http://browser.1000genomes.org), dbSNP (http://www.ncbi.nlm.nih.gov/snp), dbVar (http://www.ncbi.nlm.nih.gov/dbvar), GnomAD (http://www.gnomad-sg.org/), NHLBI GO Exome Sequencing Project (https://evs.gs.washington.edu/E), Hapmap (www.hapmap.org) and Scripps Wellder-Genome Resource (https://www.scripps.org/).

Following the American College of Medical Genetics (ACMG) 2015 criteria, twelve pathogenicity prediction software programs were used to predict the variants to be damaging, deleterious and disease-causing. These included the SIFT < 0.05, the MutationAssessor > 1.938, the FATHMM < -1.5, the GERP++ > 3, the PhyloP > 2.5, the PhastCons > 0.6, the PolyPhen2_HDIV (Probably damaging >= 0.957, possibly damaging 0.453 <= pp2_hdiv <= 0.956; benign <= 0.452) and the PolyPhen2_HVAR (Probably damaging >= 0.909, possibly damaging 0.447 <= pp2_hdiv <= 0.909; benign <= 0.446). The pathogenic variants predicted from more than two software programs were selected and analysed. Variants without patients’ hereditary source were excluded. The types of variants included missense, frameshift, inframe insertion, inframe deletion, splice region, splice donor, splice acceptor, stop gained and stop lost. The predicted pathogenicity of the gene variants, especially on those genes associated with tooth resorption and development, bone development, saliva functions, odontoclasts and osteoclastogenesis, were analysed. All the variants were also verified on ClinVar, OMIM and HGMD databases.

The present authors also considered compound heterozygous variants that met the condition above. The compound heterozygous variant was found when the proband had more than two variation sites in the same gene and the different sites were inherited from his father and mother separately. If the proband’s sister did not have the same compound heterozygous variants as him, the compound heterozygous variant was reserved.

Since the patient’s parents and sister did not have similar phenotypes, the mode of inheritance in the family was considered autosomal recessive or X-linked inheritance. The de novo variants were also considered from the possible four inheritance patterns (Fig 1).

**Results**

**Clinical findings**

Upon initial diagnosis of MICRR in February 2022, the intraoral examination of the patient showed that multiple teeth (12 to 17) in the right maxilla were missing due to having been extracted previously. In addition, multiple tooth defects were detected using a dental probe in the cervical region under the CEJ, including teeth 25, 26, 27, 28, 33, 34, 35, 36, 42, 43, 44, 45, 46 and 47. Sensitivity during cervical probing of teeth was observed in teeth 42 to 47. Dental percussion examination revealed slight discomfort in teeth 34, 44, 45 and 46. Transient pulp sensitivity occurred in teeth 34, 44, 45 and 46 during cold pulp sensitivity testing and was accompanied by radiating pain in tooth 34. Furthermore, electric pulp testing of tooth 34 demonstrated a negative response. Teeth 42 to 47 had undergone gingivectomy and surgical crown lengthening to expose the subgingival defect before images were taken, so the lesion area of multiple teeth is visible and located supragingivally (Fig 2).

After further radiographic examination, many low-density areas were found in the cervical regions of teeth 26, 27, 28, 33, 34, 35, 36, 42, 43, 44, 45, 46 and 47. Teeth 45, 46, 47 exhibited severe cervical resorption and radiographs revealed typical apple core–like lesions at the CEJ. This severe resorption almost resulted in the separation of the crown and root of the tooth, which is the typical X-ray finding of MICRR (Fig 2). 3D reconstruction showed worm-eaten lacunar-like resorption on the inner surfaces of crowns and cervical resorptive regions of the affected teeth. Tooth 25 had received root canal treatment, and teeth 38 and 48 were mesially impacted. None of the remaining teeth were affected by secondary apical periodontitis.

Family history revealed that other family members had no similar phenotypes of cervical root resorption. No other identifiable cause was found for the proband such as orthodontic treatment, trauma, apical lesions or tumors or cysts. The proband had no direct or indirect contact with cats, no history of allergy to drugs/food, no habit of eating sweets or acidic foods, and no history of hereditary diseases in his family or any other systemic disease. The proband had not received radio-
therapy and had good function of the salivary glands and good oral hygiene. These characteristics helped to rule out the possibility of rampant caries.

