External apical root resorption in orthodontic patients: molecular and genetic basis

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ABSTRACT

External apical root resorption is one of the most deleterious complications after orthodontic treatment. Studies to explain the causal relationship between orthodontic tooth movement and external apical root resorption have been inconclusive till date. Individual variations in external apical root resorption sometimes overshadow the treatment related factors which indicate genetic predisposition and/or multifactorial etiology. Mechanism of root resorption is not completely understood. Inflammatory root resorption induced by orthodontic treatment is a part of process of elimination of hyaline zone. An imbalance between bone resorption and deposition may contribute to root resorption by the cementoclasts/osteoclasts. This narrative review article explains the molecular pathway involved in external apical root resorption and also role of various genes involved at different level. It also reviews the literature published during the past 20 years concerning the association studies linking EARR to genetic polymorphisms. This literature review provides an insight into genetic predisposition of external apical root resorption that can be used in orthodontic practice to enable ‘high-risk’ subjects to be identified on the basis of their genetic information before orthodontic treatment is initiated.

Keywords: Etiology, external apical root resorption, genetic polymorphism

Background

EARR (External apical root resorption) is the reduction of root structure involving the apical region to the extent that it can be seen on standard radiographs.[1] Orthodontic force applied to teeth over a short period can produce resorption lacunae on the cementum root surface histologically which is a preliminary step towards EARR. When root resorption exceeds the reparative capacity of cementum, EARR is seen.[2]

Studies to explain the causal relationship between orthodontic tooth movement and external apical root resorption have been inconclusive till date. Maxillary incisors are the most commonly affected teeth by EARR during orthodontic treatment.[3-4] Occlusal forces have been presumably attributed as the causative factor for EARR.[5-7] In addition, Harris et al. studied the hypothesis of genetic influence on the EARR and found a great possibility of inheritance.[8]

The prevalence of EARR associated with orthodontic treatment greatly varies in the literature, depending on the methods used to determine it in the studies. More than one-third of patients undergoing orthodontic treatment have root resorption greater than 3 mm and severe root resorption (>5mm) has been found to occur in 2%-5% of the population.[4,9,10]

Risk factors for EARR

EARR is a complex phenomenon caused by a combination of poorly understood environmental and host factors. Biomechanical or orthodontic treatment-related risk factors may...
include treatment duration, type of orthodontic appliance, tooth extraction, intrusive movement, root torque, extensive tooth movement and force magnitude.[11] Orthodontic tooth movement or “biomechanics” has been found to account for approximately from one-tenth to one-third of total variation in EARR.[12]

There was considerable individual variation in the EARR associated with orthodontic treatment which overshadowed the force magnitude and force type, indicating an individual predisposition and multifactorial etiology.[8,12,13-17]

The role of genetic factors was first suggested by Newman in 1975.[15] Then in 1997, Harris et al. gave findings of his research and reported the involvement of genetic variation in EARR concurrent with orthodontic treatment through a heritability study.[20] Later, Hartsfield et al. confirmed that genetic variation was associated with as much as 50%-66% of the variations observed with EARR during orthodontic treatment.[4] Since then, various authors have studied the role of various genes in the occurrence of EARR.

The genetic aspect of EARR is of utmost importance to the general care physicians also. Various genetic markers involved in EARR are also associated with various systemic and bone metabolism disorders. They need to be aware of dental implications of such polymorphisms. Sometimes dental findings can prove to be very helpful in early diagnosis of systemic and bone metabolic disorders.

Materials and Methods

This article reviews the literature published during the past 20 years concerning the association studies linking EARR to genetic polymorphisms. The literature search was performed on PubMed and Science Direct using the following keywords: “external apical root resorption and gene and polymorphism”. All suitable articles were selected and their references were rechecked for any relevant articles overlooked during the electronic searches. Other relevant articles were handpicked from the institutional library. The research findings to date are discussed with emphasis on several candidate genes without constraints on population, sample size and treatment duration.

Main Text

Molecular and Genetic pathway of root resorption with orthodontic force

Orthodontic force application leads to a cascade of events in compression and tension region leading tooth movement. Figure 1 describes the molecular pathway during orthodontic tooth movement. This is mediated through two pathways: 1) activation of control of osteoclasts through the ATP/P2RX7/IL-1B inflammation modulation pathway; and 2) RANK/RANKL/OPG osteoclast activation control pathway.[8] Following section describes various mediators of tooth movement and their associated genetic polymorphisms responsible for external apical root resorption [Tables 1 and 2].

