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REVIEW ARTICLE

External apical root resorption concurrent with orthodontic forces: the genetic influence

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ABSTRACT

Root resorption is a pathological process of multifactorial origin related to the permanent loss of dental root structure in response to a mechanical, inflammatory, autoimmune or infectious stimulus. External apical root resorption (EARR) is a frequent clinical complication secondary to orthodontic tooth movement; apart from variables related to treatment, environmental factors and/or interindividual genetic variations can confer susceptibility or resistance to its occurrence. In this context, genetic predisposition has been described as an etiological factor, together with mechanical factors derived from orthodontic treatment. In recent years, international research groups have determined the degree of influence of some genetic biomarkers in defining increased/reduced susceptibility to postorthodontic EARR. The influences of the *IL1* gene cluster (*IL1B, IL1A, IL1RN, IL6*), *P2RX7, CASP1*, OPG (*TNFRSF11B*), RANK (*TNFRSF11A*), *Osteopontin* (*OPN*), *TNFα*, the vitamin D receptor (*TaqI*), *TNSALP* and *IRAK1* have been analyzed. The objective of the present review study was to compile and analyze the latest information about the genetic background predisposing to EARR during orthodontic treatment. Genetics-based studies along with other basic science research in the field might help to clarify 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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Introduction. External apical root resorption (EARR)

Definition, prevalence and diagnosis of EARR

External apical root resorption (EARR) is a frequent iatrogenic effect of orthodontic intervention. EARR refers to a specific type of root resorption characterized by a shortening of the apical third of the root that can be detected on routine radiographs used in the dental office [1,2] and a side effect related to the biological tissue response [3] that enables teeth to be moved during orthodontic treatment [4]. Nevertheless, EARR has also been described without the application of orthodontic forces associated with increased periodontal probing depth and reduced crestal bone height [2]. In addition, it has been detected in patients with missing teeth [2], and even as a result of occlusal forces [5].

Histological root resorption detectable by microscopy represents the first stage toward EARR as a permanent pathology with limited reparative potential and detectable by radiography. In histologically examined teeth, EARR has been found in up to 100% of orthodontically treated teeth, but less frequently in teeth examined by panoramic or intraoral radiography [3,6]. It is not known at present how orthodontic treatment factors influence EARR [7] but reports in the literature indicate that subjects undergoing orthodontic forces are more predisposed to apical root resorption of varying degrees of severity. In this regard, histologic research indicates a high (more than 90%) occurrence of histological root resorption when intrusive orthodontic forces are applied to teeth [7]. It has been reported that orthodontically induced root resorptions after ∼2 months of treatment can be detected histologically but are not observable on serial radiographs [8]. It has been stated that seven to thirteen per cent of untreated subjects display a moderate degree of EARR, between 1 and 3 mm by radiographic analysis [9].

In one study, the incidence of severe EARR of the incisors after orthodontic treatment was found to be 14.5% [10]. Other studies found that 3% of examined teeth in almost two hundred patients experienced apical root resorption after orthodontic treatment [11], whereas EARR was found in nearly all of 439 patients undergoing orthodontic treatment [12]. Other research has reported the incidence of EARR as 15% before treatment and 73% after treatment [13]. Aggressive EARR (loss of >5 mm) has been reported as occurring in 2–5% of orthodontic patients [14,15]. It is little use to compare frequencies of root resorption between different studies because the criteria used to define resorption are so diverse and generally undefined. Ethnic origin has been described as one important factor, with subjects of Asian origin being less predisposed to EARR than those of Hispanic or white origin [16]. This could imply that cultural variables may

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also play an important role [16]. This study reported that 25% of treated patients showed ≥2mm of EARR [16]. While earlier, other authors reported a 30% frequency of EARR of >3mm [14,17]. Moreover, the teeth most frequently affected by EARR, and with varying degrees of severity, are in descending order the upper incisors, the mandibular incisors and the first molars, respectively [16–18]. It has not been established whether this is because more movement is required of these teeth due to transversal or saggital malocclussions [19] or because of their spindly cone-shaped single root. The frequency of EARR in the upper central incisors (>1 mm) was reported to oscillate from 27% in the maxillary central incisors to 2% in the maxillary premolars [18]. The type of root resorption typically associated with orthodontics most often occurs at the apex. This might be partially explained by the fact that the apical third is covered with cellular cementum whereas the middle and coronal thirds contain acellular cementum [20].

