Curr Osteoporos Rep (2016) 14:292–309
DOI 10.1007/s11914-016-0340-1

CRANIOFACIAL SKELETON (WE ROBERTS, SECTION EDITOR)

Bone Density and Dental External Apical Root Resorption

Alejandro Iglesias-Linares[1] · **Lorri Ann Morford**[2] · **James Kennedy Hartsfield Jr**[2]

Published online: 20 October 2016

Abstract When orthodontic patients desire shorter treatment times with aesthetic results and long-term stability, it is important for the orthodontist to understand the potential limitations and problems that may arise during standard and/or technology-assisted accelerated treatment. Bone density plays an important role in facilitating orthodontic tooth movement (OTM), such that reductions in bone density can significantly increase movement velocity. Lifestyle, genetic background, environmental factors, and disease status all can influence a patients' overall health and bone density. In some individuals, these factors may create specific conditions that influence systemic-wide bone metabolism. Both genetic variation and the onset of a bone-related disease can influence systemic bone density and local bone density, such as observed in the mandible and maxilla. These types of localized density changes can affect the rate of OTM and may also influence the risk of unwanted outcomes, i.e., the occurrence of dental external apical root resorption (EARR).

This article is part of the Topical Collection on *Craniofacial Skeleton*

✉ James Kennedy Hartsfield, Jr
James.Hartsfield@uky.edu

Alejandro Iglesias-Linares
aleigl01@ucm.es

Lorri Ann Morford
Lorri.Morford@uky.edu

[1] Department of Orthodontics, Complutense University of Madrid, Plaza Ramon y Cajal sn, Madrid, Spain

[2] University of Kentucky Center for the Biologic Basis of Oral/Systemic Diseases, 1095 Veterans Administration Drive, HSRB Room 414, Lexington, KY 40536-0305, USA

Keywords Orthodontics · Tooth movement · Bone density · Genetics · Root resorption · EARR · *P2RX7* · *IL1B* · *OPG*

Introduction

Bone mass is a measure of the combined amount of bone matrix and mineral content within a segment of bone. Bone mineral density (BMD) is a clinical proxy for estimating bone mass that takes into account the concentration of calcium and other minerals and estimates bone strength. An individuals' BMD changes over a lifetime such that it peaks in or around the middle 20s to 30s and then declines, particularly in women who exhibit a dramatic decline with the onset of menopause. Calcium intake can aid in increasing and/or maintaining BMD, especially later in life, as can regular, weight-bearing exercise. Environmental factors, such as diet, smoking, drinking status, and types of bacteria found in our bodies (particularly the microbiome of the digestive track), [1, 2] can also alter BMD (Fig. 1).

Genetics and epigenetics also contribute to characteristics of our BMD. Various disease states have been shown to have profound effects on overall bone health. Measuring BMD is especially important in the diagnosis, monitoring, treatment, and/or management of such bone-centered diseases as osteomalacia/rickets, osteopenia, osteoporosis, and osteogenesis imperfecta. Chronic inflammatory diseases including obesity, diabetes, and inflammatory bowel disease (IBD) are known to have systemic effects that have the ability to affect bone quality and mass.

BMD measurements of the jaws and spine show similar rates of age-related deterioration [4]. With this in mind, measurement of jawbone density has been proposed as a good predictor of systemic-wide alteration in bone metabolism, such as with the onset of osteoporosis which could affect other

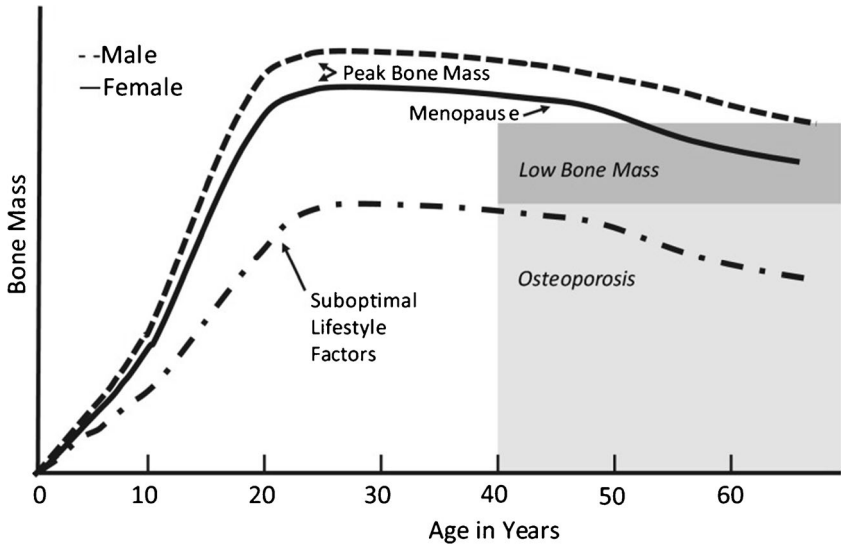

Fig. 1 Changes in bone mineral density (BMD) over a lifetime. (Used with permission from Weaver C, Gordon C, Janz K, Kalkwarf H, Lappe J, Lewis R et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporosis International, 2016;27(4):1281–386) [3]

anatomical regions that are distant to the jaws like the lumbar vertebrae. It can be inferred from this evidence that systemic variation or alterations of bone metabolism would directly affect maxillary and mandibular bone density, specifically of alveolar bone [5].

Orthodontists use force to move teeth in a controlled fashion in order to facilitate the proper positioning of the teeth and achieve a uniform distribution of forces during occlusion. Tooth movement, through the alveolar bone envelope triggered by orthodontic strain, is a phenomenon that depends directly on the coordinated activity of osteoblasts, osteocytes, and osteoclasts. External apical root resorption (EARR) is root resorption that can be seen on standard diagnostic radiographs caused by undesirable activity of osteoclastic cells on the root surface [6]. Although It can occur in the absence of orthodontic treatment, its incidence increases when concurrent with orthodontic treatment [7].

Irrespective of whether or not EARR is facilitated by orthodontic mechanical factors, the process leading to EARR implicates specific molecular pathways that orchestrate non-physiological cellular activation for root demineralization and the creation of dental root resorption pits [7]. Differing alveolar bone densities and bone modeling/remodeling processes affect the strain on the dental root, thus influencing the orthodontic tooth movement (OTM) process and the increased occurrence of EARR as a deleterious secondary effect.

Natural Tooth Position and the Modeling and/or Remodeling of Bone Associated with OTM

Under normal circumstances, the positions of individual teeth in the oral cavity are determined by an equilibrium state created between the soft tissue forces being applied to the crowns of the teeth (i.e., from the tongue, lips, and/or buccal mucosal) and the occlusal forces generated on each tooth root encased within the alveolar bone. A familiar saying in orthodontics is that there is nothing more stable than a malocclusion. This adage infers that external forces must be placed on teeth, forces strong enough to alter the natural equilibrium and to promote movement of the teeth into a new position. OTM requires the purposeful application of force on teeth to correct a malocclusion. Modeling of the alveolar bone through the periodontal ligament (PDL) enables a tooth to change its position while maintaining periodontal support.

