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Genetic polymorphisms in external apical root resorption and orthodontic tooth movements: A systematic review

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Objective: External apical root resorption (EARR) is characterized by permanent loss of dental structure at the root apex. This study aimed to systematically review gene polymorphisms associated with EARR in orthodontic patients. **Methods:** Electronic database searches were performed across several databases. **Results:** This systematic review included 21 studies. Outcome measures were based on tooth dimensions observed on radiographs obtained before and after treatment. Polymorphisms in the following genes were genotyped using polymerase chain reaction-restriction fragment length polymorphism analysis: purinergic-receptor-P2X, ligand-gated ion channel 7 (*P2RX7*), caspase-1/interleukin-converting enzyme (*CASP1/ICE*), caspase-5 (*CASP5*), IL-1beta (*IL1B*), IL-1alpha (*IL1A*), interleukin-1 receptor antagonist gene (*IL1RN*), tissue non-specific alkaline phosphatase (*TNSALP*), tumor necrosis factor-alpha (*TNFα*), tumor necrosis factor receptor superfamily gene member 11a (*TNFRSF11A*), secreted phosphoprotein 1 (*SPP1*), tumor necrosis factor receptor superfamily gene member 11b (*TNFRSF11B*), interleukin 17A (*IL17*), interleukin 6 (*IL6*), receptor activator of nuclear factor-kappa B (*RANK*), osteoprotegerin (*OPG*), stromal antigen 2 (*STAG2*), vitamin D receptor (*VDR*), cytochrome P450 family 24 subfamily A member 1 (*CYP24A1*), cytochrome P450 family 27 subfamily B (*CYP27B1*), group-specific component (*GC*), and interleukin-1 receptor-associated kinases 1 (*IRAK1*). **Conclusions:** Almost all studies suggested that *IL1* gene is associated with EARR. Additionally, *P2RX7* may be an important factor contributing to the etiopathogenesis of EARR. *TNFRSF11A*, *SPP1*, *IL1RN*, *IL6*, *TNFRSF11B*, *STAG2*, *VDR*, *IRAK1*, *IL-17*, *CASP1/ICE* and *CASP5* have been identified in isolated studies. Further observational studies are needed to better explain the association between these genes and EARR.

Key words: Root resorption, Genetic polymorphism, Genetic research

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INTRODUCTION

External apical root resorption (EARR) is an inflammatory process involving osteoclast activation and activity, and is characterized by permanent destruction of the dental root apex structure (cementum and dentin).[1] Although EARR is a common and undesirable phenomenon associated with orthodontic treatment,[2] there have been reports of this condition in individuals with no history of orthodontic treatment.[3,4] Various clinical factors, such as age, sex, ethnicity, habits, malocclusion, root shape, history of trauma, and the type and duration of orthodontic treatment,[5,6] are associated with EARR.

Studies have indicated that moderate EARR (> 3 mm) is the most prevalent form in patients subjected to orthodontic tooth movement (OTM), while severe EARR (> 5 mm) occurs in approximately 5% of cases.[3,7,8] To understand the etiopathogenesis of OTM-related EARR, several studies have investigated the influence of individual genetic predispositions on EARR development.[1,2,9-14]

Genetic predisposition may be helpful in understanding the mechanisms of EARR. Polymorphisms of interleukin-1 (*IL1*) genes[1] such as IL-1beta (*IL1B*),[1,8,11,14-21] IL-1alpha (*IL1A*),[8,14-17] and interleukin-1 receptor antagonist gene (*IL1RN*)[8,14,18-23] have frequently been associated with EARR and OTM. Moreover, other genes such as tissue non-specific alkaline phosphatase (*TNSALP*), tumor necrosis factor-alpha (*TNF*α), tumor necrosis factor receptor superfamily gene member 11a (*TNFRSF11A*) encoding receptor activator of nuclear factor-kappa B (*RANK*)[1,19,24] as tumor necrosis factor receptor superfamily gene member 11b (*TNFRSF11B*),[19,25] secreted phosphoprotein 1 (*SPP1*),[26] purinergic-receptor-P2X, ligand-gated ion channel 7 (*P2RX7*),[18,19,27,28] caspase-1/interleukin-converting enzyme (*CASP1/ICE*)[25,27] and *caspase-5* (*CASP5*),[27] interleukin 6 (*IL6*),[23,25] interleukin 17A (*IL17*),[28] *SPP1*,[21,28] interleukin-1 receptor-associated kinases 1 (*IRAK1*),[20] *TNFRSF11B*,[28] stromal antigen 2 (*STAG2*) and *RP1-30E17.2*,[29] vitamin D receptor (*VDR*), cytochrome P450 family 27 subfamily B (*CYP27B1*), and cytochrome P450 family 24 subfamily A member 1 (*CYP24A1*),[30] are some genes that have also been investigated. Although several gene polymorphisms have been described as risk factors for EARR after OTM, conflicting results have been reported due to heterogeneous methodologies.[1,9,11,14]

Given the potential connection between genetic polymorphisms, EARR and orthodontic treatment, this study aimed to perform a systematic review of the association of EARR, OTM, and gene polymorphisms (*IL1A*;[8,11,22,26,27] *IL1B*;[1,11,14-17,19-21,25] *IL1RN*;[8,14,18-23] *TNSALP*; *TNF*α; *TNFRSF11A*;[9,19] *SPP1*;[26] *P2RX7*;[18,19,27,28] *CASP1/ICE*[25] and *CASP5*).[27] By organizing existing knowledge, this research aimed to present findings in a manner accessible to general orthodontists, elucidate the mechanisms underlying EARR associated with orthodontic treatment, facilitate risk assessment through genetic testing before treatment begins, and establish a foundation for future research. The PICO/PECO (P: population, I/E: intervention, E: exposure, C: comparison, O: outcome) question for this study was defined as follows: Patients, individuals treated with fixed appliances; Intervention/Exposure, genetic polymorphism; Comparison, gene polymorphisms (*IL1A, IL1B, IL1RN*, *TNSALP, TNF*α, *TNFRSF11A, P2RX7, CASP1/ICE, CASP5, IL6, IL17, TNFRSF11B, RANK, STAG2, VDR, CYP27B1, CYP24A1, RP1-30E17.2*, *SPP1*, IL1R-associated kinases [*IRAK1*], *11B,* osteoprotegerin [*OPG*]); and Outcome, EARR.

MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (registration number CRD42014007447).

Eligibility criteria

The inclusion criteria for the present study were as follows: (1) epidemiological studies (cross-sectional, case-control, cohort, and clinical trials) that evaluated the association between genetic polymorphisms and EARR in patients treated with fixed orthodontic appliances; (2) studies that used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis to evaluate genetic polymorphisms, and (3) those that documented pre- and post-orthodontic treatment outcomes. No restrictions were imposed on the type of tooth, EARR measurement criteria, length of treatment, tooth extraction, or age of the participant.

The exclusion criteria were as follows: (1) reviews or systematic reviews, case reports, case series, descriptive studies, opinion articles, abstracts, letters to the editor, laboratory and/or animal studies; (2) studies involving individuals with cleft lip, palate, or both; (3) studies involving individuals with other craniofacial deformities/syndromes; and (4) studies on unrelated topics, such as those not involving genetics or on EARR not caused by orthodontic treatment. Three review articles were excluded from the analysis because they did not include the latest findings or were not systematically reviewed, which is essential for the validity and relevance of a systematic review.

Search strategy

Electronic searches of the following databases were conducted in March 2023, and the search period was restricted to the last decade (up to May 2013): Medline through PubMed (http://www.ncbi.nlm.nih.gov/

pubmed/), Cochrane Library (http://www.cochrane.org/), Web of Science (http://www.isiknowledge.com/), Controlled-Trial Database (http://controlled-trial.com), Clinical Trials - US National Institutes of Health (http://www.clinicaltrials.gov), National Institute for Health and Clinical Excellence (http://www.nice.org.uk) and Virtual Health Library (Bireme, Latin America Literature; www.bireme.br). There were no restrictions on the publication date or language.