Etiological factors associated with EARR

Apart from tissue-related properties, the aetiology of EARR is complex and multifactorial. EARR results from a combination of genetic predisposition, individual variability and external factors [5,9,14,21,22]. Many factors have been suggested as affecting the root resorption process, although none on its own explains the variation in individual predisposition to EARR. Both genetic and acquired factors interact in the development of the phenotype [1]. The risk factors that induce EARR after undergoing orthodontic tooth movement include the magnitude of the orthodontic strain applied [6,23,24], the direction of tooth movement [25,26], treatment duration [15,16,18,25,27–32], amount of apical displacement [26,29,30,32], method of force application (intermittent versus continuous) [3,17], type of appliance [6] and treatment technique [25,33,34]. Other influential factors are the morphological characteristics of the root and abnormal development, also of the root [16,21,27,32,35–37], how close the root surface is to the cortical [28,38], maxillary and mandibular bone density [28], a history of tooth extraction [18] or previous trauma [2,3,17,27,39–44], patients with habits (bruxism, tongue thrust and chronic nail biting) [45], endodontic treatment [3,39,44], type and severity of malocclusion [2,16,22,24,29–31]; and age [9,15,17,27,30,32] and sex of the patient [5,16,21,22,30,32,38]. Dental trauma, especially tooth reimplantation, has also been associated with a greater predisposition to root resorption [43]. The previous history of EARR [2,6,37] and the pathological event itself have also been associated with genetic influences [1,2,9,16,21,46,47], craniofacial syndromes [48,49], systemic factors [50,51], including drugs (nabumetone) [52,53], hormone deficiency, hypothyroidism, hypopituitarism [54], asthma [3] and chronic alcoholism [55]. Although some studies have described a higher occurrence of post-orthodontic EARR in females than males [37,56], several studies found no sex-related differences [16,25–27,57]. Along with all these explored associations, individual susceptibility is considered to be a major factor accounting for risk of EARR, both in the context of orthodontic treatment and not [2,29,58].

Individual variability

External apical root resorption is probably the result of a mixture of acquired and individual factors. Efforts to study individual variables have focused on the role and influence of the genetic component (Table 1). Reactions to orthodontic treatment can vary depending on the patient's genetic profile. Genomic information determines or encodes proteins and signalling processes involved in cementum or/and dentin resorption and repair during orthodontic treatment [59–63].

Estimating the influence of genetic factors

Some subjects seem to have low resistance to EARR under mechanical stress, while others subjected to the same mechanical conditions are more likely to experience severe EARR [5]. In this respect, Al-Qawasmi et al. [47] investigated a possible linkage of EARR associated with orthodontic treatment with polymorphic targets in the *RANK, TNSALP* and *TNFalph*a genes in 38 pedigrees of Caucasian families. These authors found evidence of linkage between post-orthodontic EARR and the genetic variant, D18S64, and the results suggest that this locus (which lies close to the *RANK* gene) may contribute to susceptibility to EARR [47].

The same group studied 35 white American families and examined the linkage and association between genetic variants in the interleukin *IL1* gene cluster, specifically *IL1A* and *IL1B* genes, and EARR [21]. Their results showed evidence ($p = 0.0003$) of linkage disequilibrium between the *IL1B* gene variants and the occurrence of EARR. Subjects homozygous for the first allele of the *IL1B* gene were defined as having a 5.6-fold increased predisposition of post-orthodontic EARR (> 2mm) compared with heterozygous subjects and those homozygous for allele 2. Data indicate that allele 1 of *IL1B* gene may induce decreased levels of the IL-1 protein *in vivo* [64], increasing the risk of being affected by root resorption under orthodontic strain.

The overwhelming majority of current information about the influence of genetic factors on EARR comes from population association studies, a type of study that uses larger samples to help determine whether a specific nucleotide is more frequently associated in an affected cohort. In this context, significant evidence of linkage disequilibrium between a genetic variant at position +3954 of the *IL1B* gene and EARR was recently reported [47]. One group claimed that genetic influence accounted for ≤50% of variation observed in post-orthodontic external root resorption, with variations in the *IL1B* gene determining 15% of the observed differences. The result of decreased IL-1 cytokine levels could be maintained mechanical stress at the apical third of the root due to reduced bone modelling leading to apical root resorption [2], or at least increasing the predisposition to experience EARR [65].

In recent years, and after the study carry out by Al-Qawasmi et al. in 2003 [21], a series of case–control

Table 1. Association genetic studies and linkage genetic studies between specific genetic variants and EARR predisposition secondary to orthodontic treatment.