Interleukin 1 (IL 1) family

IL1α and IL1β are encoded by distinct genes but bind to the same receptor IL1R1.[19] IL1α precursor is constitutively present, fully active and is released from necrotic cells during early phases of inflammation. However, IL1β is inactive and is cleaved by caspase 1 to release the active cytokine in extracellular space.[20] The interleukin receptor antagonist, IL1ra is a unique, naturally occurring cytokine that inhibits IL1 activity by binding to IL1R1 receptors with high affinity thereby preventing signal transduction.[21]

IL-1β is a potent bone-resorptive cytokine and plays a key role in the complex pathways leading to root resorption.[18] IL-1B (+3954) polymorphism in orthodontically treated subjects plays a role in EARR and IL-1B allele is a risk factor of EARR.[22] A study by Bastos Lages et al.[23] also found similar results in 61 Brazilian orthodontic patients. IL-1B gene polymorphism, rs1143634 (C3954T) and EARR has frequently been found to be associated in several geographical patient populations[22-24] and in knock-out animal models.[25] Furthermore, this polymorphism was implicated in approximately 15% of the variation in EARR of maxillary central incisors of orthodontic patients.[26] However, some patient-based studies obscured this association[11,12,16-28].

Gulden et al.[24] found an association of IL-1A polymorphism (-889TT genotype) with root resorption in a German sample of 45 EARR patients and 40 anonymous controls. However, Sharab et al.,[27] Al Qawasmi et al.,[23] Iglesias-Linares et al.[28,29] and Linhartova et al.[30] in their studies found no significant association of IL-1A polymorphism with EARR.

IL-1ra might affect bone resorption during orthodontic treatment by blocking IL-1 from stimulating the osteoclasts and thus lead to root resorption. IL-1RN gene polymorphisms have been correlated with a high expression of IL-1ra and hence, with EARR.[11,32] Iglesias-Linares et al.[28] showed that the TT genotype of IL-1RN Single Nucleotide Polymorphism (SNP) rs419598 is highly and positively correlated with EARR.

IL1Receptor-associated kinase 1 (IRAK1)

IL1β roles are mainly dependent on IL-1 receptor 1 (IL1R1) binding. Activation of IL1R1 leads to the recruitment of adaptor molecules like IRAK1, with subsequent activation of signalling transduction pathways.[25] Hyper-phosphorylation of IRAK1, switch on the signal transduction pathway activation, and later, its ubiquitination and proteasome degradation switches off the signalling.[34] IRAK1 gene is located on chromosome X at position q28. IRAK1 polymorphism (rs1509703) has been associated with EARR by Pereira et al.

Interleukin-6 (IL-6)

IL-6 acts as a multifunctional cytokine with both inflammatory and anti-inflammatory effects. IL-6 and its receptors mainly
activate two signal pathways: the JAK kinase, signal transduction and transcriptional activation (JAK/STAT) pathway and mitogen-activating protein kinases (MAPK) pathway.\[^{35-37}\] IL-6 was observed to increase in the gingival crevicular fluid (GCF) and PDL in orthodontic patients. It was discerned from the studies that IL-6 is instrumental in local regulation of bone remodelling and acute inflammation at the commencement of orthodontic treatment.\[^{38}\] Thus, Guo \[^{39}\] et al. conducted a study where IL-6 SNP (rs1800796) with GC genotype was found to have greater root resorption than CC genotype.

**Interleukin 17**

Proinflammatory interleukin-17A (IL-17A) stimulated odontoclastogenesis and influenced the mRNA expression of RANKL from human dental pulp cells in vitro.\[^{40}\] Thus, Hayashi \[^{41}\] et al. suggested that T-helper 17 cells may aggravate the process of orthodontically induced inflammatory root resorption. Linhartova \[^{30}\] et al. investigated IL-17A gene variability in postorthodontic EARR but found a non-significant association.

**Purinergic receptor P2X, ligand gated ion channel 7 (P2RX7)**

P2RX7 is expressed in osteoblasts and osteoclasts and seem to have a pro-osteogenic effect, activating osteoblast function and inducing osteoclast apoptosis. It also stimulates the release of inflammatory cytokines such as IL-1B by immune cells by acting through ATP/P2RX7/IL-1B inflammation modulation pathway. In the study by Sharab \[^{12}\] et al. SNP, rs208294, located in the P2RX7 gene was found to be associated with EARR. Linhartova \[^{30}\] et al. in the recent study\[^{42}\] revealed that variability in the P2RX7 gene and the length of orthodontic treatment may be important factors contributing to the etiopathogenesis of postorthodontic EARR.