**Genetic findings**

A mean coverage of > 150× for 99% of the target regions reads map indicated that the reference sequence selection was accurate and sufficient for the analysis. A total of 45,158 variants were observed among the family members, including 31,789 variants in the proband, 31,527 in his father, 30,825 in his mother and 29,505 in his sister. Based on the inheritance pattern, 74 variants fitting X-linked recessive inheritance and 304 homozygous variants fitting autosomal recessive inheritance were screened out. Additionally, there were 372 de novo homozygous variants in the autosomal genes and seven variants in X-linked genes. Furthermore, there were 4,293 de novo heterozygous variants in the autosomal genes, 90 in X-linked genes and 12 in the Y-linked genes. After initial exclusion of variants with an MAF > 0.005 in public databases (ExAC, EVS, 1KGP, dbSNP, dbVar, GnomAD, ESP, Hapmap, Wellderly and BGI internal database) further analysis, considering the variation type and software prediction, enabled a significant reduction of the candidate variants. Further evaluation considering the variant consequence, severity, and duplication of genes and unknown reads resulted in the identification of...
of 35 variants (Fig 1). These were divided into 8 genes with transmitted variants and 27 genes with non-transmitted variants (de novo variants) based on the source of variation.

Transmitted variants

Based on X chromosomal recessive modes, variants in four genes (SHROOM2, SYTL5, MAGED1 and FLNA) were identified (Table 1). No homozygous variant was found in accordance with the typical autosomal recessive inheritance mode (Fig 1). The proband had four genes (NBPF9, SYNE1, NPIPB12 and MUC4) with compound heterozygous variants. We filtered a compound heterozygous variant c.1077C > A/c.349 + 2T > C (p.Pro360Thr/*) in NBPF9, c.14868C > A/c.599G > A (p.Ser4956Arg/p.Gly200Asp) in SYNE1 and c.1074_1085dupTCCACCCTCAGC/c.1838C > A (p.Pro359_Ala362dup/p.Pro613His) in NPIPB12 (Table 2). The proband also had a compound heterozygous variant with six variation sites, of which four were inherited from his father and two from his mother, of the MUC4 gene (Table 3).

Non-transmitted variants

The proband had 27 genes with non-transmitted autosomal heterozygous variants and one with a non-transmitted autosomal homozygous variant (Fig 1). The de novo

### Table 1  Pathogenic genes fitted X-linked inheritance pattern in the transmitted ways.

<table>
<thead>
<tr>
<th>CHR</th>
<th>Variation type</th>
<th>Inheritance</th>
<th>Gene</th>
<th>mRNA</th>
<th>Protein</th>
<th>Annotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Missense</td>
<td>XR</td>
<td>SHROOM2</td>
<td>ENST00000380913.3:c.1549C &gt; T</td>
<td>p.Arg517Cys</td>
<td>Nasopharyngeal carcinoma</td>
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<tr>
<td>X</td>
<td>Missense</td>
<td>XR</td>
<td>SYTL5</td>
<td>NM_001163335.1:c.1409A &gt; G</td>
<td>p.Asn470Ser</td>
<td>NF-κB</td>
</tr>
<tr>
<td>X</td>
<td>Missense</td>
<td>XR</td>
<td>MAGED1</td>
<td>NM_001005332.1:c.865G &gt; C</td>
<td>p.Gly289Arg</td>
<td>Osteoclastogenesis; mineralisation of rEMSCs</td>
</tr>
<tr>
<td>X</td>
<td>Missense</td>
<td>XR</td>
<td>FLNA</td>
<td>ENST00000369856.3:c.227C &gt; T</td>
<td>p.Thr76ile</td>
<td>Osteogenic and osteoclastic differentiation</td>
</tr>
</tbody>
</table>

CHROMOSOME; rEMSCs, rat ectomesenchymal stem cells; XR, X-chromosome recessive.

![Intraoral image and radiographs. Black arrows indicate the cervical root resorption. 3D reconstruction showed worm-eaten lacunar resorptions in the inner surfaces of crowns and cervical resorptive regions. Red arrows in the digital radiovisiography show typical apple core–like change in the affected teeth. Teeth 42 to 47 had undergone gingivectomy and surgical crown lengthening to expose the subgingival defect before the pictures were taken.](image-url)
autosomal homozygous variant is a frameshift variant in the FOXO6 gene, whereas the other 26 de novo variants are autosomal heterozygous variants. Among these variants, there were nine genes (BCL11A, OSR2, MUC6, KRT18, MEOX1, TOLL6, KCTD1, ELAVL3 and CD93) with missense variants, eight (NBPF12, FAM78A, AGAP4, LIP1, DHX32, HERC2P4, TP53 and DDX52) with splice variants, two (FOXO6 and AP003062.1) with frameshift variants, two (MUC19 and NPIPA5) with inframe insertions, four (NPIPB11, CHD3, MAP2K4 and TRB2) with inframe deletions, and one (LOC101927628) with a stop gained variant (Tables 4 and 5).