Study	Type of study	IL1B	IL1A	IL1RN	P2RX7	CASP1	TNFRS11A	TNFRSF11B	SPP1	TNF alpha	TNSALP	IRAK1	IL-6	IL-17A
Al-Qawasmi et al. [23]	LD	↑ SNP +3954 allele 1 (OR: 5.6; CI: 1.9–21.20; $p = 0.0003$)	X SNP-899	–	–	–	–	–	–	–	–	–	–	–
Al-Qawasmi et al. [47]	LD	–	–	–	–	–	↑ SNP marker D18S64 (LOD: 2.5; $p = 0.02$)	–	–	X No evidence of linkage was found	X No evidence of linkage was found	–	–	–
Shank et al. (2007) [66]	A	X SNP rs13032029 C113316646T ($p = 0.8458$)	–	–	–	–	X SNP rs922996 A42076671G (p = 0.1352).	↑SNP rs2073618 G1181C (p = 0,003)	–	–	–	–	–	–
Bastos Lages et al. (2009) [67]	A	↑ SNP +3954. 2/2; [OR: 4.0; CI: 1.23–12.9; $p = 0.0349$]. 2/2 versus 1/1; (OR: 7.33; CI: 1.81–29.6; $p = 0.0095$)	–	–	–	–	–	–	–	–	–	–	–	–
Gülden et al. (2009) [68]	A	X SNP +3954	↑ SNP-899 2/2 ($p < 0.032$)	–	–	–	–	–	–	–	–	–	–	–
Iglesias Linares et al. (2012) [69,70]	A	↑ SNP rs1143634 CC (OR: 3.47; CI: 1.12–10.72; $p = 0.027$)	X SNP rs1800587 CC (OR: 2.51; CI: 0.8–7.57; $p = 0.097$)	↑ SNP rs419598 TT (OR: 6.75; CI: 2.04–22.27; $p = 0.001$)	–	–	–	–	–	–	–	–	–	–
Iglesias-Linares et al. (2013) [71]	A			↑ SNP rs419598 TT (OR: 10.85; CI: 3.97–29.6; $p = 0.001$)	–	–	–	–	–	–	–	–	–	–
Linhartova et al. (2013) [73]	A	X SNP rs1143634 CT	X SNP rs1800587 CT	↑ IL1RN VNTR variants in girls (OR: 2.50; CI: 1.13–5.53; $p = 0.020$).	–	–	–	–	–	–	–	–	–	–
Iglesias-Linares et al. (2014) [84]	A	–	–	–	–	–	–	–	↓ SNP rs9138 AA (OR: 0.20; CI: 0.05–0.81; $p = 0.025$) ↓ SNP rs11730582 CT (OR: 0.035; CI: 0.062–0.90; $p = 0.035$) ↑ SNP rs9138 CC [OR: 4.10; CI: 1.03–16.35; $p = 0.045$] ↑ SNP rs11730582 CC (OR: 11.68; CI: 1.12–121.06; $p < 0.039$)	–	–	–	–	–	–
Pereira et al. (2014) [74]	A	X SNP rs1143634	–	–	↑ SNP rs1718119 GG ($p < 0.01$)	–	X SNP rs1805034 RANKL	X SNP rs3102735 OPG	–	–	–	–	–	–
Sharab et al. (2015) [75]	A	X SNP rs1143634 CC/CT versus TT ($p = 0.0533$)	X SNP rs1800587	X SNP rs419598	↑ SNP rs208294 CC/CT versus TT ($p = 0.0028$) X rs1718119 AA/GG versus GA ($p = 0.0813$) X rs2230912 CC versus. CT ($p = 0.1564$)	X SNP rs530537 TT versus CC/TC ($p = 0.1527$) X rs580253 X rs554344	–	–	–	–	–	–	–	–
Pereira et al. (2016) [77]	A	X SNP rs1143634 CC	–	X SNP rs315952 CC versus CT	–	–	–	–	–	–	–	↓SNP rs1059703 - CC ($p = 0.018$)	–	–
Guo et al.	A	–	–	X SNP rs419598 CT	–	–	–	–	–	–	–	–	↑ SNP	–

(*continued*)