Bone modeling changes the shape of bone resulting in changes in bone morphology. The ability to change bone morphology is due to bone resorption and formation occurring in an uncoupled manner and on separate surfaces. In contrast, bone remodeling is the mechanism based on the coupled and balanced activities of bone resorption and formation along specific sites on the same bone surface that ensures turnover while maintaining bone mass and gross morphology. This allows for adaptation to both mechanical loading and the requirements of calcium and phosphate metabolism (Fig. 2) [8, 9]. While modeling along the periosteal surface is key for maintaining alveolar bone support during tooth movement [10], both bone modeling and remodeling are involved in the orthodontic response (Fig. 3) [9, 11].

When the PDL is maximally compressed by orthodontic force, heavy functional loads are transferred directly to a relatively small area of the lamina dura. Thus, orthodontic force is a static load superimposed on function [12]. It is hypothesized that the dynamic (repetitive) loading of mastication results in accelerated fatigue damage in bone adjacent to the compressed necrotic PDL. This leads to undermining resorption removing the resisting bone, allowing the tooth to move. The unique biomechanical properties of the PDL allow it to generate a bone modeling response to even light loads [13, 14]. However, bone modeling of the alveolar process during

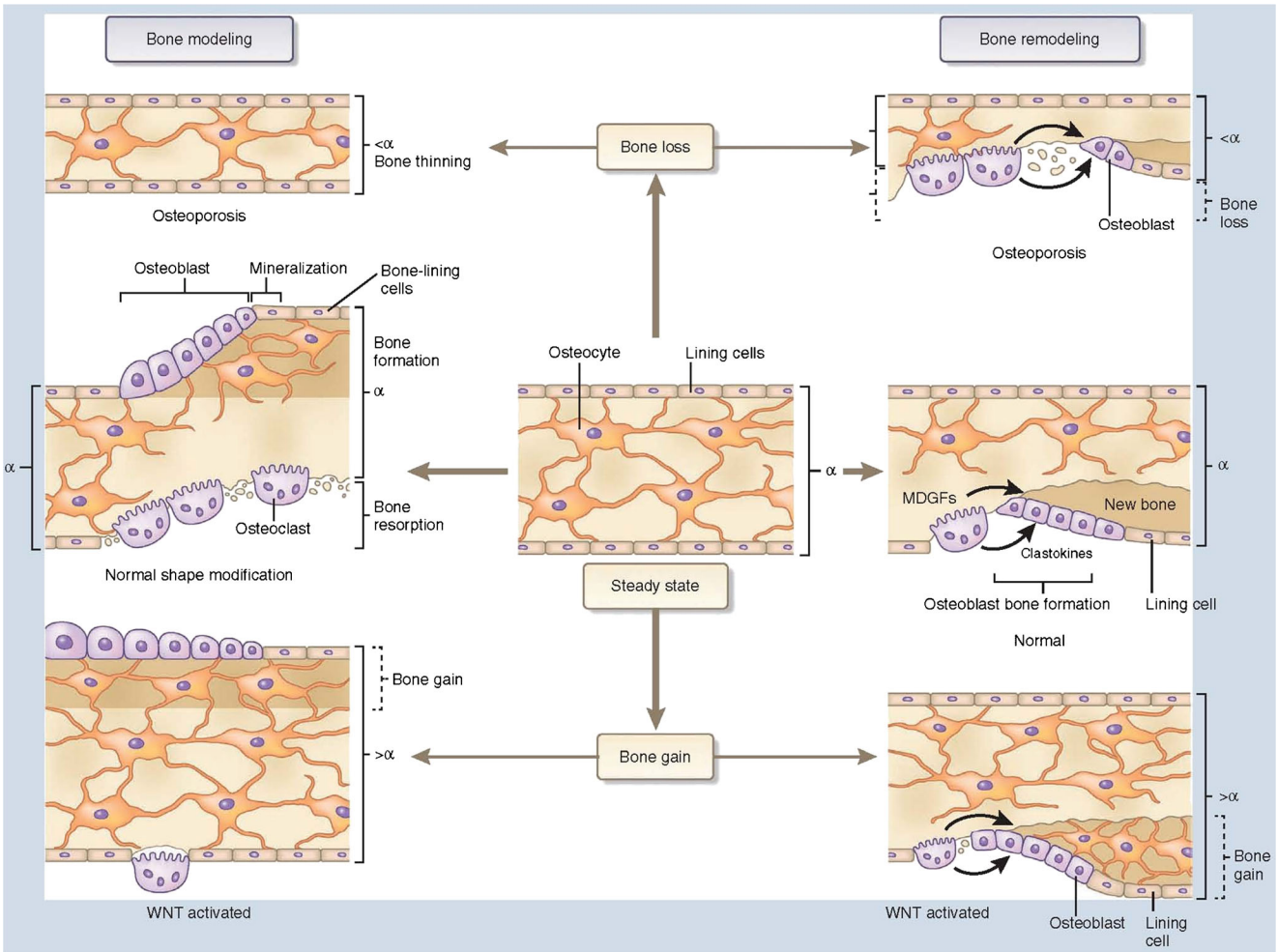

Fig. 2 Comparison of bone modeling and remodeling. (Used with permission from Baron R, Kneissel M. WNT signaling in bone homeostasis and disease: from human mutations to treatments. Nature medicine, 2013;19(2):179–92) [8]

sustained tooth movement appears to utilize the same atrophic and hypertrophic mechanisms for functional adaptation throughout the skeleton.

Root Strain as a Testable Mechanism of EARR in Animal Models

Animal studies on root resorption historically used histological sections of root resorption lacunae to measure the extent of root resorption. Human studies comparing control teeth that were to be extracted for orthodontic treatment to teeth that have some orthodontic force placed on them prior to extraction for treatment reasons have also historically used histological sections. Micro CT or cone beam CT are now also used to measure the resorption lacunae and changes in volume. These microscopic resorption lacunae are not seen on standard diagnostic radiographs. It has been presumed that an increase in resorption lacunae over a short period of time would indicate the start of a process that if continued would result in an extent of root loss that would be observable on standard radiographs, i.e., EARR.

In lactating calcium-deficient female Sprague-Dawley rats, a decrease in alveolar bone density resulted in more rapid orthodontic tooth movement of maxillary molars compared to non-lactating rats on a control diet. In addition to the observed increase in tooth movement velocity, there was decreased cratering of the outer cementum layer of the roots for the teeth being moved. This data suggested that a reduction in bone density effectively reduced the orthodontically induced strain on the dental root, enabling the tooth to move faster with differential resorption of alveolar bone versus root structure [15].