**Vitamin D receptor gene**

Vitamin D is responsible for the regulation of certain genes at the transcription level, via interaction with the vitamin D receptor,\[^{43}\] and influences host immune responses and aspects of bone development, growth, and homeostasis.\[^{44}\] Vitamin D stimulates osteoclastogenesis acting through its nuclear receptor, Vitamin D receptor in immature osteoblast/stromal cells via RANKL/OPG regulatory pathway\[^{45-47}\][Figure 1]. Also, Vitamin D enhanced IL-1β expression via a direct transcriptional mechanism during the inflammatory process.\[^{48}\]

Polymorphisms in Vitamin D receptor gene have been associated with bone mineral density, bone turn over and diseases in which mineral loss is a cardinal sign. A study by Fontana \[^{49}\] et al. in the Brazilian population in 2012 reported that Vitamin D receptor TaqI (rs 731236) polymorphism is associated with EARR.\[^{49}\]

**Osteopontin (OPN) gene**

Osteopontin is an acidic phosphorylated glycoprotein containing an Arg-Gly-Asp (RGD) motif, which can interact with various receptors including αv-β3 and other integrins and so cause the odontoclast to adhere to root surface at the onset of physiological or pathologic resorption.\[^{50,51}\] OPN plays role in odontoclast activation during the root resorption process. Iglesias-Linares \[^{52}\] et al. showed that OPN gene (rs9138; 3'UTR and rs 11730582; 5' near region) are determinants of a genetic predisposition to suffer EARR secondary to orthodontic treatment.\[^{52}\]

**RANK/RANKL/OPG**

Osteoblasts and stromal stem cells express receptor activator of NF-kappa B ligand (RANKL), which binds to its receptor activator of nuclear factor-kappa B (RANK, coded by TNFRSF11A gene), on the surface of osteoclasts and their precursors. Osteoprotegerin (OPG, coded for by the...
Table 1: Genes involved in external apical root resorption

| Gene                                           | Gene code          | SNP     | SNP location | Effect of variation                                                                 | Exon/intron | Chromosome | Nucleotide       | Amino acid      | Type of variation          |
|------------------------------------------------|--------------------|---------|--------------|-------------------------------------------------------------------------------------|-------------|------------|------------------|----------------|--------------------------|
| Interleukin-1 alpha (OMIM#147760)              | IL-1A              | rs1800587 | −889         | TT genotype (EARR causing)                                                          | -           | 2q4.1      | C to T           |                | Promoter variation        |
| Interleukin-1 beta (OMIM#147720)               | IL-1B              | rs1143634 | +3953/+3954  | TT genotype (Increased IL-1B production)                                            | Exon 5      | 2q4.1      | TTC to TTT       | Phel05Phe       | Synonymous variant        |
| Interleukin-1 receptor antagonist (OMIM#147679)| IL-1RN             | rs315952  | +390         | CC genotype (EARR causing)                                                          | Exon 4      | 2q4.1-2    | AGT to AGC       | Ser133Ser       | Synonymous variant        |
|                                                |                    | rs419598  | +2018        | TT genotype (EARR causing)                                                          | Exon 2      |            | GCT to GCC       | Ala60Ala        | Synonymous variant        |
|                                                |                    | 86 bp VNTR|              | Short allele (allele 2, 2 repeats)                                                  | Intron 2    |            |                 |                |                          |
|                                                |                    |          |              | Long alleles (allele 4, 3 repeats)                                                  |             |            |                 |                |                          |
|                                                |                    |          |              | Long alleles (allele 1, 4 repeats)                                                  |             |            |                 |                |                          |
|                                                |                    |          |              | Long alleles (allele 3, 5 repeats)                                                  |             |            |                 |                |                          |
|                                                |                    |          |              | Long alleles (allele 5, 6 repeats)                                                  |             |            |                 |                |                          |
| Interleukin-1 receptor-associated kinase (OMIM#300283) | IRAK1             | rs1059703 | +6434        | CC genotype (protective for EARR)                                                   | Exon 12     | Xq28       | TCG to TTG       | Ser532Leu       | Non-synonymous variant    |
| Receptor activator of nuclear factor-κB (RANK)(OMIM#603499) | TNFRSF11A         | rs1805034 | D18864       | -                                                                                   | Exon 6      | 18q21.33   | GCG to GTG       | Val192Ala       | Non-synonymous variant    |
| Osteoprotegerin (OMIM#602643)                  | TNFRSF11B (OPG)    | rs2073618 | +1181        | G allele was associated with EARR                                                  | Exon 1      | 8q24.12    | AAC to AAG       | Asn3Lsn         | Non-synonymous variant    |
| Osteopontin/ Bone sialoprotein 1 (BSP1/BNSP)/Secreted phosphoprotein 1 (SPP1) | OPN                | rs11730582| rs9138       | A allele is EARR protective                                                        | Exon 6      | 4q22.1     | T to C           | A to C          | Non-synonymous variant    |
| Interleukin-6 (OMIM#147620)                    | IL-6               | rs1800796 | −634         | G allele (EARR causing)                                                             | -           | 7p15.3     | C to G           |                | Promoter variation        |
| Interleukin-17A (OMIM#603149)                  | IL-17A             | rs2275913 | −197         | -                                                                                   | -           | 6p12.2     | G to A           |                | Promoter variation        |
| Purinergic-receptor-P2X, ligand-gated ion channel 7(OMIM#602566) | P2RX7             | rs208294  | +489         | C allele (EARR causing)                                                             | Exon 5      | 12q24.31   | CAT to TAT       | His155Iyr       | Non-synonymous variant    |
|                                                |                    | rs171819  | +1068        | G allele (EARR causing)                                                             | Exon 11     | CAT to ACT | GCT to ACT       | Ala348Thr       | Non-synonymous variant    |
|                                                |                    | rs2230912 | +1405        | T allele (lower IL-1beta production)                                               | Exon 13     | CAG to CGG | GAG to AGG       | Gln460Ag        | Non-synonymous variant    |
| Interleukin-1beta converting enzyme/Caspase 1 (OMIM#147678) | CASP1              | rs530537  | -            | T allele (lower IL-1beta production)                                               | Intron 7    | 11q22.3    | T to C           | Leu to Leu   | Synonymous variant        |
|                                                |                    | rs580253  |               | C allele (lower IL-1beta production)                                               | Exon 6      | C to C     | CTA 10370 TTA   |                  |                          |
|                                                |                    | rs554344  |               |                                            | 3' UTR       |            | G to C           |                  |                          |
| Tumour necrosis factor alpha (OMIM#191160)     | TNFα               | rs1800629 | −308         | A allele (more TNFα production)                                                     | -           | 6p21.33    | G to A           |                | Promoter variation        |
| Vitamin D receptor (OMIM#601769)               | VDR                | rs731236  | -            | C allele (EARR protective)                                                          | Exon 9      | 12q13.11   | ATT to ATC       | Ile352Ile       | Synonymous variant        |