The following search strategy was used on Web of Science, Medline, and Cochrane Library: (root resorption [Mesh] OR tooth resorption [Mesh], OR root resorption orthodontic, OR external root resorption*, OR tooth movement [Mesh], OR external resorption*, OR apical root resorption*, OR orthodontic treatment*, OR EARR) AND (genetic polymorphism [Mesh], OR single nucleotide polymorphism [Mesh], OR mutation [Mesh], OR genetic*, OR genetic association studies [Mesh], OR genetic research [Mesh], OR genetic variation [Mesh], OR genetic testing [Mesh], OR genes [Mesh]). For Controlled-Trial Database, Clinical Trials–US National Institutes of Health, National Institute for Health and Clinical Excellence–UK National Institute for Health, and Virtual Health Library, the search was performed using combined uniterms 'polymorphism' and 'apical root resorption.' Grey literature was searched in the following databases for registration of epidemiological studies: Controlled-Trial Database, Clinical Trials–US National Institutes of Health, National Institute for Health and Clinical Excellence–UK National Institute for Health. A manual search was performed of the reference lists of the included studies.

Our electronic search yielded 408 abstracts and titles (Figure 1). We inputted these references into the Reference Manager Software® (Reference Manager, Thomson Reuters, version 12.0.3; Toronto, ON, Canada). After removing duplicates, 348 abstracts and titles were independently reviewed and analyzed by two calibrated reviewers (ILAL, JDC). The calibration process involved determination of the inclusion and exclusion criteria. The

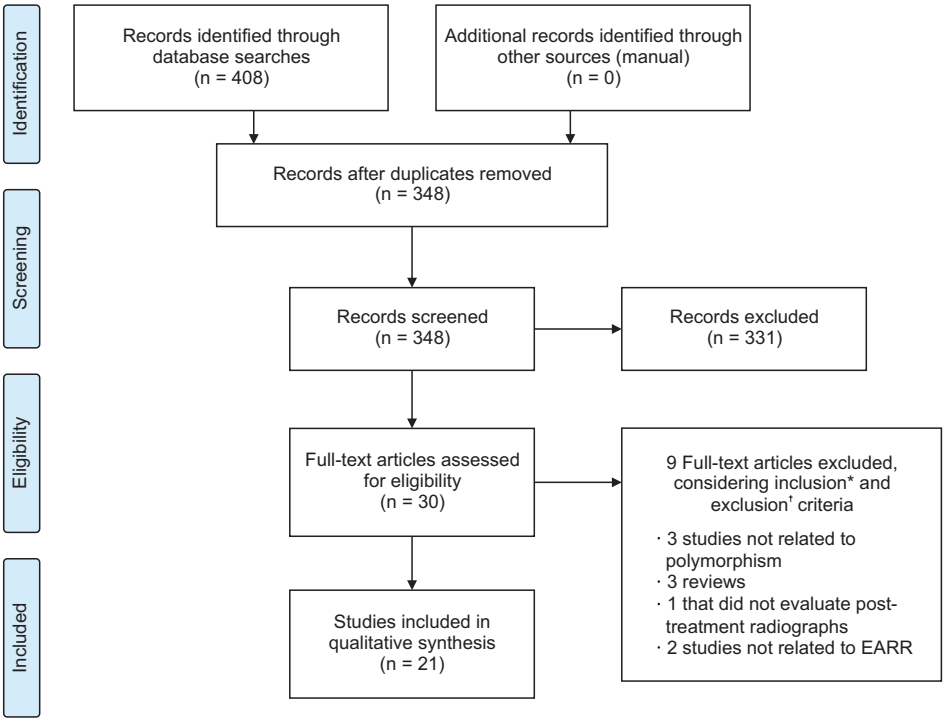

Figure 1. PRISMA flow diagram showing the process of article selection.
EARR, external apical root resorption.
*Inclusion criteria: epidemiological studies (cross-sectional, case-control, cohort and clinical trials) that evaluated the association of genetic polymorphisms and EARR in patients treated with fixed appliances; studies that used polymerase chain reaction-restriction fragment length polymorphism analysis to evaluate genetic polymorphisms; and, studies that reported pre- and post-orthodontic treatment.
†Exclusion criteria: reviews, articles or other systematic reviews; case reports; case series; descriptive studies; opinion articles; abstracts; letters to the editor; laboratory and/or animal studies; subjects with cleft lip, palate or both; studies on individuals with other craniofacial deformities/syndromes; studies on unrelated topics that had no association with genetics or those that presented data of EARR not caused by orthodontic treatment.

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reviewers thoroughly discussed these criteria, which were applied to 20% of the retrieved studies. This exercise was repeated until adequate agreement was obtained based on Cohen's kappa coefficient (kappa: 0.74).

Of the 348 abstracts reviewed, 30 were selected for full-text analysis. To include all related articles, we contacted one author to obtain the full texts of articles that were not accessible online. After the full-text analysis, 21 studies were included in this systematic review (Figure 1).

Data extraction

Data were independently extracted by the same two reviewers (ILAL, JDC). Inter-examiner conflicts were resolved by consensus. The extraction was performed according to the manufacturer's instructions.

The forms used for data extraction included the year of publication, location, study design, population, sample size, participants' age, teeth evaluated, EARR quantification criteria, main results, conclusions, and types of gene polymorphisms (Table 1). Most of the described gene polymorphisms were of the single nucleotide polymorphism (SNP) type, identified by the same "rs" (reference SNP) number. However, one polymorphism was of the variable number tandem repeat (VNTR) type.[8] Data on genotype distribution and allelic frequency were also included in this systematic review (Table 2).

As different types of polymorphisms have been described, a qualitative analysis was conducted. However, the data were not sufficiently comparable for meta-analysis.

RESULTS

Characteristics of studies

Twenty-one studies were included in this systematic review: 15 case-control studies and six cross-sectional studies (Figure 1). In general, studies recruited cases from university services,[1,8,9,11,14-17,21-23,28,29] with seven studies also including patients from private practice,[1,9,19-21,24,30] and four studies recruited patients exclusively from private practice.[11,18,25,27] The sample sizes ranged from 54[14,15] to 480[29] individuals. The age of participants ranged from 8.4 to 55.4 years.[27]

The outcomes were based on tooth dimensions (root and crown lengths) measured directly on radiographs obtained before and after treatment. Lateral cephalometric,[1,9,14,16,18,22,25,26,28,30] panoramic,[1,9,14,16,18-22,25,26,28-30] periapical,[11,24] and occlusal radiographs were used, in addition to cone beam computed tomography (CBCT).[23] Control groups comprised the following: (1) non-exposed individuals; (2) patients treated with fixed orthodontic appliances; and (3) patients with a history of EARR of < 2 mm. Three categories of control groups were seen in this review: (1) orthodontically treated patients with an EARR of < 2 mm;[11-18,21-26,28] (2) orthodontically treated patients from the same family (parents or siblings) with an EARR of < 2 mm[1,9] and (3) orthodontically treated patients with resorption lower than the apical third.[22] Furthermore, most studies included in this systematic review performed PCR-RFLP analysis for polymorphisms.[1,9,11-18,22-25,28,30]

Different teeth were evaluated among the articles retrieved: maxillary central incisors,[1,9,11,14,15,18-21,23-30] lateral maxillary incisors,[11,14,18-21,26-29] maxillary canine,[19,20] maxillary premolars,[14,16,22] mandibular central incisors and mandibular molars,[1,9,15,18,25] and mandibular first molars.[18,25,30]