Table 1. Continued

Study	Type of study	IL1B	IL1A	IL1RN	P2RX7	CASP1	TNFRS11A	TNFRSF11B	SPP1	TNF alpha	TNSALP	IRAK1	IL-6	IL-17A
(2016) [78]				versus TT									rs1800796 GC ($p = 0.008$)	
Linhartova et al. (2017) [79]	–	–	–	–	↑ SNP rs208294 CT and rs1718119 GA (OR: 4.06; CI: 1.05–15.66; $p < 0.05$)	–	–	X SNP rs3102735 CT and rs2073618	X SNP rs11730582 TC and rs9138 AC	–	–	–	–	X SNP rs2275913 GA
Iglesias-Linares et al. (2016) [93]	–	–	–	↑ SNP rs419598 TT (OR: 3.121; CI: 1.93–5.03; $p < 0.001$)	–	–	–	–	–	–	–	–	–	–

EARR: external apical root resorption; LD: linkage disequilibrium study; A, genetic association study; X: not associated with EARR; ↑ ↓: associated with EARR; SNP: single nucleotide polymorphisms; OR: odds ratio; CI: confidence interval; LOD: logarithm of the odds (to the base 10).

studies were carried out to investigate the association between genetic variants and the risk of EARR in patients with orthodontic treatment (Table 1) [47,66–79]. Bastos Lages et al. [67] conducted a study to examine the relationship between *IL1B* gene polymorphisms and EARR after orthodontic treatment. The sample consisted of 61 patients from Brazil who were classified into two groups according to the presence of EARR in maxillary incisors after orthodontic treatment. They determined that a variation of the *IL1B* (+3954) gene led to increased risk of developing EARR [63]. Gülden et al. [68] associated the *IL1A* genetic variant (-889) with the appearance of EARR. Recently, Iglesias-Linares et al. [69] showed that there was an increased risk of patients with the homozygous *IL1B* (+3953 CC) genotype being affected by root resorption, with no positive/negative association correlation for the *IL1A* gene (-889), in patients of Spanish origin. This group recently added that variants in *IL1RN* [2018 (rs419598)] were found to be directly associated with post-orthodontic EARR [69]. However, differences of predisposition to EARR during orthodontic treatment were found not only in vital teeth but also in endodontically filled teeth. Genetic polymorphisms of the *IL1RN* gene were observed to be associated with an increased risk of being affected by orthodontic root damage in endodontically filled teeth compared to control teeth among the contralateral vital teeth [70–72]. More recently, Linhartova et al. [73] in a study carried out in a Czech population sample, corroborated these findings about variations in the *IL1RN* gene and the appearance of this complication during orthodontic treatment.

Another group [74] showed that the main variables that can lead to root resorption during orthodontic treatment were sex, length of treatment, use of rapid maxillary expansion, bicuspid extraction treatment and variant rs1718119 in the *P2RX7* gene [74]. P2RX7 codifies the purinergic receptor P2X ligand-gated ion channel 7, a non-selective ion channel expressed in clastic cells of the bone and seems to have a 'protective' effect on bone, activating bone formation and promoting osteoclast death. P2RX7 stimulates the production of proteins as IL-1β by immune cells [74]. According to the authors, these specific clinical factors could be responsible for 30% of phenotypic variability, which suggests the action of additional etiologic factors [74]. Significantly, other researchers quantified interleukin-1 beta and tumour necrosis factor alpha levels in monocytes obtained from orthodontically treated patients who were affected and not affected by aggressive EARR and found no differences in mean protein production between the two groups of patients, supporting the likelihood that this type of pathology is compatible with a heterogeneous genetic influence [75].

Recently, other groups have studied the role of genetic variants in *IRAK1, IL17* and *IL6* genes on EARR, observing that homozygous subjects for the C allele of the *IRAK1* variant were protected against EARR while heterozygous patients in the case of variants of *IL17A* and *IL6* gene variants were found not to be associated or at a higher risk of suffering EARR, respectively [76–79].

On the contrary, osteopontin (OPN) is an extracellular protein and hence an essential part of the non-mineral component of alveolar bone. OPN has a major role in alveolar bone