**Gene**: The gene name associated with the corresponding variation.

**Gene code**: The gene symbol or identifier used in genetic studies.

**SNP**: Single nucleotide polymorphism associated with the gene.

**SNP location**: The position of the SNP in the gene.

**Effect of variation**: The effect of the SNP on the gene expression or protein function.

**Exon/intron**: The location of the SNP in the gene sequence.

**Chromosome**: The chromosome on which the gene is located.

**Nucleotide**: The nucleotide change at the SNP location.

**Amino acid**: The change in the amino acid sequence due to the SNP.

**Type of variation**: The type of genetic variation associated with the SNP.
Table 2: Summary of various studies assessing association of different gene-polymerisms with external apical root resorption

| Author, Year, Journal | Country (Ethnicity) | Sample size | Gene and polymorphisms studied | Mean age | Treatment duration | Radiograph Technique | Result |
|-----------------------|---------------------|-------------|--------------------------------|----------|-------------------|----------------------|--------|
| Iglesias-Linares et al, 2017, AO | Spain (Caucasian) | 372 subjects (174 cases and 198 controls) treated with either fixed or removable appliances | IL-1β rs1143634, IL-1RN rs419598, Osteopontin (SPP1) rs11730582, rs9138 | 27.69+13.6 years (28.48+13.60 years, 26.29+13.66 years) | Not mentioned | OPG | Predisposition to EARR is similar for invisalign and fixed appliances. Homozygous subjects (TT genotype of IL1RN, rs419598) were found to be three times more predisposed to experience EARR compared with the other genotypes. |
| Linhartova et al, 2017, OD | Czech Republic (Caucasian) | 30 cases (11 boys and 19 girls) with EARR in maxillary incisors/69 controls (26 boys and 43 girls) | IL-17 rs2275913, Osteopontin (SPP1) rs11730582, rs9138, P2RX7 rs208294, rs1718119, TNFRSF11B rs3102735, rs2073618 | 14.6±3.2 years, 15.2±5.3 years | Not mentioned | OPG, Lateral Cephalogram | CG haplotype (rs208294+rs1718119) was associated with EARR while no association was seen for individual SNP |
| Pereira et al, 2016, OD | Portugal (Caucasian) | 195 (72 males and 123 females); six maxillary anterior teeth were assessed | IL-1β rs1143634, IL-1RN rs315952, IRAK1 rs1059703 | 17.24±6.8 years | 36±10 months | OPG | C allele of SNP rs1059703 (IRAK1) is protective for EARR. |
| Guo et al, 2016, AJODO | China (Han Chinese) | 174 patients (68 males and 106 females; left maxillary central incisors were monitored) | IL-1RN rs419598, IL-6 rs1800796 | 12-34 years | 20.55±6.54 months (14-28 months) | CBCT | GC allele of SNP rs1800796 (IL-6) is associated increased risk for EARR. |
| Sharab et al, 2015, OCR | USA (Caucasian) | 67 cases (38 females, 29 males) with EARR of maxillary incisors/67 age- and sex-matched controls | P2RX7 (rs208294, rs1718119, rs2230912), CASP1 (rs530537, rs580253, rs554344), IL-1α rs1800587 (-889 C/T), IL-1β rs1143634 (+3953), IL-1RN rs419598 | 15.78±1.13 years, 15.79±1.14 years | 2.49±0.10 years, 1.97±1.14 years | OPG, occlusal | CC or CT genotype of rs208294 (P2RX7) polymorphism is associated with EARR. |
| Lim et al, 2014, AJODO | Mice | Not applicable | Wnt signalling | Not applicable | Not applicable | Not applicable | Reduced wnt signalling causes spontaneous root resorption |
| Iglesias-Linares et al, 2014, OD | Spain (Caucasian) | 37 cases with (EARR>2mm) / 50 controls | Osteopontin rs9138, rs11730582 | 24.7±5.95 y, 23.8±5.33 y | 27.5±8.3 months | Lateral cephalogram, OPG | Allele 2/Allele 2 (CC genotype) in rs9138 rs11730582 (osteopontin gene) predispose to EARR secondary to orthodontic treatment. Allele 1(T) in rs9138 is protective for EARR. Allele 1(A) in rs11730582 is protective for EARR. |