Data synthesis

Qualitative analysis of polymorphisms and EARR

Not all studies described the same variables. There was considerable clinical and methodological heterogeneity as studies have described different types of polymorphisms and SNPs. One study specifically examined tooth-based samples rather than patient-based samples; in this study, *IL1B* (rs1143634) was not associated with EARR ($P > 0.05$).[15] However, another study found a significant association between *IL1B* (rs1143634) and EARR (95% confidence interval [CI]: 1.9–21.2) after orthodontic treatment.[1] Three other studies examined the association between EARR, gene polymorphisms, and OTM in endodontically treated teeth.[14,16,22] They demonstrated that it was not *IL1A* (rs1800587) but variations in *IL1B* SNPs that might contribute to the occurrence of EARR.[14,16] Furthermore, variants of allele 1 of *IL1RN* (rs419598) are associated with an increased risk of post-orthodontic EARR in endodontically treated teeth.[22] In genetics, an SNP is a variation at a single position in the DNA that can influence disease and drug response. A 'CC' genotype implies that both alleles at a gene are cytosine, while a 'T' genotype has at least one thymine allele, and a 'TT' genotype implies that both alleles are thymine. Homozygosity refers to the presence of identical alleles (either CC or TT) in a specific gene. A haplotype is a set of inherited genes that can provide insight into an individual's genetic predispositions. Microsatellite polymorphisms involve variations in the short DNA sequences used for genetic testing. Linkage disequilibrium describes how certain alleles at different loci are associated more frequently than expected by chance, aiding genetic mapping and disease studies. Only homozygous individuals for the T allele of *IL1RN* were more prone to orthodontic-induced EARR.[21] *IL1RN* and *P2RXT* analyses have indicated that the presence of SNPs in these genes can predispose individuals to EARR.[18] *IL1RN* VNTR polymorphism 86-bp in two introns was also related to EARR, specifically in girls.[8]

The *STAG2* gene, located on the X chromosome, was

Table 1. Characteristics of the case-control and cross-sectional studies included in this systematic review

Study/ country	Design	Population	Sample size analyzed (case)	Sample size analyzed (control)	Participant age (yr)	Tooth evaluation	Measure-ment criteria	Gene polymor-phism	Result	Conclusion
Al-Qawasmi et al.[1] (2003)/ USA	Cross-sectional	University clinic and private orthodontic practice	118	-	12.1 ± 1.89	MxCI with the longest root, MndCI with the longest root, and the mesial and distal roots of both the MndFM	Ceph and PAN	*IL1A* (rs1800587) *IL1B* (rs1143634)	*IL1*β allele 1 had a 5.6-fold (95% CI: 1.9–21.2) increased risk of EARR greater than 2 mm compared with those who are not homozygous for the *IL-1B* allele 1 (P = 0.004)	*IL1B* polymorphisms are associated with EARR
Al-Qawasmi et al.[9] (2003)/ USA	Cross-sectional	University clinic and private orthodontic practice	124	-	12.3 ± 1.82	MxCI with the longest root, MndCI with the longest root, and the mesial and distal roots of both the MndFM	Ceph and PAN	*TNSALP* (rs not informed) *TNF*α (rs1800629) *TNFRSF11A* (rs1805034)	*TNFRSF11A* (LOD = 2.5; P = 0.02)	No evidence of linkage was found with EARR and the *TNF*α and *TNSALP* genes *TNFRSF11A* is associated with EARR
Bastos Lages et al.[11] (2009)/ Brazil	Case-control	Private orthodontic practice	23	38	18.9 ± 5.2	MxCI, MxLI	Periapical radio-graphs	*IL1B* (rs1143634)	2/2 vs. 1/2 + 1/1, OR = 4.00; 95% CI:1.23–12.9; P = 0.0349	The *IL1B* polymorphism associated with EARR
Tomoyasu et al.[15] (2009)/ Japan	Case-control	University clinic	54	-	Male 19 Female 21	MxCI, MndCI, FM	Ceph and PAN	*IL1B* (rs1143634)	*IL1B* Maxillary central incisor (P = 0.47) Mandibular central incisor (P = 0.48) Mandibular first molar, metal root (P = 0.08) Mandibular first molar, distal root (P = 0.22)	No association

Table 1. Continued

Study/ country	Design	Population	Sample size analyzed (case)	Sample size analyzed (control)	Participant age (yr)	Tooth evaluation	Measure-ment criteria	Gene polymor-phism	Result	Conclusion
Iglesias-Linares et al.[17] (2012)/ Spain	Case-control	University clinic	73	73	23.78 ± 5.91	Maxillary root-filled PM and the contralateral tooth with a vital pulp	Ceph and PAN	*IL1B* (rs1143634) *IL1A* (rs1800587)	CC vs. CT/TT 5.143 1.38–19.10 (P = 1.00) TT vs. CT/CC 2.032 1.99–14.773 (P = 0.031) CT vs. CC/TT 10.66 0.72–158.50 (P = 0.625)	*IL1B* polymorphisms are associated with a twofold increased predisposition to have EARR secondary to orthodontic treatment in endodontically treated teeth
Linhartova et al.[8] (2013)/ Czech Republic	Case-control	University clinic	32	74	15.0 ± 4.1 and 15.2 ± 5.3	MxCI, MxLI	Ceph and PAN	*IL1A* (rs1800587) *IL1B* (rs1143634) *IL1RN* (86pb VNTR)	*IL1RN* Variants in girls – short allele P = 0.020, OR = 2.50; 95% CI: 1.13–5.53	No significant role of *IL1A* and *IL1B* variants in EARR *IL1RN* may be associated with EARR, especially in girls
Iglesias-Linares et al.[14] (2012)/ Spain	Case-control	University clinic	25	29	22.25 ± 5.30 and 23.89 ± 5.03	MxCI, MxLI with the longest root	Ceph and PAN	*IL1A* (rs1800587) *IL1B* (rs1143634) *IL1RN* (rs419598)	*IL1B* CC vs. CT/TT OR = 3.477 (1.12–10.72); P = 0.027 *IL1A* CC vs. CT/TT OR = 2.51 (0.8–7.57); P = 0.097 *IL1R* TT vs. CC/TC OR = 6.750 (2.04–22.27); P = 0.001	Variations in the *IL1RN* and not only in the *IL1B* gene are determinants of a predisposition to post-orthodontic EARR

Table 1. Continued

Study/ country	Design	Population	Sample size analyzed (case)	Sample size analyzed (control)	Participant age (yr)	Tooth evaluation	Measure-ment criteria	Gene polymor-phism	Result	Conclusion
Iglesias-Linares et al.[16] (2012)/ Spain	Case-control	University clinic	39	54	24.54 ± 5.85 and 23.89 ± 5.72	Upper second root-filled PM	Ceph and PAN	*IL1A* (rs1800587) *IL1B* (rs1143634)	*IL1B* CC vs. CT/TT OR: 2.54 (1.05–6.12); $P = 0.035$ TT vs. CT/CC OR: 11.59 (1.36–98.61); $P = 0.006$ CT vs. CC/TT OR: 0.12 (0.03–0.39); $P = 0.001$	*IL1B* gene polymorphisms are associated with EARR
Iglesias-Linares et al.[22] (2013)/ Spain	Case-control	University clinic	39	54	24.54 ± 5.85 and 23.89 ± 5.72	Upper second root-filled PM	Ceph and PAN	*IL1RN* (rs419598)	*IL1RN* CC vs. CT/TT OR: 10.857 (3.97–29.6); $P = 0.001$ CT vs. TT/CC OR: 0.18 (0.06–0.50); $P = 0.001$ CC vs. CT/CC OR: 0.10 (0.13–0.83); $P = 0.011$	*IL1RN* polymorphisms are associated with an increased risk of suffering post-orthodontic EARR in root-filled teeth
Iglesias-Linares et al.[26] (2014)/ Spain	Case-control	University clinic	37	50	24.70 ± 5.95 and 23.80 ± 5.33	MxCI, MxLI with the longest root	Ceph and PAN	*SPP1* (rs9138, rs11730582)	rs9138 CC vs. CA/AA OR: 4.10 1.03–16.35 ($P = 0.045$) AA vs. CA/CC OR: 0.20 0.05–0.81 ($P = 0.025$) CA vs. CC/AA OR: 0.8 0.20–3.53 ($P = 0.823$) rs11730582 CC vs. CT/TT OR: 11.68 1.12–121.06 ($P = 0.039$) TT vs. CT/CC OR: 0.45 0.07–2.80 ($P = 0.39$) CT vs. CC/TT OR: 0.035 0.062–0.90 ($P = 0.035$)	Specific allele (not informed) of the *SPP1* is associated with genetic susceptibility to EARR