Stress analysis of orthodontically stimulated rat molars has indicated that mechanically induced bone resorption is due to fatigue failure in the bone itself [16]. This supports the hypothesis that root resorption might be related to a reduced rate of bone resorption at the PDL interface manifested as a prolonged inductive (lag) phase that is associated with compressed necrotic areas in the PDL [17]. Furthermore, root

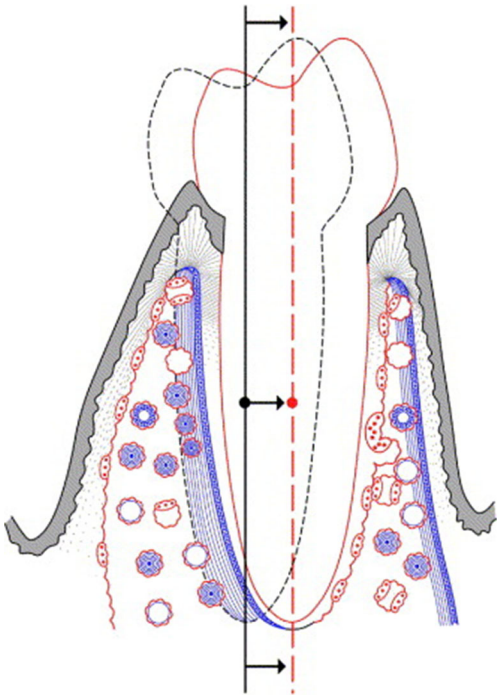

Fig. 3 A schematic diagram showing the bone physiology associated with translation of a tooth. Note that there is a coordinated bone modeling and remodeling response leading and trailing the moving tooth. This mechanism allows a tooth to move relative to basilar bone while maintaining a normal functional relationship with its periodontium. Osteoclastic and osteoblastic activities are in *red* and *blue*, respectively. (Used with permission from Roberts WE, Roberts JA, Epker BN, Burr DB, Hartsfield JK. Remodeling of mineralized tissues, part I: the Frost legacy. Seminars in orthodontics; 2006: Elsevier) [9]

resorption under loading stress in the apical and cervical thirds was found to be more severe than in root regions that were not mechanically stressed. In this respect, the mean hardness and elastic modulus of premolars subjected to orthodontic loading were similar to those of untreated control premolars observed in other studies, decreasing from the cervical to the apical regions [18]. In contrast, the direction as well as the magnitude of stress in the PDL, root, and alveolar bone may help define mechanotransduction during tooth movement. In silico models found an approximately 3:1:1 ratio between radial, circumferential, and longitudinal stress magnitudes for tipping movement and 2:1:1 for translation movement [19]. These results suggest that direction plays a critical role in triggering a biological response for tooth movement to take place, as well as an iatrogenic response, like root resorption, in particular regions of the root specific to each type of movement.

A hypothetical scheme of the model that focused on the structure of the root judged that when an orthodontic force was applied, tensile and compressive longitudinal stresses would tend to simultaneously separate and crush the dentinal tubules, so affecting the underlying cementum layer and provoking microcracks; furthermore, when the cementum layer was also defective, these simultaneous differential tensile and compressive effects might have an increased impact on root resorption, taking into account that osteoclastic cell activity is upregulated due to the stimulus to orthodontic tooth movement [19]. The single-tooth numeric simulation provided other explanations of mechanically induced root resorption, even though single-tooth stress levels were reported as being considerably less than in the multi-tooth system [20]. Numeric studies have helped explain how root resorption might be initiated by hydrostatic compressive stress-induced tissue necrosis [20, 21].

Genetic Influence in EARR and Its Biological Scenario

Incorporating the effect of pro-resorptive cytokines on alveolar bone modeling during OTM to the treatment factors yields a more complex explanatory model. Interleukin-1β (IL-1β) is a potent stimulus for osteoclastic cell recruitment and bone resorption during OTM [22, 23]. It is proposed that a deficiency of IL-1β inhibits the alveolar bone resorptive response to orthodontic loads. Thus, less bone resorption might result in prolonged stress concentrated on the root of the tooth, triggering a cascade of fatigue-related events leading to root resorption (Fig. 4) [15, 24].

It is notable that the cluster of *IL1* gene polymorphisms associated with EARR concurrent with orthodontic treatment has a positive correlation with IL-1β production rates in vitro. Specifically, allele 1 (G) of the *IL1B* polymorphism at +3954 (rs1143634) is related with relatively low production of IL-1β [25, 26]. Monocytes from subjects homozygous for the *IL1B* 3954 allele 2 (A) produce 4-fold more IL-1β, while heterozygous cells produce approximately 2-fold more IL-1β, than cells from those homozygous for allele 1 [26, 27]. Allele 2 (A) of *IL1B* +3954 has in some studies been associated with adult periodontitis, consistent with the observation that excessive IL-1β activates the degradation of extracellular matrix and bone in the periodontal tissues [28, 29]. As a potent stimulus of osteoclast recruitment and bone resorption, IL-1β [22, 23], low IL-1β production in the case of allele 1 (G) might result in relatively less catabolic bone modeling (resorption) at the cortical bone interface with the PDL. Essentially, increased risk of root resorption associated with allele 1 (G) of IL-1β might be facilitated through impairment of alveolar resorption, resulting in prolonged stress and strain of the adjacent tooth root due to dynamic functional loads.

The pro-inflammatory function of IL-1β is antagonized by the interleukin 1 receptor antagonist (IL1Ra) protein encoded by the *IL1RN* gene. In this regard, two other genes of the *IL1* gene cluster, *IL1A* and *IL1RN*, have been explored in populations of different origin. The polymorphisms analyzed (rs1800587 and rs419598) were found to account differently for the risk of EARR. In a study from Spain, there was no