Discussion
To determine the disease as a recessive inheritance mode, a large sample of pedigree separation analysis is often required.¹⁸ For a small sample size, determin-
The negative clinical phenotypes in the proband’s sister helped us to exclude the unrelated variants from the possible inheritance mode, and four genes (SHROOM2, SYTL5, MAGED1 and FLNA) were selected with a higher chance of causing MICRR. The proband carried variants in SHROOM2, SYTL5, MAGED1 and FLNA genes from his mother. His sister carried heterozygous variants in SHROOM2, SYTL5 and MAGED1 and did not carry a variant allele in the FLNA gene but did not show disease. SYTL5, MAGED1 and FLNA are related to osteoclastogenesis or osteoclast differentiation, and SYTL5 is involved in NF-kB function (Table 1). Four genes (NBPF9, SYNE1, NPIPB12 and MUC4) with compound heterozygous variants were also considered (Tables 2 and 3); however, the bias caused by a single sample cannot be excluded. Because no other affected family members could help to narrow down the pathogenic gene\textsuperscript{11}, we considered the de novo variants were not found from his parents.

Filtering genes with variants may be associated with tooth or bone development, saliva functions, odontoclasts and osteoclastogenesis (Tables 2 to 5). FOXO6, OSR2, TP53, MAP2K4 and TBX2 play important roles in osteoclast function or the osteogenic process. OSR2, CHD3 and TBX2 are involved in the tooth development.
process, and CHD3 may play a particularly significant role in tooth root development and subsequent cementogenesis. KCTD1 is also possibly involved in cementoblast differentiation and mineralisation. CD93 gene was downregulated in patients with human dental fluorosis and Kashin-Beck disease. MUC19 and MUC4 were related to saliva functions. There were four genes with compound heterozygous variants in which NBPF9 was associated with mandibular prognathism (Table 2).

Here, we used the criteria for rare variants defined as having frequency < 0.5%, and common variants as having frequency > 5% according to the 1000 Genomes Project. One article also defined rare variants as having a frequency of <1%. If the selecting condition was changed to 1%, two more genes (SP100 and TIA1) with splice variants would be reserved (Table 4). TIA1 was associated with Paget disease which is one inducement of ECR; however, no typical phenotype of Paget disease was observed in the proband's physical examination, such as bone pain, arthopathy, deformity, fracture, hearing loss, neurological complications or osteosarcoma. The present study showed the unreported pathogenic genes in MICRR, which enriched the genetic investigation of rare diseases.

MICRR originates from the mesial or distal CEJ and then spreads to the entire cervical region. It is mainly limited to the cervical region and less extended to the apical part. It advances rapidly and sometimes can be accompanied by extensive gingivitis and periodontitis, but there is no direct evidence of a relationship between MICRR and these two diseases. Caries are usually a chronic process that commonly occurs in pits and fissures of teeth. Rampant caries frequently occur in children. Adults suffering from rampant caries usually have some specific causes, such as an addiction to sweet foods, radiotherapy, salivary gland dysfunction, xerostomia or a habit of keeping cariogenic food in the mouth and then going to sleep. However, the proband in the present study did not have a clear trigger, and the resorption progressed rapidly. Over a short period of 9