Table 1. Continued

Study/ country	Design	Population	Sample size analyzed (case)	Sample size analyzed (control)	Participant age (yr)	Tooth evaluation	Measure-ment criteria	Gene polymor-phism	Result	Conclusion
Sharab et al.[27] (2015)/USA	Case-control	Private orthodontic practice	67	67	15.78 ± 1.13 and 15.79 ± 1.14	MxCI, MxLI	Occlusal	*P2RX7* (rs208294, rs1718119, rs2230912) *CASP1/ICE* (rs580253, rs530537) *CASP5* (rs554344) *IL1B* (rs1143634) *IL1A* (rs1800587) *IL1Ra* (rs419598)	*P2RX7*, rs208294 CC: 28 (41.8%) CT: 33 (49.3%) TT: 6 (9.0%) *P* = 0.0028 *P2RX7*, rs1718119 GG: 32 (47.8%) GA: 25 (37.3%) AA: 10 (14.9%) *P2RX7*, rs2230912 AA: 53 (79.1%) AG: 13 (19.4%) GG: 1 (1.5%) *CASP1/ICE*, rs530537 TT: 24 (35.8%) TC: 30 (44.8%) CC: 13 (19.4%) *CASP1/ICE*, rs580253 GG: 52 (77.6%) GA: 14 (20.9%) AA: 1 (1.5%) *CASP5*, rs554344 GG: 52 (77.6%) GC: 14 (20.9%) CC: 1 (1.5%) *IL1B*, rs1143634 GG: 37 (55.2%) GA: 26 (38.8%) AA: 4 (6.0%) *IL1Ra*, rs419598 TT: 41 (61.2%) TC: 23 (34.3%) CC: 3 (4.5%) *P* = 0.0533 *IL1A*, rs1800587 GG: 28 (41.8%) GA: 28 (41.8%) AA: 11 (16.4%)	*P2RX7* rs208294 was associated with EARR

Table 1. Continued

Study/ country	Design	Population	Sample size analyzed (case)	Sample size analyzed (control)	Participant age (yr)	Tooth evaluation	Measure-ment criteria	Gene polymor-phism	Result	Conclusion
Borilova Linhartova et al.[28] (2017)/ Czech Republic	Case-control	University clinic	30	69	15.0 ± 4.7	MxCI, MxLI rooth and crown lengths	Ceph and PAN	*IL-17* (rs2275913); *SPP1* (rs11730582, rs9138); *P2RX7* (rs208294, Tyr155His, rs1718119); *11B* (rs3102735, rs2073618)	No significant differences were observed in allele or genotype frequencies of all seven studied SNPs. Specific haplotype of *P2RX7* (rs208294 and rs1718119) modified the risk of EARR development ($P < 0.05$)	The variability in the *P2RX7* gene may be important factor contributing to the etiopatho-genesis of post-orthodontic EARR
Ciurla et al.[25] (2021)/ Poland	Case-control	Private orthodontic practice	40	61	22.9 ± 6.3	MxCI, MxLI, MndCI, MndLI, FM	Ceph and PAN	*IL1RN* (rs419598) and *P2RX7* (rs208294)	*P2RX7* (rs208294) and *IL1RN* (rs419598) modified the risk of EARR development ($P < 0.05$)	The analysis of the *P2RX7* and *IL1RN* gene polymorphisms showed that the presence of SNPs of these genes may predispose individuals to EARR
Guo et al.[23] (2016)/ China	Case-control	University clinic	174	-	14.07 ± 3.10	MxCI	CBCT	*IL1RN* (rs419598); *IL-6* SNP (rs1800796)	The *IL-6* SNP rs1800796 GC was associated with EARR, and root resorption	*IL-6* SNP rs1800796 GC is a risk factor for EARR

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Table 1. Continued

Study/ country	Design	Population	Sample size analyzed (case)	Sample size analyzed (control)	Participant age (yr)	Tooth evaluation	Measure-ment criteria	Gene polymor-phism	Result	Conclusion
Ciurla et al.[18] (2021)/ Poland	Case-control	Private orthodontic practice	101	-	21.32 ± 7.28	MxCI, MxLI, MndCI, MndLI, FM	Ceph and PAN	*IL-1*β, *TNFRSF11B*, *CASP1*, and *IL-6*	A significant association was found between EARR presence and the SNP for the *IL-1*β gene but not for the *TNFRSF11B*, *CASP1*, and the *IL-6* genes. *IL-1*β gene increases the odds of developing EARR by around four times	A significant association between EARR occurrence and the SNP for the *IL-1*β gene. Conversely, the effect of SNPs for *CASP1*, *TNFRSF11B*, and *IL-6* genes on EARR presence was not confirmed by the present study
Borges de Castilhos et al.[24] (2019)/ Brazil	Case-control	University clinic and private orthodontic practice	178	160	14.9 (8–21)	MxCI	Periapical radio-graphs	*RANKL*, *RANK*, *OPG*	For polymor-phisms of *RANKL*, no significant association was found with EARR. For *RANK* polymorphisms, only rs12455775 was associated with EARR Regarding *OPG* polymorphisms, an association of rs3102724, rs2875845, rs1032128, and rs3102728 with EARR was found	Regarding the analysis of polymorphisms in the genes *RANKL*, *RANK*, and *OPG*, several SNPs in *RANK* and *OPG* were associated with EARR, but only the association of the allele A of the rs3102724 in *OPG* remained after multivariate analysis

Table 1. Continued

Study/ country	Design	Population	Sample size analyzed (case)	Sample size analyzed (control)	Participant age (yr)	Tooth evaluation	Measure-ment criteria	Gene polymor-phism	Result	Conclusion
Silva et al.[19] (2022)/ Portugal	Cross-sectional	University clinic and private orthodontic practice	195	-	< 14 (n = 63); 14–18 (n = 85); 18 > (n = 47)	MxCI, MxLI, MxCanine	PAN	rs1143634 (in *IL1B* gene) and rs3102735 (*TNFRSF11B* gene, encoding *OPG*) and (rs315952 from *IL1RN*), rs1805034 from *TNFRSF11A*, encoding *RANK*, and rs1718119 from *P2RX7*	For genes encoding *OPG*, *RANK* and the *IL1* and *IL1RN*, the effect of analyzed variants changed from protective to deleterious depending on the duration of treatment and the age of the patient	This work shows that in OIEARR the impact of genetic susceptibility factors is dynamic changing according to clinical variables
Iber-Díaz et al.[29] (2020)/ Spain	Cohort	University clinic	101	361	21.52 ± 11.65 and 22.83 ± 11.66	MxCI, MxLI	PAN	Genes located in the X chromosome, specifically, *STAG2* (rs151184635) and *RP1-30E17.2* (rs55839915)	Two novel putative genes located in the X chromosome, specifically, *STAG2* gene, rs151184635 and *RP1-30E17.2* gene, rs55839915, were associated with aggressive EARR These variants were found to be associated with an increased risk of aEARR, particularly restricted to male. Marginal associations were found at previously studied variants such as *SPP1*: rs11730582, *P2RX7*: rs1718119, and *TNFRSF11A*: rs8086340, found solely in females	Multiple putative genetic variants located at chromosomes X and Y are potentially implicated in an extreme phenotype of aggressive EARR