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| Author, Year, Journal | Country (Ethnicity) | Sample size | Gene and polymorphisms studied | Mean age | Treatment duration | Radiograph Technique | Result |
|-----------------------|---------------------|-------------|---------------------------------|----------|--------------------|----------------------|--------|
| Pereira et al., 2014, OD | Portugal (Caucasian) | 195 cases (72 males and 123 females); six maxillary anterior teeth were assessed. | IL-1β rs1143634 (+3953) TNFRSF11A rs1805034 P2RX7 rs1718119 TNFRSF11B rs3102735 | 17.24±6.8 years | 36±10 months | OPG | GG genotype of rs1718119 (P2RX7 gene) is associated with EARR. |
| Linhartova et al., 2013, OD | Czech Republic (Caucasian) | 32 cases with EARR in maxillary incisors/74 controls without EARR | IL-1α rs1800587 (−889) IL-1β rs1143634 (+3953) IL-1RN (86bp VNTR) | 15.0±4.1 years (cases) 15.2±5.3 years (controls) (15.2±5 years average) | 34.5±15.6 months | OPG, Lateral Cephalogram | IL1RN*12, *22 genotypes and short allele *2 is associated with EARR in girls. |
| Iglesias-Linares et al., 2013, HH | Spain (Caucasian) | 93 patients (39 cases with EARR > 2mm in root-filled teeth/54 controls without EARR in root-filled teeth) | IL-1RN rs419598 (+2018) | 24 years 1 month+5 years 5 months | 27.21 months+4.9 months | Lateral cephalogram, OPG | Genotype TT of IL-1RN is associated with EARR in root filled teeth |
| Iglesias-Linares et al., 2012, OD | Spain (Caucasian) | 54 patients (25 cases with EARR>2mm/29 controls) | IL-1α rs1800587 (−889) IL-1β rs1143634 (+3953) IL-1RN rs419598 (±2018) | 23.08±5.08 years | 31.1±6.4 months | Lateralecephalogram, OPG | Genotypes CC of rs1143634 (IL-1β) and TT of rs419598 (IL-1RN) are associated with EARR. |
| Iglesias-Linares et al., 2012, IEJ | Spain (Caucasian) | 73 root canal filled teeth (35 with EARR>2 mm and 38 non EARR teeth)/73 vital control teeth (30 with EARR>2 mm and 43 non-EARR teeth) | IL-1α rs1800587 (−889) IL-1β rs1143634 (+3953) | 23+5 years per 8+9 months | 27+4.3 months | Lateral cephalogram, OPG | Homozygous (TT, rs114364) subjects has two times risk of EARR in root-filled teeth as compared to vital teeth. |
| Iglesias-Linares et al., 2012, JOE | Spain (Caucasian) | 93 RC treated teeth; 39 with EARR>2 mm/54 with EARR≤2mm | IL-1α rs1800587 (−889) IL-1β rs1143634 (+3953) | 24 years 1 month + 5 years 5 months | 27.21 months+4.9 months | Lateral cephalogram, OPG | Genotype TT of IL-1β is associated with EARR in endodontically treated teeth. |
| Fontana et al., 2012, AJODO | Brazil (Mixed whites) | 377 Class II div 2 individuals; group 1 (EARR≤1.43 mm; treated)=157; group 2 (EARR≤1.43 mm; treated)=175; group 3 (untreated)=35 | Vitamin D receptor rs731236 | 14.9 years | EARR measured at 6 months of treatment | IOPA | Allele C is weakly associated with protection against EARR |
| Tomoyasu et al., 2009, OW | Japanese | 54 Japanese (18 males and 36 females); 24 Han Chinese; 24 African Americans; 24 European Americans; and 24 Hispanics (maxillary and mandibular central incisors, mesial and distal roots of mandibular first molars were analysed) | IL-1β rs1143634 (+3953) | males = 19 years, females = 21 years | 3 years 1 month | Lateral cephalogram, OPG | rs1143634 SNP is not associated with EARR. |

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TNFRSF11B (OPG) gene is secreted by osteoblasts and osteogenic stromal stem cells and protects from excessive bone resorption by binding to RANKL and preventing it from binding to RANK.\textsuperscript{[18]} Study by Hartsfield et al.\textsuperscript{[19]} evaluated the association between single nucleotide polymorphism (SNP) rs2073618 of TNFRSF11B (OPG) gene and EARR in orthodontically treated patients and showed that OPG polymorphism accounted for approximately 8% of total EARR variation.