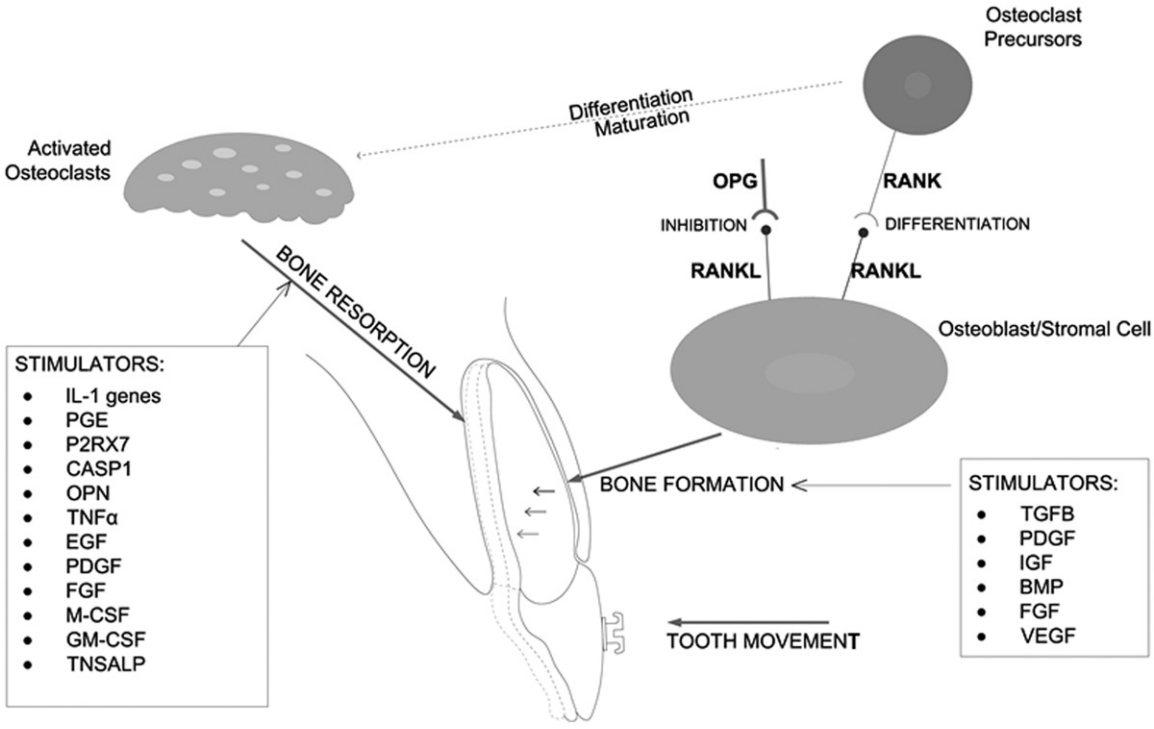

Figure 1. Interaction of the RANK/RANKL/OPG biomolecular complex during tooth movement with orthodontics. *IL1* genes: interleukin-1 genes; PGE: prostaglandin; P2RX7: P2X purinoceptor 7; CASP1: caspase 1; OPN*:* osteopontin; TNFalpha: tumour necrosis factor alpha; EGF: epidermal growth factor; PDGF: platelet-derived growth factor; FGF: fibroblast growth factor; M-CSF: macrophage colony-stimulating factor; GM-CSF: granulocyte macrophage colony-stimulating factor receptor; TNSALP: tissue-nonspecific alkaline phosphatase; TGFB: transforming growth factor-B; IGF: insulin-like growth factors; BMP: bone morphogenetic proteins; VEGF: vascular endothelial growth factor.

modelling; more specifically, scientific evidence suggests that it mediates in the attachment process of clastic cells to the mineral component of bone surfaces [80]. OPN allows initiation of the intracellular signalling pathways in which osteoclasts develop the ruffled border that leads to bone resorption [80]. One group demonstrated that lack of osteopontin gene (*SPP1*) suppressed the mechanically induced proliferation of odontoclasts and minimized the occurrence of external root resorption [81]. Another group found similar findings in humans [82]. In other studies, it was determined that post-orthodontic EARR was associated with genetic variations in *SPP1* (89253600) in humans, so that inheriting the specific variation of osteopontin could be a factor of genetic susceptibility to apical root resorption in the analyzed sample group [83]. These authors suggested that the *SPP1* gene (rs11730582 and rs9138) could be an influential factor for developing EARR secondary to orthodontic treatment [83].

Results obtained from animal studies constitute another source of data for estimating the influence of genetic factors. Mouse models are becoming popular for studying genetic effects due to the significant genetic homology (80%) between humans and mice. Brudvik and Rygh validated mice as models for investigating tissue response to mechanical force, including EARR after orthodontic treatment [84]. The role of the IL-1β cytokine on apical root shortening was tested using an *IL1B*$^{-/-}$ model in which both controls (C57BL/6J) and *IL1B*$^{-/-}$ mice had the same initial histological root resorption without mechanical forces. When mechanical strain was applied, histological root resorption in the *IL1B*$^{-/-}$ mice increased significantly compared with the control animas [85]. This not only confirmed that IL-1β was at least one contributory factor to histological root resorption but also indicated, in this instance, that the mechanism was not a more aggressive inflammatory response because of IL-1β, since it was demonstrated that the KO mice lacked IL-1β production [86].