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Table 1. Continued

Study/ country	Design	Population	Sample size analyzed (case)	Sample size analyzed (control)	Participant age (yr)	Tooth evaluation	Measure-ment criteria	Gene polymor-phism	Result	Conclusion
Marañón-Vásquez et al.[30] (2023)/ Germany	Cross-sectional	University clinic and private orthodontic practice	143	-	13.5 ± 4.5	MxCI, FM	Ceph and PAN	*VDR* rs731236 – TaqI (A/G); *VDR* rs 7975232 – ApaI (C/A); *VDR* rs1544410 – BsmI (T/C); *VDR* rs2228570 – FokI (A/G); GC rs4588 (T/G); *CYP27B1* rs4646536 (G/A); CYP24A1 rs927650 (T/C)	Individuals carrying the AA genotype in *VDR* rs2228570 had a 21% higher EARRmol than those having AG and GG genotypes. EARRmol in heterozygous rs2228570, was 12% lower than for homozygotes. Participants with the CCG haplotype (rs1544410-rs7975232-rs731236) in *VDR* had an EARRmol 16% lower than those who did not carry this haplotype. Regarding *CYP27B1* rs4646536, EARRinc in participants who had at least one G allele was 42% lower than for homozygotes AA	Although these results did not remain significant after multiple testing adjustment, potential associations may still be suggested

Table 1. Continued

Study/ country	Design	Population	Sample size analyzed (case)	Sample size analyzed (control)	Participant age (yr)	Tooth evaluation	Measure-ment criteria	Gene polymor-phism	Result	Conclusion
Pereira et al.[20] (2016)/ Portugal	Cross-sectional	University clinic and private orthodontic practice	195	-	17.24 ± 6.8	MxCI, MxLI, MxCanine	PAN	*IL1B* (rs1143634), *IL1RN* (rs315952) *IRAK1* (rs1059703)	Homozygosity/ hemizygosity for variant C from *IRAK1* gene (P = 0.018) proved to be a protective factor	*IRAK1* polymorphism is proposed as a protective variant for EARR
Iglesias-Linares et al.[21] (2017)/ Spain	Case-control	University clinic and private orthodontic practice	174	198	28.48 ± 13.6 and 26.29 ± 13.66	MxCI, MxLI root	PAN	*IL1B* (rs1143634), *IL1RN* (rs419598), *SPP1* (rs9138/ rs11730582)	Only subjects homozygous for the T allele of *IL1RN* (rs419598) were more prone to OIEARR during orthodontic treatment	Only subjects homozygous for the T allele of *IL1RN* (rs419598) were more prone to OIEARR during orthodontic treatment

Values are presented as number only, mean ± standard deviation, or mean (range).
MxCI, maxillary central incisor; MxLI, maxillary lateral incisor; MndCI, mandibular central incisor; MndFM, mandibular first molar; FM, first molar; PM, premolars; Ceph, lateral cephalogram; PAN, panoramic radiograph; EARRmol, external apical root resorption of the lower first molars; EARRinc, external apical root resorption of the upper central incisors; OR, odds ratio; CI, confidence interval; EARR, external apical root resorption; LOD, logarithm of odds; OIEARR, orthodontically induced external apical root resorption; VNTR, variable number tandem repeat; MndLI, mandibular central incisor; SNP, single-nucleotide polymorphism; CBCT, cone beam computed tomography; MxCanine, maxillary canine adenine.

Table 2. Gene profiles evaluated in the retrieved articles

Gene	SNP	Previous designation	Allele	Position	Function
IL1A	rs1800587	–889	C > G	Chr: 2q14; NG_008850.1:g.5012C > G	UTR-5; NA
IL1B	rs1143634	+3,954	C > T	Chr: 2q14; NG_008851.1:g.8967C > T	Synonymous [Phe105Phe]
IL1RN	rs419598	+2,018	T > C	Chr: 2q14.2; NG_021240.1:g.16738T > C	Synonymous [Ala23Ala]
	VNTR 86bp	+2,018	C > T	Chr: 2q14.2	NA
	rs315952	NA	T > C	Chr: 2q13; NG_021240.1:g.19835T > C	Synonymous [Ser130Ser]
TNFa	rs1800629	–308	G > A	Chr: 6p21.3; NG_007462.1:g.4682G > A	nearGene-5; NA
TNFRSF11A	rs1805034	NA	C > T	Chr: 18q21.2; NG_008098.1:g.39694C > T	Missense [Ala192Val]
P2RX7	rs208294	+489	T > C	Chr: 12q24; NG_011471.2:g.34576T > C	Missense [Tyr155His]
	rs1718119	+1,068	T > C	Chr: 12q24; NG_011471.2:g.49426G > T	Missense [Ala348Thr]
	rs2230912	NA	A > G	Chr: 12q24; NG_011471.2:g.56519A > G	Missense [Gln357Arg]
SPP1	rs9138	NA	A > C	Chr: 4q22.1; NG_030362.1:g.12541A > C	UTR´3; NA
	rs11730582	–443	T > C	Chr: 4q22.1; NG_030362.1:g.4620T > C	nearGene-5; NA
Casp1/ICE	rs580253	NA	C > T	Chr: 11q23; NG_029124.1:g.10370C > T	Synonymous [Leu163Leu]
Casp1	rs530537	NA	A > G	Chr: 11q23; NG_029124.1:g.12345A > G	Intron 7; NA
Casp5	rs554344	NA	C > G	Chr: 11q22.2-q22.3; NG_029124.1:g.15661C > G	nearGene-5; NA
IL-17	rs2275913	–197	A > G		
TNFRSF11B	rs3102735	–163	C > T		
	rs2073618	+1,181	C > G		[Lys3Asn]
SPP1	rs11730582	–443	T > C		
	rs9138	+1,239	A > C		
IL-6	rs1800796	NA	C > G		
RANK	rs12455775	NA	G > T	Chr: 18q22.1	
OPG	rs3102724	NA	A > G	Chr: 8q24	
	rs2875845	NA	G > A		
	rs1032128	NA	A > G		
	rs3102728	NA	C > T		
STAG2	rs151184635				Stromal antigen 2 [Source:HGNC Symbol;Acc:11355]
	rs55839915				*RP1-30E17.2*; Clone-based (Vega) gene
VDR	rs731236		A > G	Chr: 12q13.11; (GRCh37) 48,238,757	Synonymous variant
	rs7975232		C > A	Chr: 12q13.11; (GRCh37) 48,238,837	Intron variant
	rs1544410		T > C	Chr: 12q13.11; (GRCh37) 48,239,835	Intron variant
	rs2228570		A > G	Chr: 12q13.11; (GRCh37) 48,272,895	Missense variant
CYP27B1	rs4646536		G > A	Chr: 12q14.1; (GRCh37) 58,157,988	Intron variant
GC	rs4588		T > G	Chr: 4q13.3; (GRCh37) 72,618,323	Missense variant
CYP24A1	rs927650		T > C	Chr: 20q13.2; (GRCh37) 52,772,741	Intron variant
IRAK1	rs1059703		T > C	Chr: Xq28; NG_008387.1:g.11514C > T	Missense [Ser532Leu]

IL1RN specific polymorphism, variable number tandem repeat of an 86bp in the second intron (VNTR 86bp) on chromosome 2q was also included in this analysis.
SNP, single-nucleotide polymorphism; rs, reference SNP; NA, not available; NG, Reference Sequence Gene Mapping.