### Wnt

Wnt signalling pathways are a group of signal transduction pathways made of proteins that pass signals into a cell through cell surface receptors. OPG/RANKL regulates bone formation, and studies in the literature suggest that disruptions in OPG/RANKL contribute to low bone mass phenotypes in humans\textsuperscript{[15,36]} and root resorption as well.\textsuperscript{[15,36]} The OPG/RANKL pathway, in turn, is mediated by Wnt signalling; a positive Wnt stimulus simultaneously downregulated RANKL and upregulated OPG, thus enhancing bone formation and inhibiting bone resorption.\textsuperscript{[54,57]} Lim et al. in their study showed that genetically reducing Wnt signalling in the environment of the periodontal complex is sufficient to cause spontaneous root resorption.\textsuperscript{[54]}

### Discussion

The present review attempted to review genetic risk factors for orthodontic treatment-induced external apical root resorption. We located 21 studies on different genes, which might influence EARR [Table 2]. 19 were human studies and 2 were on mice.

Fifteen studies have been reported for IL1 gene involving association with EARR.\textsuperscript{[11,13,22,26,30,60,62]} IL-1α has been investigated in seven studies\textsuperscript{[12,22,24,26,30,60,61]} involving four ethnic groups (German, Czech, Hispanics and US Caucasians) where only German Caucasians with TT genotype of IL-1α was observed to have a significant association with orthodontically induced EARR. The occurrence of the rare genotypes of the SNP rs1800587 was associated with an almost fourfold increase in IL-1 protein levels in the gingival crevicular fluid.\textsuperscript{[20]}

There were 13 studies\textsuperscript{[11,13,22,26,30,60,61]} which investigated the association of IL-1β with EARR. 7 studies (3 Hispanics, 1 US, 1 Portugal, 1 Brazil and 1 mice knock out model) found an increased risk of IL-1β with EARR. 4 studies revealed CC genotype as associated with EARR\textsuperscript{[12,22,24]} while 2 studies\textsuperscript{[60,61]} on Root canal treated teeth in Hispanics showed association with TT genotype. These contrasting results may be pulp

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Table 2: Contd...

| Author, Year, Journal | Country (Ethnicity) | Sample size | Gene and polymorphisms studied | Mean age | Treatment duration | Radiograph Technique | Result |
|----------------------|---------------------|-------------|--------------------------------|----------|-------------------|----------------------|--------|
| Gulden et al., 2009, JOO | Germany (Whites) | 49 cases (45 sporadic patients, 2 pairs of siblings)/40 controls | IL-1α rs1800587 (-889); IL-1β +3954 | >12 years | Not mentioned | OPG | Genotype TT (rs1800587) of IL-1α is associated with EARR. |
| Hartsfield, 2009, OCR | USA (Caucasian) | 135 cases (EARR>2mm in at least one maxillary central incisor) | TNFRSF11B rs2073618 | 14.6+6.9 years | 1.6+0.5 years | OPG | G allele was associated with EARR. |
| Lages et al., 2007, AJODO | Brazil (Brazilian whites) | 23 affected/38 controls (Maxillary incisors were evaluated) | IL-1β +3954 | 18.9+5.2 years | Not mentioned | IOPA | Allele C of IL-1β is associated with EARR. |
| Al-Qawasmi et al., 2004, JMNI | Mice | Not applicable | IL-1β | Not applicable | Not applicable | Not applicable | IL-1β is significantly associated with orthodontic root resorption. |
| Al-Qawasmi et al., 2003, AJODO | USA (Caucasian) | 35 families (118 persons: 73 siblings and 45 parents) | IL-1α rs1800587 (-889); IL-1β +3954 | 12.1+1.89 years | 2.82+1.09 years | Lateral cephalogram, OPG | Genotype CC of IL-1β is associated with EARR. |
| Al-Qawasmi et al., 2003, JDR | USA (Caucasian) | 38 families (124 persons: 79 siblings and 45 parents); EARR evaluated in Maxillary and mandibular central incisors and mandibular first molars | TNFSF11A (D18S64) | 12.3+1.82 years | 2.77+1.13 years | Lateral cephalogram, OPG | Linkage of D18S64 with EARR in maxillary central incisors. |