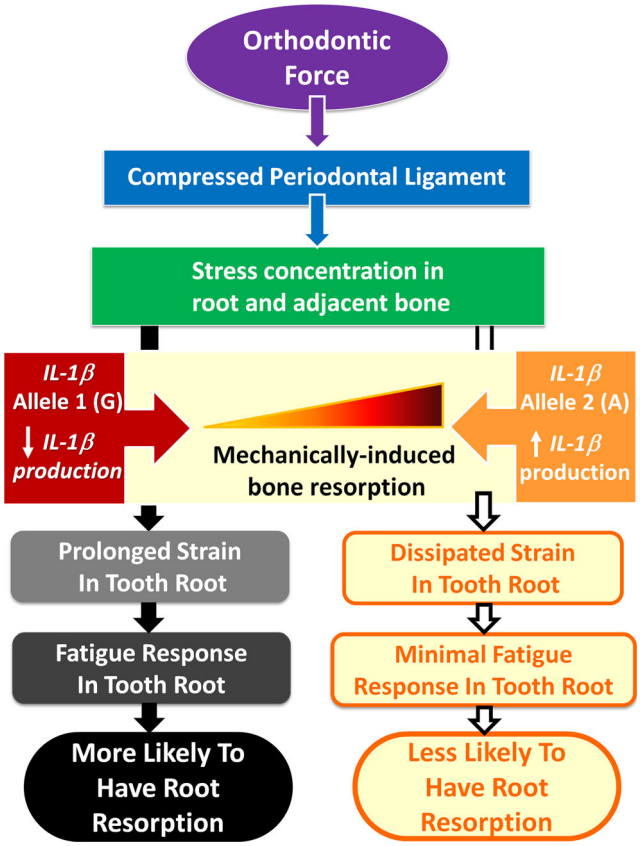

Fig. 4 Proposed model for pathway through which the *IL-1B* +3954 genotype (rs1143634) modulates the extent of root resorption experienced during orthodontic tooth movement. This model suggests that low IL-1 production in case of allele 1 (*G*) results in relatively less catabolic bone modeling in cortical bone interface of periodontal ligament (PDL) because of decreased number of osteoclasts associated with lower levels of this cytokine. Inhibition of bone resorption in direction of tooth movement results in maintaining prolonged dynamic loading of tooth root adjacent to compressed PDL, resulting in more root resorption because of fatigue failure of root. In case of high IL-1 production associated with allele 2 (*A*), compressed PDL space is restored by resorption of bone interface of PDL, resulting in only mild root resorption that is controlled by cementum-healing mechanism. This is one model for how these various factors might be implicated in clinical expression of root resorption. However, as EARR is a complex trait, it is not projected as the only model in its development. (Used with permission from Al-Qawasmi RA, Hartsfield JK, Everett ET, Flury L, Liu L, Foroud TM et al. Genetic predisposition to external apical root resorption. Am J Orthod Dentofacial Orthop, 2003;123(3):242–52) [17]

statistical association with the *IL1A* gene, although subjects homozygous for the T allele of the *IL1RN* gene were 6.7 times more likely to be affected by EARR [30]. Similarly, a significant association was observed in a sample from the Czech Republic between a variable number tandem repeat (VNTR) in the *IL1RN* gene and EARR. Interestingly, there was a predisposition for EARR in females heterozygous or homozygous for the second allele [31].

There is disagreement in the literature regarding the variation of IL1ra protein levels due to *IL1RN* gene polymorphisms [32–34]. The *IL1RN* +2018T>C polymorphism is in complete linkage disequilibrium with a penta-allelic 86 bp VNTR polymorphism in intron 2 of the gene and is strongly linked to increased production of IL1Ra [32]. The *IL1RN* +2018T>C SNP showing a strong association with EARR during orthodontic strain could be consistent with an increase in IL1Ra protein levels, as previous in vitro and in vivo studies have found. Any cytokine level variation in the IL1Ra/IL-1β axis might have influence not only on bone modeling/remodeling but also on the subsequent increase in radicular stress during orthodontic tooth movement. Again, these results point to the potentially central role of this cluster of genes in the EARR process and their effect on the process of alveolar bone resorption and density during orthodontic tooth movement.

In the same vein, recent studies by using different experimental approaches and study designs have provided further data about variations in candidate genes—usually single nucleotide polymorphisms (SNPs)—that influence the process of EARR development secondary to orthodontic forces [17, 30, 35]. An age-matched and sex-matched case-control study comparing orthodontic treatment factors and genotyping results for 134 unrelated Caucasian subjects described a marginally significant association with EARR in the purinergic receptor P2X, ligand-gated ion channel 7 (*P2RX7*) gene when no other cofactors were included, specifically between individual carriers of two T alleles in *P2RX7* at SNP rs208294 [CC and CT vs. TT], while other *P2RX7* variants (rs1718119 and rs2230912) were not be associated with EARR [36••]. This conflicts with results reported by Pereira et al. in a sample of Portuguese origin, who found a statistically significant association between subjects with the *P2RX7* gene (GG genotype) rs1718119 variant and an increased risk of being affected by EARR concurrent with orthodontia [37••].

The P2X7 receptor coded for by the *P2RX7* gene is commonly found on the surface of macrophages involved in the response to orthodontic loading. Specifically, necrotic tissue deriving from apoptotic cells leads to the release of ATP from the damaged cells and its binding to the P2X7 receptor. Activation of this receptor leads, in turn, to autocrine and paracrine cell stimulation with overexpression of IL-1 cytokines and other inflammatory-related molecules. The released molecules all function as a chemotactic stimulus of the phagocytic cellular system responsible for eliminating necrotic tissue, so allowing tooth movement to take place. This, in turn, is directly associated with the alveolar bone remodeling process after applying orthodontic strain.

Apart from the IL1 gene cluster and associated pathways, other potentially predisposing genetic variants have been analyzed. The regions coding for *TNFRSF11B (OPG)* and *TNFRSF11A (RANK)* rs3102735 and rs1805034, respectively, for example, were not associated with EARR in orthodontics in that study [37••]. Nevertheless, other authors genotyped single nucleotide polymorphism rs2073618 in the *TNFRSF11B (OPG)*

gene in orthodontically treated patients and concluded that subjects carrying the C allele at this position on the *TNFRSF11B* gene were 1.9 times more likely to be affected by EARR than those not carrying the C allele ($p = 0.02$) [38]. Furthermore, subjects homozygous for the C allele, that is, carriers of CC alleles, were found to be 2.8 times more likely to be affected than those with GG or GC genotypes. The hypothesis about the influence of the OPG/RANK/nuclear factor-κB ligand (RANKL) pathway on the EARR process is also consistent with findings from knockout mouse models, in which a dramatic increase in EARR concurrent with orthodontic forces was observed when there was an imbalance in *OPG*/*RANKL*, suggesting that the OPG gene, or perhaps certain variations in its regulation/function, may be influencing EARR in some way.

In this connection, under permissive levels of receptor activator of RANKL and macrophage colony-stimulating factor (M-CSF), the transformation of odontoblasts or progenitors into resorbing odontoclasts was described in cells derived from dental papilla that are mainly found in the apical area, which is known to be a target for EARR. The authors suggested that RANKL is directly involved in inducing odontoblast-like cells to differentiate into odontoclast-like cells or to function as odontoclasts [39]. Other predisposing genetic markers have been found in the vitamin D receptor gene [40]. These variants have been associated with homeostatic imbalances of bone that could affect the pathological process of root resorption. This variation has been associated with affording some protection (for carriers of the C allele) against EARR during orthodontic treatment.

Finally, a hypothetical alternative or simultaneous regulatory pathway of EARR was recently explored and studied, focusing on the possible role of two specific epigenetic regulators in EARR during orthodontic treatment [41•]. The main role of histone deacetylases (HDACs) is to regulate transcription by removing acetyl groups from lysine residues in histone tails [42]. A recent meta-analysis found that specific HDAC gene variants are associated with bone remodeling disorders [5]. In this study, carriers of two copies of the least frequent allele of the rs228769 SNP in the *HDAC5* gene were significantly predisposed to develop EARR, compared to other genotypes.