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found to be associated with an increased risk of EARR, particularly restricted to the male sex.[9] Another study demonstrated that *IRAK1* polymorphism is a protective variant of EARR.[20] For genes encoding *OPG*, *RANK, IL1,* and *IL1RN*, the effect changed from protective to deleterious depending on the duration of treatment and the age of the patient.[19]

Regarding *RANKL* polymorphisms, no significant association was found with EARR. Among *RANK* polymorphisms, only rs12455775 was associated with EARR. Regarding *OPG* polymorphisms, an association was found between EARR and rs3102724, rs2875845, rs1032128, and rs3102728.[24]

TNSALP, *TNFα,* and *TNFRSF11A* polymorphisms were also investigated. It was concluded that *TNFRSF11A* (rs1805034) is associated with EARR (P = 0.02), but *TNSALP* and *TNFα* are not.[9] Additionally, *SPP1* gene polymorphisms (rs9138 and rs11730582) were related to genetic susceptibility of EARR: rs9138 CC vs. CA/AA (odds ratio: 4.10; 95% CI: 1.03–16.35); rs9138 AA vs. CA/CC (odds ratio: 0.20; 95% CI: 0.05–0.81); rs11730582 CC vs. CT/TT (odds ratio: 11.68; 95% CI: 1.12–121.06); and rs9138 CT vs. CC/TT (odds ratio: 0.035; 95% CI: 0.062–0.90).[26] One study observed that the presence of a specific *P2RX7* (rs208294) was significantly associated with EARR (P = 0.0028) (Table 1).[27,28]

According to Ciurla et al.[25] the effect of SNPs in *CASP1, TNFRSF11B,* and *IL 6* genes on EARR was not confirmed however, Guo et al.[23] showed that *IL 6* increased the risk of EARR.

Marañón-Vásquez et al.[30] showed that individuals with the AA genotype of *VDR* rs2228570 had a higher risk of EARR than those with the AG and GG genotypes. In addition, the incidence of EARR in heterozygous rs2228570 was lower than that in homozygotes. In addition, participants with the CCG haplotype (rs1544410-rs7975232-rs731236) in the *VDR* showed a lower EARR than those who did not carry this haplotype. Regarding *CYP27B1* rs4646536, participants with at least one G allele showed a lower risk of EARR than those with homozygote AA. Although these results were not significant after multiple test adjustments, potential associations may still be suggested.[30]

DISCUSSION

Herein, we conducted a systematic review on the association of EARR, OTM, and gene polymorphisms.

Assessment of bias in included studies

The present review presents no bias related to the language or year of publication. The search strategy identified only articles published in English[1,9,11,14-30] between 2003 and 2023. Although there is a possibility of bias due to the small sample sizes of some reports, this is a relatively new field of investigation, and the retrieved studies presented high methodological quality.

Assessment of methodological quality

All case-control studies presented an adequate definition of EARR through radiographic evaluation.[8,11,14-17,22,26,27] The cases analyzed were from the same family or clinic, and the study participants were controlled for age.[8,11,14-17,22,26,27] The control group comprised orthodontically treated patients with an EARR of < 2 mm,[11-17,22] orthodontically treated patients from the same family (parents or siblings) with an EARR of < 2 mm, and orthodontically treated patients with resorption limited to the apical third.[27] Individuals presenting with EARR of ≥ 2 mm[11,14-17] or resorption equal to or more than the apical third[27] were considered as cases. In addition, the same method of ascertainment (PCR-RFLP analysis) was employed for both cases and controls.

All cross-sectional studies in this systematic review included clinically diagnosed cases of EARR.[1,9] Secure records with no indication of EARR at the start of the study were presented and radiographs of the patients after the end of treatment were used to evaluate the presence of EARR. Therefore, the follow-up was considered adequate. The details of blind processes have rarely been reported.

Strength of evidence

In 1975, EARR was described as familial,[31] and in 1997, a hypothesis of genetic influence on EARR was proposed using a sib-pair model with an estimated heritability of approximately 70%.[32] The current understanding is that EARR has a multifactorial etiology influenced by a combination of environmental and host factors. Genetic predisposition to an exaggerated inflammatory response may contribute to EARR in some patients during OTM. Accordingly, many studies have attempted to demonstrate the association between gene polymorphisms involved in inflammatory responses and EARR. In this regard, the *IL1* gene is the most frequently described, as it may be an early critical mediator in inflammatory processes.[33] *IL1* plays a critical role in the inflammatory response related to orthodontic treatment; it recruits large immune cells and affects transmigration to the tooth movement area. Moreover, *IL1* directly or indirectly amplifies osteoclast differentiation,[34] affecting root resorption. Elevated *IL1β* levels in gingival crevicular fluid and gingival tissues during OTM further support its role in tooth resorption.[35]

Some studies have investigated *IL1* polymorphisms in the context of EARR; however, conflicting results have been reported, mainly associated with ethnic populations. These discrepancies may arise due to the geo-

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graphic restrictions of each study.[15] Tomoyasu et al.[15] demonstrated that *IL1B* (rs1143634) was not associated with a predisposition to EARR. Accordingly, a meta-analysis revealed that *IL1B* polymorphisms were not found to be associated with the susceptibility to EARR.[36] In contrast, other studies found an association between *IL1* polymorphisms and EARR following OTM.[1,17] Studies report that the presence of haplotype +3,954 and −889 with "T" allele increases the production of *IL1B* and *IL1A*, respectively,[8,15,17] suggesting an association with EARR.[1,11,14] A link between EARR and *IL1B* SNPs has also been described.[25] On the contrary, other studies found that the presence of "CC" genotype increase the risk of EARR.[1,11,27] This result agrees with a previous study showing that the absence of *IL1B* gene causes root resorption in mouse molar.[13]

IL1A (rs1800587) and *IL1B* (rs1143634) polymorphisms were analyzed in four case-control studies.[8,14,18,21] Linhartova et al.[8] found no association between *IL1* (rs1800587 and rs1143634) and EARR, while Iglesias-Linares et al.[14] reported a relationship between *IL1B* (rs1143634) and EARR. Although both studies used similar methods, the number and age of the participants could explain these differences. The study by Linhartova et al.[8] included 106 participants (mean age: 15.0 ± 4.1 years in EARR group and 15.2 ± 5.3 years in the control group), whereas Iglesias-Linares et al.[14] included 54 patients (mean age: 22.9 ± 6.3 years). Silva et al.[19] showed that for *IL1*, the effect changed from protective to deleterious depending on the duration of treatment and the age of the patient.

Perrier et al.,[37] demonstrated that allele 2 (two repeats) of *IL1RN* (VNTR 86bp) polymorphism downregulates *interleukin-1 receptor antagonist* (*IL1Ra*) production in saliva, increasing *IL1* expression. One study that evaluated the role of *IL1RN* polymorphism VNTR 86bp in EARR[8] showed that the allele 2 variant was specifically related to EARR and OTM in girls.[8] Individuals that are homozygous for the T allele of *IL1RN* rs419598 were more prone to EARR during orthodontic treatment.[21] There is further evidence that "TT" genotype of *IL1RN* rs419598 increases the risk of EARR in endodontically treated teeth.[22] In addition, *IL1RN* rs419598 and VNTR 86bp haplotypes are in linkage disequilibrium, affecting *IL1Ra* and *IL1B* production.[22] Another study[18] concluded that the presence of *IL1RN* SNP (rs419598) may predispose individuals to EARR.