\[EARR\]: External apical root resorption, \[AO\]: The Angle Orthodontist, \[OD\]: Oral Diseases, \[AJODO\]: American Journal of Orthodontics and Dentofacial Orthopaedics, \[OCR\]: Orthodontics and Craniofacial Research, \[HH\]: Histology and Histopathology, \[IEJ\]: International Endodontic Journal, \[JOE\]: Journal of Endodontics, \[OW\]: Orthodontic Waves, \[JOO\]: Journal of Orofacial Orthopedics, \[JMNI\]: Journal of Musculoskeletal and Neuronal Interactions, \[JDR\]: Journal of Dental Research, \[IL\]-1α: Interleukin 1 alpha, \[IL\]-1β: Interleukin 1 beta, \[IL\]-1RN: Interleukin Receptor Antagonist, \[IL\]-17: Interleukin 17, \[P2RX7\]: Purinergic receptor, \[TNFRSF\]: Tumor necrosis factor receptor superfamily, \[IRAK1\]: Interleukin 1 receptor associated kinase-1, \[IL\]-6: Interleukin 6, \[CASP\]-1: Caspase 1, \[TNSALP\]: Tissue non-specific alkaline phosphatase, \[TNF\] α: Tumor necrosis factor alpha

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related as it is the major IL-1B producing. Other studies in the US, Portugal, Czech, Germany, Spain and Japan didn't find a significant association. Different results in different studies may be due to different allele frequencies in different ethnic groups and sample size variation. The minor allele frequency of IL-1B (+3954) is reported at 21%–29% in Caucasians, 14.7% in Hispanics and 5.6% in Japanese.\(^{[3,4]}\) Failure to detect a statistically significant difference in frequency of IL-1B polymorphism between EARR cases and control in Japanese is due to low minor allele frequency. C3954T polymorphism is present on exon and is synonymous (Phe105Phe) and does not result in a change in protein conformation but was observed to increase IL-1B production which caused relatively more catabolic bone modeling in the cortical bone interface of the periodontal ligament owing to the increased number of osteoclasts associated with higher levels of this cytokine. The variation might influence mRNA splicing, nuclear RNA stability, or, conceivably, levels of mRNA expression. Alternatively, the polymorphic site might be in strong linkage disequilibrium with another polymorphic site, within either the coding or the regulatory regions of these genes.\(^{[4,5]}\) Al-Qawasmi et al.\(^{[22]}\) further reported a greater increase in resistance to EARR with IL1 composite genotype involving the combined presence of T alleles of IL1A and IL1B. This expounded the stronger linkage of variation in IL1-B site as compared to the variation at the IL-1A marker and it further reflects the complex nature of these loci in determining susceptibility to orthodontically induced EARR.

Seven studies investigated the association of IL-1RN on EARR with 4 studies\(^{[22,29,30,62]}\) (Czech, Spain) revealing a positive association and studies in US\(^{[1,2]}\), Portugal\(^{[28]}\) and China\(^{[99]}\) didn't find any association. A polymorphism in the second intron of IL1RN gene gives rise to VNTR (variable number tandem repeat) of 86 bp sequence and thus to different alleles. At least one copy of allele 2 is associated with decreased secretion of IL-1ra and increased IL-1B synthesis. IL1RN VNTR short allele with 2 repeats was associated with EARR in Czech females which might be due to more prevalence of this allele in women. This allele was controversial regarding the reporting of both increased and decreased IL-1ra levels. Moreover, this VNTR polymorphism is strongly correlated with other IL1RN polymorphisms.\(^{[30]}\) The +2018T > C polymorphism in exon 2 of the gene is in complete linkage disequilibrium with a penta-allelic 86 bp VNTR polymorphisms in intron 2 of the gene. Genotype TT of this polymorphism is associated with EARR in both vital and root-filled teeth, which is consistent with an increase in IL-1ra levels.\(^{[24,29,62]}\) This genotype is not associated with EARR in Chinese\(^{[99]}\) and the US.\(^{[13]}\) C allele of rs315952 is associated with increased IL-1ra levels but was not found to be significantly associated with EARR.\(^{[28]}\)

IL-6 polymorphism is associated with EARR only in the Chinese population.\(^{[19]}\) According to this study, root resorption of patients carrying the GC genotype was greater than that of patients carrying the CC genotype. Moreover, Gu et al. observed lesser blood IL-6 levels in patients with G allele as compared to C allele. This indicates that IL-6 has predominantly inflammatory action in orthodontic tooth movement with bone-resorbing effects thereby preventing EARR. However, Liu et al. detected IL-6 on both compression and tension sides of the teeth in mice after orthodontic force application. Hence, this association needs further validation by studies in other populations.