<table>
<thead>
<tr>
<th>CHR</th>
<th>Inheritance</th>
<th>Gene</th>
<th>mRNA</th>
<th>Protein</th>
<th>Exon</th>
<th>Annotation</th>
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<tr>
<td>Frameshift</td>
<td>1</td>
<td>AR</td>
<td>FOXO6</td>
<td>XM_002342102.5:c.1008_1009insGGGACGCCGGCTACTCGGCGGCTGCAAGGC</td>
<td>p.Gln337GlyfsTer177</td>
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<tr>
<td></td>
<td>11</td>
<td>AD</td>
<td>AP003062.1</td>
<td>ENST00000597621.1:c.280_314delAGTGGAGACCCAGCTTGCAGGAGCCATCAGAGGCTG</td>
<td>p.Arg100SerfsTer285</td>
<td>'1/1'</td>
</tr>
<tr>
<td>Inframe insertion</td>
<td>12</td>
<td>AD</td>
<td>MUC19</td>
<td>XM_003846356.2:c.14442_14443insGCT</td>
<td>p.Arg14814_Asn14815insAla</td>
<td>'55/171'</td>
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<tr>
<td></td>
<td>16</td>
<td>AD</td>
<td>NPIPA5</td>
<td>ENST00000360151.4:c.834delG</td>
<td>p.Ala278_Asp279insLeu-ProSerAla</td>
<td>'8/8'</td>
</tr>
<tr>
<td>Stop gained</td>
<td>15</td>
<td>AD</td>
<td>LOC101927268</td>
<td>XM_005255006.1:c.46C&gt;T</td>
<td>p.Arg16Ter</td>
<td>'1/1'</td>
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<td>AD</td>
<td>NPIP811</td>
<td>ENST00000524087.1:c.1495_1620delCCGTCCTGAGCAATCTCAAGACACCTTCTGAGCTCACTCTCCCTTCCACCTGTCACCTGAGCAGCATCAGACAA</td>
<td>p.Pro499_Thr540del</td>
<td>'8/8'</td>
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<td></td>
<td>17</td>
<td>AD</td>
<td>CHD3</td>
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<td>p.Pro74del</td>
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<td>AD</td>
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<td>p.Gly10del</td>
<td>'1/11'</td>
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<td></td>
<td>17</td>
<td>AD</td>
<td>TBX2</td>
<td>ENST00000419047.1:c.187_189delGC</td>
<td>p.Ala63del</td>
<td>'1/7'</td>
</tr>
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</table>

AD, autosomal dominant; AR, autosomal recessive; CHR, chromosome.
In the early stages, typical MICRR is usually asymptomatic but sometimes presents pink colour changes in the tooth neck. Resorption is usually invasive and progresses rapidly, and may form a cavity with sharp edges and a large amount of granulation tissue inside. The pulp vitality test is positive. Radiographs show a thin cervical pulp wall, a small amount of dentine around the pulp and apple core–like lesions at the CEJ.14,22 In later stages, the dentine may be resorbed completely, causing crown fracture and ultimately dentition defects.13 Many studies have reported that tooth loss is closely associated with overall health.22-26 Tooth loss had a positive association with accelerated aging27, new-onset Parkinson’s disease28, coronary heart disease and stroke28, diabetes29 and oro-digestive cancers.30 Tooth loss and hypertension showed a bidirectional association.31

<table>
<thead>
<tr>
<th>Variant</th>
<th>Type</th>
<th>Gene</th>
<th>Software predictionb</th>
</tr>
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<tr>
<td>c.1549C &gt; T</td>
<td>Missense</td>
<td>SRRM02</td>
<td>0.01 0.83 0.23 0.063963 0.003511 1.525 2.24 0.94 0.163 5.2155 0.94 0</td>
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<td>c.1409A &gt; G</td>
<td>Missense</td>
<td>SYTL5</td>
<td>0.02 0.997 0.984 0 0.9784 2.59 -0.7 5.88 1.973 15.2041 5.88 1</td>
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<tr>
<td>c.865G &gt; C</td>
<td>Missense</td>
<td>MAGED1</td>
<td>0.78 0.99 0.961 0.117001 0.14329 1.04 4.07 0.442 -0.021 0.5291 0.442 0.94</td>
</tr>
<tr>
<td>c.227C &gt; T</td>
<td>Missense</td>
<td>FLNA</td>
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<tr>
<td>c.1565C &gt; G</td>
<td>Missense</td>
<td>BCL11A</td>
<td>0.28 0.99 0.984 0.032386 0.989977 1.7 3.34 5.46 2.563 18.9177 5.46 1</td>
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<tr>
<td>c.602A &gt; G</td>
<td>Missense</td>
<td>OSR2</td>
<td>U 0.998 0.995 0 0.996931 1.795 3.39 3.42 2 9.2997 3.42 0.906</td>
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<tr>
<td>c.5709C &gt; A</td>
<td>Missense</td>
<td>MUC6</td>
<td>0.11 0.998 0.993 U U 1.735 3.37 -2.72 -0.74 1.8545 -2.72 0</td>
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<td>Missense</td>
<td>KRT18</td>
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<td>0.2 0.747 0.41 0 0.700611 1.15 2.92 3.68 2.231 3.7517 3.68 0.998</td>
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<td>c.346T &gt; G</td>
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<td>CD93</td>
<td>0 1 1 3.60E-05 U 3.825 2.63 5.49 2.194 15.0546 5.49 1</td>
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<td>NBPF9</td>
<td>0 1 1 U 0.002793 U 1.7 0.553 0.567 U 0.553 0.001</td>
</tr>
<tr>
<td>c.6002C &gt; T</td>
<td>Missense</td>
<td>MUC4</td>
<td>U 0.773 0.546 U 0.000972 -0.55 3.13 U -2.622 2.7646 0 0.002</td>
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<td>Missense</td>
<td>NPIBP12</td>
<td>0.01 0.999 0.996 U U 0.3 U U U U U</td>
</tr>
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<td>c.14888C &gt; A</td>
<td>Missense</td>
<td>SYNE1</td>
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<td>SYNE1</td>
<td>0.02 0.25 0.152 0.00341 0.983255 -0.04 -2.12 4.8 1.411 14.1097 4.8 0.921</td>
</tr>
</tbody>
</table>