Al-Qawasmi et al.,[1] Bastos Lages et al.,[11] and Iglesias-Linares et al.[14,16,22] suggested a possible link between *IL1A* (rs1800587), *IL1B* (rs1143634), and EARR. Moreover, Ciurla et al.[25] showed that *IL1B* increased the odds of developing EARR four-fold. Although Al-Qawasmi et al.[1] and Bastos Lages et al.[11] used similar methods, the ethnic diversity of the samples may have influenced the results. They found that the "CC" genotype increases the risk of EARR, although the presence of "T" allele 4-fold increased the level of *IL1B*.[9] In contrast, Iglesias-Linares et al.[14,16,22] evaluated endodontically treated teeth, which may have been a confounding factor.

TNFSF11A, involved in *RANK* encoding, plays a crucial role in osteoclastogenesis, a major mechanism involved in mineral matrix destruction. An important association between *TNFRSF11A* rs1805034 microsatellite polymorphism (D18S64) and EARR has been discussed based on linkage disequilibrium between them.[9] Although *TNSALP* is important for cementum formation and mineralization and *TNF*α is critical in bone remodeling, no evidence of association or linkage disequilibrium was found between them and EARR.[9]

SPP1, which regulates the release of pro- and anti-inflammatory mediators (mainly *IL1B*) by human monocytes, has also been studied. Iglesias-Linares et al.[26] found that "C" allele of *SPP1* gene polymorphisms "rs9138 and rs11730582" increase the risk of EARR, and they are associated with elevated *osteonectin* expression.

The purinergic receptor (P2X) is a member of the cationic channel family, in which receptor *P2RX7* plays an important role in the immune response, mainly in bone metabolism, inflammation (upstream of *IL1B* maturation and release), cell proliferation, and the central nervous systems.[38] Association between EARR and *P2RX7* gene polymorphisms "rs208294 and rs1718119" have been reported; the "T" allele was associated with a protective role while "G" allele increased the risk for EARR.[27] Borilova Linhartova et al.[28] also found that variability in *P2RX7* may be an important factor contributing to the etiopathogenesis of EARR. Furthermore, an association of caspase 1—involved with *IL1B* maturation and release—with EARR was investigated; the "T" allele of rs530537 increases the risk of EARR.

Altogether, existing evidence suggests that *IL1* is associated with EARR, however, pinpointing the specific *IL1* allele (*IL1A, IL1B,* or *IL1RN*) implicated in EARR remains challenging. Several factors contribute to this uncertainty. First, the retrieved studies exhibited significant heterogeneity in gene polymorphism analyses. Second, variations in radiographic techniques—ranging from periapical and occlusal radiographs to CBCT—yield varying measurement accuracies of EARR. This could represent bias in the diagnosis of EARR. Additionally, the lack of important data related to the sample, such as sex and age, are often absent.

Moreover, isolated studies have explored other candidate genes. These include *TNFRSF11A*, *TNFRSF11B, SPP1, IL6, STAG2, VDR, IRAK1,* and *IL17*. However, further research is needed to confirm the possible association of these genes with EARR and OTM.

CONCLUSIONS

This systematic review demonstrated that the majority of studies pointed to a possible association between EARR, OTM, and *IL1* gene polymorphisms. Yet, the specific IL1 allele driving this association remains elusive. Additionally, *P2RX7* may be an important factor contributing to the etiopathogenesis of EARR. *TNFRSF11A*, *SPP1*, *IL1RN*, *IL6*, *TNFRSF11B*, *STAG2*, *VDR*, *IRAK1*, *IL17*, *CASP1/ICE* and *CASP5* have been identified in isolated studies. Further research is recommended to unravel the genetic susceptibility underlying EARR associated with orthodontic treatments. Furthermore, identifying specific genes associated with EARR, given its multifactorial nature, will enhance orthodontic management of patients at a high risk of EARR.

AUTHOR CONTRIBUTIONS

Conceptualization: ILAL, JDC. Data curation: ILAL, JDC. Formal analysis: ILAL, JDC. Investigation: All authors. Methodology: All authors. Project administration: ILAL. Resources: ILAL, JDC, FRM, DAM. Software: ILAL, JDC, FRM, DAM. Supervision: ILAL. Validation: ILAL, JDC, FRM, DAM. Visualization: ILAL, JDC, FRM, DAM. Writing–original draft: ILAL, JDC. Writing–review & editing: ILAL, ALCÁA, YDAP, BEBM.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Al-Qawasmi RA, Hartsfield JK Jr, Everett ET, Flury L, Liu L, Foroud TM, et al. Genetic predisposition to external apical root resorption. Am J Orthod Dentofacial Orthop 2003;123:242-52. https://doi.org/10.1067/mod.2003.42
2. Brezniak N, Wasserstein A. Orthodontically induced inflammatory root resorption. Part II: the clinical aspects. Angle Orthod 2002;72:180-4. https://pubmed.ncbi.nlm.nih.gov/11999942/
3. Harris EF, Robinson QC, Woods MA. An analysis of causes of apical root resorption in patients not treated orthodontically. Quintessence Int 1993;24:417-28. https://pubmed.ncbi.nlm.nih.gov/8234648/
4. Harris EF, Butler ML. Patterns of incisor root resorption before and after orthodontic correction in cases with anterior open bites. Am J Orthod Dentofacial Orthop 1992;101:112-9. https://doi.org/10.1016/0889-5406(92)70002-R
5. Hartsfield JK Jr, Everett ET, Al-Qawasmi RA. Genetic factors in external apical root resorption and orthodontic treatment. Crit Rev Oral Biol Med 2004;15:115-22. https://doi.org/10.1177/154411130401500205
6. Brezniak N, Wasserstein A. Root resorption after orthodontic treatment: part 2. Literature review. Am J Orthod Dentofacial Orthop 1993;103:138-46. https://doi.org/10.1016/S0889-5406(05)81763-9
7. Killiany DM. Root resorption caused by orthodontic treatment: an evidence-based review of literature. Semin Orthod 1999;5:128-33. https://doi.org/10.1016/s1073-8746(99)80032-2
8. Linhartova P, Cernochova P, Izakovicova Holla L. IL1 gene polymorphisms in relation to external apical root resorption concurrent with orthodontia. Oral Dis 2013;19:262-70. https://doi.org/10.1111/j.1601-0825.2012.01973.x
9. Al-Qawasmi RA, Hartsfield JK Jr, Everett ET, Flury L, Liu L, Foroud TM, et al. Genetic predisposition to external apical root resorption in orthodontic patients: linkage of chromosome-18 marker. J Dent Res 2003;82:356-60. https://doi.org/10.1177/154405910308200506
10. Ngan DC, Kharbanda OP, Byloff FK, Darendeliler MA. The genetic contribution to orthodontic root resorption: a retrospective twin study. Aust Orthod J 2004;20:1-9. https://doi.org/10.2478/aoj-2004-0001
11. Bastos Lages EM, Drummond AF, Pretti H, Costa FO, Lages EJ, Gontijo AI, et al. Association of functional gene polymorphism IL-1beta in patients with external apical root resorption. Am J Orthod Dentofacial Orthop 2009;136:542-6. https://doi.org/10.1016/j.ajodo.2007.10.051
12. Gülden N, Eggermann T, Zerres K, Beer M, Meinelt A, Diedrich P. Interleukin-1 polymorphisms in relation to external apical root resorption (EARR). J Orofac Orthop 2009;70:20-38. https://doi.org/10.1007/s00056-009-8808-6
13. Hartsfield JK Jr. Pathways in external apical root resorption associated with orthodontia. Orthod Craniofac Res 2009;12:236-42. https://doi.org/10.1111/j.1601-6343.2009.01458.x
14. Iglesias-Linares A, Yañez-Vico R, Ballesta-Mudarra S, Ortiz-Ariza E, Ortega-Rivera H, Mendoza-Mendoza A, et al. Postorthodontic external root resorption is associated with IL1 receptor antagonist gene variations. Oral Dis 2012;18:198-205. https://doi.org/10.1111/j.1601-0825.2011.01865.x
15. Tomoyasu Y, Yamaguchi T, Tajima A, Inoue I, Maki K. External apical root resorption and the interleukin-