C-allele of IRAK1 (rs1509703) has been observed to have a protective effect against EARR whether in homozygous/heterozygous form in Portuguese Caucasians population.\(^{[20]}\) T allele is the high-risk genotype for EARR and encodes leucine. As IRAK1 locus is influenced by X-inactivation, homozygotes CC have a similar expression of serine isoform as male hemizygotes for allele C. Due to skewed X chromosome inactivation; we may anticipate that some heterozygotes will also be protected. Similar studies in other ethnic populations should be performed to further validate the proven association.

A allele of IL-17A -197A/G (rs2275913) was observed to produce more IL-17 in vitro than those without the allele\(^{[6]}\) and IL-17 plays a role in odontoclastogenesis.\(^{[8]}\) But IL-17A (-197A/G; rs2275913; Promotor) was not observed to have a significant association with EARR in the Czech population.\(^{[42]}\)

Different studies exploring the role of P2RX7 in EARR have yielded conflicting results. CC, CT genotype of rs208294 has been observed to be associated with EARR in Caucasians.\(^{[5]}\) The gain of function variant of rs1718119 (GCT > ACT; Ala348Thr) has a protective role against EARR. Hence, the GG genotype is associated with EARR in the Portuguese population.\(^{[11]}\) However, CG haplotype involving both SNPs was found to have an association with EARR in the Czech population. However, variant rs1718119 and another SNP rs2230912 were not found to be associated with EARR in Caucasians.\(^{[43]}\) There may be more SNPs that may have an inductive/protective effect on EARR. Thus, whole gene sequencing is desired for exploring the role of P2RX7.

RANKL is a membrane-bound cytokine expressed in osteoblasts that induces osteoclast differentiation and activation, mediated by osteoclast expressed receptor RANK. RANK (TNFRSF11A; 18q21.2-21.3) SNP D18864 was found to have association with EARR in US Caucasians\(^{[58]}\) but rs1805034 did not associate with EARR in Portuguese.\(^{[11]}\)

OPG is a decoy receptor for RANKL, inhibiting osteoclastogenesis and bone remodelling. Osteoprotegerin was not found to have an association with EARR in both conducted studies on Portuguese\(^{[13]}\) and Czech Caucasians.\(^{[65]}\) SNP rs3102735 (-163T/C; Promotor) in gene promoter region may affect transcription and has been associated with lower bone mineral density or higher frequency of fractures related to minor allele G. Its minor allele frequency has been observed to be low in Portuguese which might have resulted in non significant results. SNP rs2073618 (+1181 C/G; Lys3Asn; Exon1) and rs3102735 were not associated in Czech population.
This study suggests thatα
considered while doing orthodontic treatment.
overjet and presence of dilacerated roots also pose high risk for clinical risk factors like maxillary premolar extraction, increased
enhance the orthodontic tooth movement with minimal or no therapeutic intervention will ensue which will pave our way to once the molecular database is completed, the biomolecular pathway is associated with EARR while that via TNF receptor is not associated with EARR.[46]
Vitamin D showed association with EARR in Brazilian population. Fontanna et al. suggested the association of Vitamin D receptor polymorphism (rs731236) with EARR. Genotype-containing C allele was found protective against root resorption in the Brazilian population.[49]
Population stratification and variation in frequencies of SNPs in different ethnicities must be taken into consideration. Genetic variants may interact with other variants in the same (or another) gene and environmental factors that influence the observed phenotype. Hence, a minor gene effect, ethnic diversity or linkage disequilibrium contributed to variations in different studies. Also, studies must be performed with sufficient statistical power to detect the association of a minor allele effect.

Presently studies apropos of orthodontic tooth movement have constraints (a) histologic analysis is restricted as teeth moved and/or surrounding bone cannot be analysed; (b) interindividual dissimilitude in mechanobiological responses; (c) not all factors influencing tooth movement have been unmasked. It is believed that once the molecular database is completed, the biomolecular therapeutic intervention will ensue which will pave our way to enhance the orthodontic tooth movement with minimal or no root resorption.
Recent literature suggests that EARR is multifactorial and clinical risk factors like maxillary premolar extraction, increased overjet and presence of dilacerated roots also pose high risk for development of EARR. Therefore, these factors must also be considered while doing orthodontic treatment.[47,48]

| Conclusions |
| --- |
| • The outcome of this review shows that different gene polymorphisms may indicate the occurrence of EARR and also proposes certain recommendations for prospective researchers for further studies. |
| • Timely and repeated estimation of cytokine levels at the site of localized force application must be performed concomitant with the determination of genetic polymorphisms to authenticate the proposed association between a potential mediator and EARR. |
| • Genetics based studies along with other basic science research in the field might help to understand the exact nature of EARR, the influence of genetic inheritance and possibly lead to the prevention or even eradication of this phenomenon during orthodontic treatment. |

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**Conflicts of interest**

There are no conflicts of interest.

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