aXR, recessive variation on the X-chromosome.
bPathogenicity of missense variants was predicted using 12 software platforms: SIFT, PolyPhen2_HDIV, PolyPhen2_HVAR, LRT, Mutation Taster, MutationAssessor, FATHMM, GERP, PhyloP, SiPhy, Gerp and PhastCons (from 1 to 12). Damaging, SIFT < 0.05, PolyPhen2_HDIV (probably damaging >= 0.957, possibly damaging 0.453 <= pp2_hdiv <= 0.956; benign <= 0.452), PolyPhen2_HVAR (probably damaging >= 0.909, possibly damaging 0.447 <= pp2_hdiv <= 0.909; benign <= 0.446) MutationAssessor > 1.938, FATHMM < -1.5, GERP++ > 3, PhyloP > 2.5, PhastCons > 0.6.

Table 6 Prediction results of missense variants from different software.

months, most of the maxillary right teeth were lost due to rapid resorption in the tooth neck, and the rest of the teeth were widely involved in cervical resorption.

In the early stages, typical MICRR is usually asymptomatic but sometimes presents pink colour changes in the tooth neck. Resorption is usually invasive and progresses rapidly, and may form a cavity with sharp edges and a large amount of granulation tissue inside. The pulp vitality test is positive. Radiographs show a thin cervical pulp wall, a small amount of dentine around the pulp and apple core–like lesions at the CEJ.14,22 In later stages, the dentine may be resorbed completely, causing crown fracture and ultimately dentition defects.13 Many studies have reported that tooth loss is closely associated with overall health.22-26 Tooth loss had a positive association with accelerated aging27, new-onset Parkinson’s disease28, coronary heart disease and stroke28, diabetes29 and oro-digestive cancers.30 Tooth loss and hypertension showed a bidirectional association.31
The pathogenic aetiology of MICRR is currently unclear. Most scholars believe it is associated with the enhanced activity of odontoclasts.\(^6,11,13,22\) Numerous lysosomes containing high-density particulate surrounding mitochondrion in the granulation tissue were observed in MICRR cases.\(^14\) MICRR was regarded as similar to feline odontoclastic resorptive lesions in cats.\(^6,32\) Few genetic studies have been performed in MICRR cases.\(^11,33\) The variants in \(IRF8\) and \(FLNA\) has been reported to be associated with MICRR.\(^33\) However, the inheritance mode of the pedigree was not fully considered, and should be validated experimentally in gene-edited mice. The evidence would have been more convincing had there been experimental verification. Sanger sequencing should be performed to confirm the possible pathogenic genes in the future. The variants selected in this study were used as predictions only, which cannot explain the causal relationship between these variants and MICRR.

**Conclusion**

In the present study, 35 genes were filtered and found to be potentially associated with MICRR, but no conclusion could be drawn regarding the genetic pattern of MICRR. These data will strengthen the aetiological diagnosis of MICRR, and the authors expect to increase the understanding of pathogenetic mechanisms of MICRR in the future.

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**Conflicts of interest**

The authors declare no conflicts of interest related to this study.

**Author contribution**

Dr Yu Meng WANG collected the clinical data, performed the bioinformatic analysis and drafted the manuscript; Dr Wen Yan RUAN revised the manuscript; Dr Dan Dan CHI collected the DNA samples and performed the original sequencing; Dr Xiao Hong DUAN designed and supervised the study and revised the manuscript.

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