To explain these findings, it should be borne in mind that variants in the intronic region of *HDAC5* were previously found to be highly associated with alterations in the bone mineral remodeling process, where HDAC5 is needed for TGF-β-mediated osteoblast differentiation, which occurs when Smad3 inhibits the function of Runx2 [43]. More closely connected to dental development, however, altered pulp cell differentiation was observed with accelerated mineralization when two HDAC inhibitors were administered [44]. More importantly, recent evidence, which surprisingly contrasts with these results, has contributed the insights that HDAC5 negatively regulates sclerostin levels secreted by osteocytes in vitro and in vivo and that sclerostin is an inhibitor of bone formation by osteoblasts [45]. Therefore, HDAC5 itself may indirectly be an enhancer of alveolar bone mineral density.

A suggested explanatory hypothesis would be that the HDAC5 genetic variant genotyped in this study induced a post-translational epigenetic modification in the sclerostin/MEF-2 pathway and hence a different dental root-alveolar bone scenario [46]. The osteocyte, regarded as the key regulatory cell in orthodontic tooth movement, would have a different gene expression pattern in orthodontic tooth movement induced in subjects homozygous for the rare allele G that would lead to the normal bone modeling/remodeling process being impaired. Meanwhile, odontoblast-like cells may respond in a contrary way, with reduced reparative capabilities on dentin and root surfaces. This may predispose to increased EARR secondary to orthodontic forces.

A study in a Chinese Han sample found that while sex and the amount of root movement were not risk factors for EARR, variation in *IL-6* rs1800796 is a risk factor for EARR [47]. This last study is a good example of how the relative frequency of polymorphic alleles for a specific SNP among different ethnic groups may affect the outcome of studies and hamper their comparison. In summary, support for treatment-related risk factors has varied among studies, with a longer of treatment being associated with increased likelihood of EARR being the most consistent.

It is likely that the genetic factors that influence EARR are heterogeneous, with different mechanisms in affected persons or even site-specific responses in the same person (Table 1) [56]. It has been put forth that incorporating this type of single gene variant into clinical practice is of benefit, although as would be expected, any single genetic factor that is associated with what is in most patients a complex trait, the benefit is questionable [57–59].

Treatment-Related Factors and Genetic Factors Influencing Human EARR

The occurrence of EARR concurrent with orthodontics is a complex trait contributed to by treatment-related and genetic factors. For example, 30 % of the EARR variability in one study from Portugal was explained by variation in or the presence of treatment duration, use of a Hyrax appliance for palatal expansion, closure of premolar extraction spaces, sex, and the *P2RX7* gene rs1718119 SNP, while age, overjet, tongue thrust, skeletal class II, and other genetic polymorphisms made minor contributions [37••]. A follow-up study found that sex, length of treatment, closure of premolar extraction space, use of a Hyrax appliance, and homozygosity/hemizygosity for variant C from the *IRAK1* gene were associated with EARR concurrent with orthodontia, the later *IRAK* polymorphism being a protective factor [51].

Table 1 Single nucleotide polymorphisms studied in conjunction with EARR

Single nucleotide polymorphisms studied in conjunction with EARR

Chr	Gene	Marker	Type of marker	Population tested	Results	Refs
2q14.1	*Interleukin-1α* (*IL-1α*; OMIM #147760)	rs1800587 (−889 C/T)	Promoter variation	35 White American families from Indiana, USA Families having at least two siblings who had received full-banded comprehensive orthodontic treatment; 2.82 years (±1.09 stdev) average length of treatment	No statistical association	[17]
2q14.1	*Interleukin-1α* (*IL-1α*; OMIM #147760)	rs1800587 (−889 C/T)	Promoter variation	45 sporadic EARR patients including two sibling pairs with EARR 44 controls All subjects from Aachen, Germany	The rs1800587 2/2 [T/T] genotype was associated with EARR compared to the control group ($p < 0.032$)	[48]
2q14.1	*Interleukin-1α* (*IL-1α*; OMIM #147760)	rs1800587 (−889 C/T)	Promoter variation	54 Caucasian orthodontic patients from Seville, Spain 25 individuals with EARR > 2 mm 29 controls	No statistical association $p = 0.09$	[30]
2q14.1	*Interleukin-1α* (*IL-1α*; OMIM #147760)	rs1800587 (−889 C/T)	Promoter variation	73 root-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) All patients were from Seville, Spain, and had undergone root canal treatment in a maxillary premolar but not in the contralateral tooth and had received comprehensive orthodontic treatment (straight-wire technique) at least 1 year later.	No statistical association of EARR with non-vital endodontically treated teeth	[49]
2q14.1	*Interleukin-1α* (*IL-1α*; OMIM #147760)	rs1800587 (−889 C/T)	Promoter variation	93 orthodontic patients from Seville, Spain 39 individuals with >2 mm of EARR on root-filled teeth after orthodontic treatment 54 controls	No statistical association of EARR with non-vital endodontically treated teeth	[50]
2q14.1	*Interleukin-1α* (*IL-1α*; OMIM #147760)	rs1800587 (−889 C/T)	Promoter variation	32 individuals with EARR of maxillary incisors (age 15.0 ± 4.1 years) 74 controls (age 15.2 ± 5.3 years) All individuals were white from Brno, Czech Republic; treated with fixed appliances	No statistical association	[31]
2q14.1	*Interleukin-1α* (*IL-1α*; OMIM #147760)	rs1800587 (−889 C/T)	Promoter variation	67 biologically unrelated Caucasians with moderate to severe EARR of maxillary incisors; 38 females and 29 males	No statistical association	[36••]

Table 1 (continued)