Many authors have used animal models to examine the influence of genotype on the predisposition to or protection against developing EARR secondary to mechanical orthodontic strain. In this respect, the results of one study indicated that inbred DBA/2J, BALB/cJ and 129P3/J mouse strains were at increased risk of being affected by orthodontically induced histological root resorption, whereas A/J, C57BL/6J and SJL/J mice were 'protected' [87]. In another study, mode of inheritance on predisposition to histological root resorption secondary to orthodontic strain was evaluated using inbred mice with different genetic information and their offspring. EARR was also evaluated for both females and males [A/J; DBA/2J; BALB/cJ strains but also A/J with DBA/2J and A/J with BALB/cJ crosses]. Sex differences were described only in BALB/cJ strain mice, and two different modes of inheritance were defined [the A/J strain had dominant resistance alleles, and offsprings from the A/J with DBA/2J cross were found to be more prone to EARR with a moderate degree between the two progenitors, which suggests a phenotype derived from different genetic sources]. These studies provided information of a noticeable polygenic component of EARR secondary to orthodontic strain in mice [85,86].

Some studies have described EARR as always associated with an increased number of TRAP + clastic cells and

increased levels of RANKL in the pressure area at the root surface [85]. Other studies have reported increased levels of OPG in the same area of the root in 'protected' compared with 'high-risk' mice. Clinical research has shown that the G1181C genetic variant in the osteoprotegerin gene is associated with an increased risk of histological root surface erosion [59] (Figure 1).

Another candidate gene for root resorption secondary to orthodontic forces is tissue-nonspecific alkaline phosphatase (*TNSALP*), which encodes a protein with an essential function during cementum formation and the root mineralization process [88]. One study determined that there was no evidence of linkage between *TNSALP*, *TNFalpha* genes and EARR in its study population [47]. Previous studies implicated *TNFalpha* in bone remodelling *in vitro* and *in vivo*. In addition, *TNFalpha* levels are increased in the human gingival sulcus during orthodontic treatment. Some data showed a more than 2-fold increase in tumour necrosis factor production collected after the application of orthodontic strain (12.9–30.5 ng) [89].

It was more recently reported that the control and regulation of transcription of specific genes by vitamin D is exerted via interactions with the human vitamin D receptor (hVDR) [90]. The hVitDr is the product of the vitamin D receptor gene (*VDR)* located on 12q13-14 [90]. A genome-wide analysis has identified more than one hundred genetic variants in the vitamin D receptor gene. One study investigated the association between clinical factors, the *VDR TaqI* enzyme genetic variant (rs731236) and root resorption after orthodontic force application [91]. The results of this study concluded that homozygous or heterozygous subjects for the C variant were likely to be 'protected' against post-orthodontic EARR (CC 1 CT3TT [OR: 0.29; $p = 0.091$]). They concluded that clinical factors and the *VDR TaqI* enzyme genetic variant were significantly associated with post-orthodontic root resorption [91].

This suggests that the differential expression of molecules governing the osteoclast/odontoclast function plays a role in defining a predisposition to EARR after the application of mechanical strain in orthodontics [92,93]. All the evidence suggests that some patients may respond with an inflated clastic response to orthodontic forces leading to root resorption [94]. Despite all the evidence presented above, to date no definite genetic targets have been widely selected to help predict which individuals are at risk of suffering mild or severe EARR during orthodontic treatment [93].

Conclusion and future perspectives

EARR is an undesirable complication of orthodontic tooth movement. Although different preventive approaches have been described, none of these is able to reliably predict, and so avoid, this pathological secondary effect. It is essential to develop a sound and well-constructed database of genetic predisposition 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. Relevant studies in this specialized area have recently begun the task [62–79,93].

The authors of the present review strongly believe that complete knowledge of genetic predisposition would also make the final objectives of orthodontic treatment dependent on the individual condition of the patient. Moreover, it is possible that future orthodontic therapy could use biomolecular techniques to facilitate orthodontic treatment, which may protect against or highly predispose to EARR in different genetic backgrounds [95,96]. In the near future, additional genetically based studies could provide insights into the nature of external apical root resorption in orthodontics, which would undoubtedly be useful for preventing or even eradicating its occurrence.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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