1B gene polymorphism in the Japanese population. Orthod Waves 2009;68:152-7. https://doi.org/10.1016/j.odw.2009.05.002
16. Iglesias-Linares A, Yañez-Vico RM, Ortiz-Ariza E, Ballesta S, Mendoza-Mendoza A, Perea E, et al. Postorthodontic external root resorption in root-filled teeth is influenced by interleukin-1β polymorphism. J Endod 2012;38:283-7. https://doi.org/10.1016/j.joen.2011.12.022
17. Iglesias-Linares A, Yañez-Vico RM, Ballesta S, Ortiz-Ariza E, Mendoza-Mendoza A, Perea E, et al. Interleukin 1 gene cluster SNPs (rs1800587, rs1143634) influences post-orthodontic root resorption in endodontic and their contralateral vital control teeth differently. Int Endod J 2012;45:1018-26. https://doi.org/10.1111/j.1365-2591.2012.02065.x
18. Ciurla A, Marruganti C, Doldo T, Szymańska J. Association between polymorphisms in the IL-1β, TNFRSF11B, CASP1, and IL-6 genes and orthodontic-induced external apical root resorption. J Clin Med 2021;10:4166. https://doi.org/10.3390/jcm10184166
19. Silva HC, Lavado N, Canova F, Lopez MG, Regateiro FJ, Pereira SA. Influence of clinical factors on the protective or deleterious impact of genetic variants in orthodontically induced external root resorption: an observational study. BMC Oral Health 2022;22:270. https://doi.org/10.1186/s12903-022-02306-y
20. Pereira S, Nogueira L, Canova F, Lopez M, Silva HC. IRAK1 variant is protective for orthodontic-induced external apical root resorption. Oral Dis 2016;22:658-64. https://doi.org/10.1111/odi.12514
21. Iglesias-Linares A, Sonnenberg B, Solano B, Yañez-Vico RM, Solano E, Lindauer SJ, et al. Orthodontically induced external apical root resorption in patients treated with fixed appliances vs removable aligners. Angle Orthod 2017;87:3-10. https://doi.org/10.2319/02016-101.1
22. Iglesias-Linares A, Yañez-Vico RM, Ballesta-Mudarra S, Ortiz-Ariza E, Mendoza-Mendoza A, Perea-Pérez E, et al. Interleukin 1 receptor antagonist (IL1RN) genetic variations condition post-orthodontic external root resorption in endodontically-treated teeth. Histol Histopathol 2013;28:767-73. https://doi.org/10.14670/HH-28.767
23. Guo Y, He S, Gu T, Liu Y, Chen S. Genetic and clinical risk factors of root resorption associated with orthodontic treatment. Am J Orthod Dentofacial Orthop 2016;150:283-9. https://doi.org/10.1016/j.ajodo.2015.12.028
24. Borges de Castilhos B, Machado de Souza C, Simas Netta Fontana MLS, Pereira FA, Tanaka OM, Trevilatto PC. Association of clinical variables and polymorphisms in RANKL, RANK, and OPG genes with external apical root resorption. Am J Orthod Dentofacial Orthop 2019;155:529-42. https://doi.org/10.1016/j.ajodo.2018.05.016
25. Ciurla A, Szymańska J, Płachno BJ, Bogucka-Kocka A. Polymorphisms of encoding genes IL1RN and P2RX7 in apical root resorption in patients after orthodontic treatment. Int J Mol Sci 2021;22:777. https://doi.org/10.3390/ijms22020777
26. Iglesias-Linares A, Yañez-Vico RM, Moreno-Fernández AM, Mendoza-Mendoza A, Orce-Romero A, Solano-Reina E. Osteopontin gene SNPs (rs9138, rs11730582) mediate susceptibility to external root resorption in orthodontic patients. Oral Dis 2014;20:307-12. https://doi.org/10.1111/odi.12114
27. Sharab LY, Morford LA, Dempsey J, Falcão-Alencar G, Mason A, Jacobson E, et al. Genetic and treatment-related risk factors associated with external apical root resorption (EARR) concurrent with orthodontia. Orthod Craniofac Res 2015;18(Suppl 1):71-82. https://doi.org/10.1111/ocr.12078
28. Borilova Linhartova P, Cernochova P, Kastovsky J, Vrankova Z, Sirotkova M, Izakovicova Holla L. Genetic determinants and postorthodontic external apical root resorption in Czech children. Oral Dis 2017;23:29-35. https://doi.org/10.1111/odi.12564
29. Iber-Díaz P, Senen-Carramolino R, Iglesias-Linares A, Fernández-Navarro P, Flores-Mir C, Yañez-Vico RM. GWAS of post-orthodontic aggressive external apical root resorption identified multiple putative loci at X-Y chromosomes. J Pers Med 2020;10:169. https://doi.org/10.3390/jpm10040169
30. Marañón-Vásquez G, Küchler EC, Hermann S, Paddenberg E, Schröder A, Baratto-Filho F, et al. Association between genetic variants in key vitamin-D-pathway genes and external apical root resorption linked to orthodontic treatment. Eur J Oral Sci 2023;131:e12916. https://doi.org/10.1111/eos.12916
31. Newman WG. Possible etiologic factors in external root resorption. Am J Orthod 1975;67:522-39. https://doi.org/10.1016/0002-9416(75)90298-5
32. Harris EF, Kineret SE, Tolley EA. A heritable component for external apical root resorption in patients treated orthodontically. Am J Orthod Dentofacial Orthop 1997;111:301-9. https://pubmed.ncbi.nlm.nih.gov/9082853/
33. Dinarello CA. The IL-1 family and inflammatory diseases. Clin Exp Rheumatol 2002;20(5 Suppl 27):S1-13. https://pubmed.ncbi.nlm.nih.gov/14989423/
34. Wei S, Kitaura H, Zhou P, Ross FP, Teitelbaum SL. IL-1 mediates TNF-induced osteoclastogenesis. J Clin Invest 2005;115:282-90. https://doi.org/10.1172/JCI23394
35. Grieve WG 3rd, Johnson GK, Moore RN, Reinhardt

RA, DuBois LM. Prostaglandin E (PGE) and interleukin-1 beta (IL-1 beta) levels in gingival crevicular fluid during human orthodontic tooth movement. Am J Orthod Dentofacial Orthop 1994;105:369-74. https://pubmed.ncbi.nlm.nih.gov/8154462/
36. Wu FL, Wang LY, Huang YQ, Guo WB, Liu CD, Li SG. Interleukin-1β +3954 polymorphisms and risk of external apical root resorption in orthodontic treatment: a meta-analysis. Genet Mol Res 2013;12:4678-86. https://doi.org/10.4238/2013.October.18.6
37. Perrier S, Coussediere C, Dubost JJ, Albuisson E, Sauvezie B. IL-1 receptor antagonist (IL-1RA) gene polymorphism in Sjögren's syndrome and rheumatoid arthritis. Clin Immunol Immunopathol 1998;87:309-13. https://doi.org/10.1006/clin.1998.4520
38. Ursu D, Ebert P, Langron E, Ruble C, Munsie L, Zou W, et al. Gain and loss of function of P2X7 receptors: mechanisms, pharmacology and relevance to diabetic neuropathic pain. Mol Pain 2014;10:37. https://doi.org/10.1186/1744-8069-10-37