Single nucleotide polymorphisms studied in conjunction with EARR						
				67 age-matched and sex-matched biologically unrelated Caucasian controls All subjects from Northern Indiana, USA, received standard orthodontic treatment		
2q14.1	*Interleukin -1β* (*IL-1β*; OMIM #147720)	rs1143634 (+3954/+3953; C/T rev) *Allele 2 (T) associated with more IL-1 production (See [a, b, c])	Synonymous variant in exon 5 TTC → TTT Phe105Phe	35 White American families in Indiana, USA Families having at least two siblings who had received full-banded comprehensive orthodontic treatment 2.82 years (±1.09 stdev) average length of treatment	rs1143634 was linked to the EARR phenotype ($p = 0.0003$) Allele-1/Allele-1 (C/C) homozygous individuals showed a 5.6-fold increase risk of EARR > 2 mm (95 % CI 1.9–21.2) compared to C/T and T/T individuals	[17]
2q14.1	*Interleukin -1β* (*IL-1β*; OMIM #147720)	rs1143634 (+3954/+3953 C/T) *See note above	Synonymous variant in exon 5 TTC → TTT Phe105Phe	61 orthodontic patients from San Paulo, Brazil 23 affected individuals 38 control individuals EARR in the central and lateral maxillary incisors in the post-treatment period	Allele 1 (C) predisposed the subjects to EARR (OR = 4.0)	[35]
2q14.1	*Interleukin-1β* (*IL-1β*; OMIM #147720)	rs1143634 (+3954/+3953 C/T) *See note above	Synonymous variant in exon 5 TTC → TTT Phe105Phe	45 sporadic EARR patients including two sibling pairs with EARR 49 controls All subjects from Aachen, Germany	No statistical association Allele-1 (C) occurred slightly less often in the EARR-affected individuals compared to controls	[48]
2q14.1	*Interleukin-1β* (*IL-1β*; OMIM #147720)	rs1143634 (+3954/+3953 C/T) *See note above	Synonymous variant in exon 5 TTC → TTT Phe105Phe	54 Caucasian orthodontic patients from Seville, Spain 25 individuals with EARR > 2 mm 29 controls	Allele-1/Allele-1 (CC) homozygous individuals had an increased risk of post-orthodontic EARR (OR 3.48; $p = 0.027$; 95 % CI = 1.12–10.72)	[30]
2q14.1	*Interleukin-1β* (*IL-1β*; OMIM #147720)	rs1143634 (+3954/+3953 C/T) *See note above	Synonymous variant in exon 5 TTC → TTT Phe105Phe	73 root-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) All patients were from Seville, Spain and had undergone root canal treatment in a maxillary premolar but not in the contralateral tooth and had received comprehensive orthodontic treatment (straight-wire technique) at least 1 year later.	Homozygous subjects 2/2 [TT] had 2× the risk of post-orthodontic EARR in non-vital, endodontically treated teeth [OR, 2.032 ($p = 0.031$); 95 % CI = 1.99–14.77] when compared to control teeth with vital pulp. There was an increased predisposition of EARR for control teeth with vital pulp and control root-filled teeth when the subject is homozygous for allele-1 (C) [OR, 5.05 ($p = 0.002$)] and [OR, 2.77 ($p = 0.037$)], respectively.	[49]
2q14.1	*Interleukin-1β* (*IL-1β*; OMIM #147720)	rs1143634 (+3954/+3953 C/T) *See note above	Synonymous variant in exon 5 TTC → TTT Phe105Phe	93 orthodontic patients from Seville, Spain	Homozygous subjects (2/2 [TT] and 1/1 [CC]) had an increased risk of post-orthodontic EARR in	[50]

Table 1 (continued)

Single nucleotide polymorphisms studied in conjunction with EARR

				39 individuals with >2 mm of EARR on root-filled teeth after orthodontic treatment 54 controls	non-vital, endondontically treated teeth (odds ratio = 11.59; $p = 0.006$; 95 % CI = 1.36–98.64 and odds ratio = 2.54; $p = 0.035$; 95 % CI = 1.05–6.12), respectively	
2q14.1	*Interleukin-1β* (*IL-1β*; OMIM #147720)	rs1143634 (+3954/+3953 C/T) *See note above	Synonymous variant in exon 5 TTC → TTT Phe105Phe	32 individuals with EARR of maxillary incisors (age 15.0 ± 4.1 years) 74 controls (age 15.2 ± 5.3 years) All individuals were white from Brno, Czech Republic; treated with fixed appliances	No statistical association	[31]
2q14.1	*Interleukin-1β* (*IL-1β*; OMIM #147720)	rs1143634 (+3954/+3953 C/T) *See note above	Synonymous variant in exon 5 TTC → TTT Phe105Phe	195 total patients from Coimbra, Portugal (72 males and 123 female patients) 17.24 + 6.8 years old (average age + stdev); average treatment time was 36 ± 10 months Portuguese Caucasian origin with completed comprehensive orthodontic treatment (straight-wire technique); six teeth were assessed: the four maxillary incisors and the two maxillary canines	No statistical association	[37••, 51]
2q14.1	*Interleukin-1β* (*IL-1β*; OMIM #147720)	rs1143634 (+3954/+3953 C/T) *See note above	Synonymous variant in exon 5 TTC → TTT Phe105Phe	67 biologically unrelated Caucasians with moderate to severe EARR of maxillary incisors; 38 females and 29 males 67 age-matched and sex-matched biologically unrelated Caucasian controls All subjects from Northern Indiana, USA, received standard orthodontic treatment	No statistical association	[36••]
2q14.1-2	*Interleukin-1 receptor antagonist* (*IL-1RN*; OMIM #147679) Aliases: IL-1ra, IL-1RA	rs315952 (+390 T/C)	Synonymous variant in exon 4 AGT → AGC Ser130Ser	195 total patients from Coimbra, Portugal (72 males and 123 female patients) 17.24 + 6.8 years old (average age + stdev); average treatment time was 36 ± 10 months Portuguese Caucasian origin with completed comprehensive orthodontic treatment (straight-wire technique); six teeth were assessed: the four maxillary incisors and the two maxillary canines	No statistical association	[51]
2q14.1-2	*Interleukin-1 receptor antagonist* (*IL-1RN*; OMIM #147679) Aliases: IL-1ra, IL-1RA	rs419598 (C/T fwd)	Synonymous variant GCT → GCC Ala → Ala	54 Caucasian orthodontic patients from Seville, Spain 25 individuals with EARR > 2 mm 29 controls	Homozygous [1/1 (TT)] more likely to be affected with EARR (OR 6.75; $p = 0.001$; 95 % CI = 2.04–22.27).	[30]

Table 1 (continued)

Single nucleotide polymorphisms studied in conjunction with EARR						
2q14.1-2	*Interleukin-1 receptor antagonist* (*IL-1RN*; OMIM #147679) Aliases: IL-1ra, IL-1RA	rs419598 (C/T fwd)	Synonymous variant GCT → GCC Ala → Ala	93 orthodontic patients from Seville, Spain 39 individuals with >2 mm EARR following orthodontic treatment on root-filled teeth 54 individuals with no EARR or EARR ≤ 2 mm following orthodontic treatment on root-filled teeth	Subjects homozygous [1/1 (TT)] for rs419598 were at increased risk of EARR in root-filled teeth (OR 10.85; $p = 0.001$; CI 95 % 3.97–29.6)	[52]
2q14.1-2	*Interleukin-1 receptor antagonist* (*IL-1RN*; OMIM #147679) Aliases: IL-1ra, IL-1RA	rs419598 (C/T fwd)	Synonymous variant GCT → GCC Ala → Ala	Case-control study; 67 biologically unrelated Caucasians with moderate to severe EARR of maxillary incisors; 38 females and 29 males 67 age-matched and sex-matched biologically unrelated Caucasian controls All subjects from Northern Indiana, USA, received standard orthodontic treatment	No statistical association	[36••]
2q14.1-2	*Interleukin-1 receptor antagonist (IL-1RN*; OMIM #147679) Aliases: IL-1ra, IL-1RA	86-bp variable number tandem repeat (VNTR) in 2nd intron	Short allele 2 repeats (240 bp) Long alleles 3 (326 bp), 4 (412 bp), 5 (498 bp), and 6 (584 bp) repeats	32 individuals with EARR of maxillary incisors (age 15.0 ± 4.1 years) 74 controls (age 15.2 ± 5.3 years) All individuals were white from Brno, Czech Republic; treated with fixed appliances	IL1RN*12, *22 genotypes and the short (*2) allele were significantly associated with EARR in the subgroup of girls ($p = 0.04$ and $p = 0.02$, $p = 0.02$, respectively)	[31]
2q14.1-2	*Interleukin-1 receptor antagonist* (*IL-1RN*; OMIM #147679) Aliases: IL-1ra, IL-1RA	rs419598 (C/T fwd)	Synonymous variant GCT → GCC Ala → Ala	174 orthodontic patients within a Chinese Han population Left maxillary central incisors monitored for EARR in 3D during straight-wire orthodontic treatment; age range 12–34 years; average 20.55 ± 6.54 months in treatment	No statistical association	[47]
Xq28	*Interleukin-1 receptor-activated protein kinase* (*IRAK1*; OMIM #300283)	rs1059703 (+6434; C/T rev)	Non-synonymous variant in exon 12 TCG → TTG Ser532Leu	195 total patients from Coimbra, Portugal (72 males and 123 female patients) 17.24 + 6.8 years old (average age + stdev); average treatment time was 36 ± 10 months Portuguese Caucasian origin with completed comprehensive orthodontic treatment (straight-wire technique); six teeth were assessed: the four maxillary incisors and the two maxillary canines	Homozygosity and hemizygosity for the C-allele was protective for EARR ($p = 0.018$)	[51]
7p15.3	*Interleukin-6* (*IL-6*; OMIM #147620)	rs1800796 (−634 C/G)	Promoter variation	174 orthodontic patients within a Chinese Han population Left maxillary central incisors monitored for EARR in 3D during straight-wire orthodontic treatment; age range	GC individuals had an increased risk of EARR	[47]

Table 1 (continued)

Single nucleotide polymorphisms studied in conjunction with EARR

				12–34 years; average 20.55 ± 6.54 months in treatment		
6p12.2	*Interleukin-17A* (*IL-17A*; *OMIM #603149*)	rs2275913 (−197 G/A)	Promoter variation	Case-control retrospective study 99 Caucasian children of Czech origin 15.0 ± 4.7 (mean age ± standard deviation) 30 individuals with EARR of maxillary incisors (11 boys/19 girls) 69 unrelated controls (26 boys/43 girls)	No statistical association	[53]
11q22.3	Caspase-1 (CASP1; OMIM #147678); Alias interleukin-1 beta converting enzyme (ICE)	rs530537 (A/G rev)	Intronic variant	Case-control study; 67 biologically unrelated Caucasians with moderate to severe EARR of maxillary incisors; 38 females and 29 males 67 age-matched and sex-matched biologically unrelated Caucasian controls All subjects from Northern Indiana, USA, received standard orthodontic treatment	No statistical association	[36••]
11q22.3	Caspase-1 (CASP1; OMIM #147678); Alias interleukin-1 beta converting enzyme (ICE)	rs580253 (C/T rev)	Synonymous variant CTA → TTA Leu → Leu	67 biologically unrelated Caucasians with moderate to severe EARR of maxillary incisors; 38 females and 29 males 67 age-matched and sex-matched biologically unrelated Caucasian controls All subjects from Northern Indiana, USA received standard orthodontic treatment	No statistical association	[36••]
11q22.3	Caspase-1 (CASP1; OMIM #147678); Alias interleukin-1 beta converting enzyme (ICE)	rs554344 (C/G fwd)	Near 3′ end of the gene	67 biologically unrelated Caucasians with moderate to severe EARR of maxillary incisors; 38 females and 29 males 67 age-matched and sex-matched biologically unrelated Caucasian controls All subjects from Northern Indiana, USA, received standard orthodontic treatment	No statistical association	[36••]
12q24.31	*Purinergic-receptor-P2-X, ligand-gated ion channel 7* (*P2RX7*; OMIM #602566)	rs208294 (+489 C/T)	Non-synonymous variant CAT → TAT His155Tyr gain of function	67 biologically unrelated Caucasians with moderate to severe EARR of the maxillary incisors; 38 females and 29 males 67 age-matched and sex-matched biologically unrelated Caucasian controls All subjects from Northern Indiana, USA, received standard orthodontic treatment	Individuals with CC and CT were at higher risk for EARR than individuals with TT ($p = 0.002$)	[36••]
12q24.31	*Purinergic-receptor-P2-X, ligand-gated ion*	rs208294 (+489 C/T)	Non-synonymous variant CAT → TAT	Case-control retrospective study 99 Caucasian children of Czech origin		[53]

Table 1 (continued)

Single nucleotide polymorphisms studied in conjunction with EARR						
	channel 7 (*P2RX7*; OMIM #602566*)*		His155Tyr gain of function	15.0 ± 4.7 (mean age ± standard deviation) 30 individuals with EARR of maxillary incisors (11 boys/19 girls) 69 unrelated controls (26 boys/43 girls)	No association with individual SNP Association seen with rs208294 + rs1718119 haplotype and EARR	
12q24.31	*Purinergic-receptor-P2-X, ligand-gated ion channel 7* (*P2RX7*; OMIM #602566*)*	rs1718119 (+1068 G/A fwd)	Non-synonymous variant exon 11 GCT → ACT Ala348Thr gain of function	195 total patients from Coimbra, Portugal (72 males and 123 female patients) 17.24 + 6.8 years old (average age + stdev); average treatment time was 36 ± 10 months Portuguese Caucasian origin with completed comprehensive orthodontic treatment (straight-wire technique); six teeth were assessed: the four maxillary incisors and the two maxillary canines	The GG genotype for rs1718119 was significantly associated with EARR ($p < 0.01$)	[37••]
12q24.31	*Purinergic-receptor-P2-X, ligand-gated ion channel 7* (*P2RX7*; OMIM #602566)	rs1718119 (+1068 G/A fwd)	Non-synonymous variant in exon 11 GCT → ACT Ala348Thr gain of function	67 biologically unrelated Caucasians with moderate to severe EARR of the maxillary incisors; 38 females and 29 males 67 age-matched and sex-matched biologically unrelated Caucasian controls All subjects from Northern Indiana, USA, received standard orthodontic treatment	No statistical association	[36••]
12q24.31	*Purinergic-receptor-P2-X, ligand-gated ion channel 7* (*P2RX7*; OMIM #602566*)*	rs1718119 (+1068 G/A fwd)	Non-synonymous variant in exon 11 GCT → ACT Ala348Thr gain of function	Case-control retrospective study 99 Caucasian children of Czech origin 15.0 ± 4.7 (mean age ± standard deviation) 30 individuals with EARR of maxillary incisors (11 boys/19 girls) 69 unrelated controls (26 boys/43 girls)	No association with individual SNP Association seen with rs208294 + rs1718119 haplotype and EARR	[53]
12q24.31	*Purinergic-receptor-P2-X, ligand-gated ion channel 7* (*P2RX7*; OMIM #602566)	rs2230912 (A/G)	Non-synonymous variant in exon 13 CAG → CGG Gln460Arg	67 biologically unrelated Caucasians with moderate to severe EARR of the maxillary incisors; 38 females and 29 males 67 age-matched and sex-matched biologically unrelated Caucasian controls All subjects from Northern Indiana, USA, received standard orthodontic treatment	No statistical association	[36••]
18q21.33	*Tumor necrosis factor receptor superfamily member 11a* (*TNFRSF11A*; OMIM #603499) Alias: receptor	D18S64 D18S64 is tightly linked to TNFRSF11A	Microsatellite	38 American Caucasian families with a total of 79 siblings who completed comprehensive orthodontic treatment Evaluated EARR in the maxillary central incisors, the mandibular central incisors,	Linkage of maxillary central incisor EARR to microsatellite marker D18S64 (LOD = 2.5; $p = 0.02$)	[54]

Table 1 (continued)

Single nucleotide polymorphisms studied in conjunction with EARR

	activator of NF-KB (RANK)			and the mesial and distal roots of the mandibular first molars		
18q21.33	*Tumor necrosis factor receptor superfamily member 11a* (*TNFRSF11A*; OMIM #603499) Alias: receptor activator of NF-KB (RANK)	rs1805034 (C/T fwd)	Non-synonymous variant in exon 6 GCG → GTG Val192Ala	195 total patients from Coimbra, Portugal (72 males and 123 female patients) 17.24 + 6.8 years old (average age + stdev); average treatment time was 36 ± 10 months Portuguese Caucasian origin with completed comprehensive orthodontic treatment (straight-wire technique); six teeth were assessed: the four maxillary incisors and the two maxillary canines	No statistical association	[37••]
Chr	Gene	Marker	Type of SNP	Population tested	Biology	Refs
8q24.12	*Tumor necrosis factor receptor superfamily member 11b* (*TNFRSF11B*; OMIM #602643) Alias: osteoprotegerin (OPG)	rs2073618 (+1181 C/G)	Non-synonymous variant AAC → AAGAsn3-Lys	135 Caucasian subjects were studied from Indiana, USA; EARR >2 mm in at least one maxillary central incisor Mean age of the patients pretreatment was 14.6 ± 6.9 years (stdev); average treatment time was 1.6 ± 0.5 years (stdev)	G allele was associated with EARR ($p = 0.003$)	[7]
8q24.12	*Tumor necrosis factor receptor superfamily member 11b* (*TNFRSF11B*; OMIM #602643) Alias: osteoprotegerin (OPG)	rs3102735 (−163 A/G rev strand)	Promoter variation	195 total patients from Coimbra, Portugal (72 males and 123 female patients) 17.24 + 6.8 years old (average age + stdev); average treatment time was 36 ± 10 months Portuguese Caucasian origin with completed comprehensive orthodontic treatment (straight-wire technique); six teeth were assessed: the four maxillary incisors and the two maxillary canines	No statistical association	[37••]
8q24.12	*Tumor necrosis factor receptor superfamily member 11b* (*TNFRSF11B*; OMIM #602643) Alias: osteoprotegerin (OPG)	rs3102735 (−163 C/T fwd strand)	Promoter variation	Case-control retrospective study 99 Caucasian children of Czech origin 15.0 ± 4.7 (mean age ± standard deviation) 30 individuals with EARR of maxillary incisors (11 boys/19 girls) 69 unrelated controls (26 boys/43 girls)	No statistical association	[53]
8q24.12	*Tumor necrosis factor receptor superfamily member 11b* (*TNFRSF11B*; OMIM #602643) Alias:	rs2073618 (+1181 C/G)	Non-synonymous variant AAC → AAG Asn3Lys	Case-control retrospective study 99 Caucasian children of Czech origin 15.0 ± 4.7 (mean age ± standard deviation) 30 individuals with EARR of maxillary incisors (11 boys/19 girls)	No statistical association	[53]

Table 1 (continued)

Single nucleotide polymorphisms studied in conjunction with EARR

	osteoprotegerin (OPG)			69 unrelated controls (26 boys/43 girls)		
6p21.33	*Tumor necrosis factor alpha* (*TNFα*; OMIM #191160)	rs1800629 (−308 G/A)	Promoter variation	38 American Caucasian families with a total of 79 siblings who completed comprehensive orthodontic treatment. Evaluated EARR in the maxillary central incisors, the mandibular central incisors, and the mesial and distal roots of the mandibular first molars	No linkage identified	[54]
1p36.12	*Tissue-nonspecific alkaline phosphatase* (*TNSALP*; OMIM #171760) Alias: alkaline phosphatase, tissue-nonspecific isozyme (*ALPL*)	AL215L		38 American Caucasian families with a total of 79 siblings who completed comprehensive orthodontic treatment Evaluated EARR in the maxillary central incisors, the mandibular central incisors, and the mesial and distal roots of the mandibular first molars	No linkage identified	[54]
4q22.1	*Osteopontin* (*OPN*) Aliases: bone sialoprotein I (BSP-1/BNSP), secreted phosphoprotein 1 (SPP1, OMIM #166490)	rs11730582 (−443 T/C)	5′ near gene	87 Caucasian orthodontic patients from Seville, Spain 37 with EARR (>2 mm) 50 controls Mean length of orthodontic treatment 27.5 ± 8.3 months (stdev); EARR measured at the completion of orthodontic treatment	Allele-2/allele-2 [CC] increased risk of EARR (OR 11.68; $p < 0.039$; 95 % CI = 1.12–121.06) compared with other genotypes; Allele-1 [A] is protective for EARR (OR 0.20; $p = 0.025$; 95 % CI = 0.05–0.81)	[55]
4q22.1	*Osteopontin* (*OPN*) Aliases: bone sialoprotein I (BSP-1/BNSP), secreted phosphoprotein 1 (SPP1, OMIM #166490)	rs11730582 (−443 T/C)	5′ near gene	Case-control retrospective study 99 Caucasian children of Czech origin 15.0 ± 4.7 (mean age ± standard deviation) 30 individuals with EARR of maxillary incisors (11 boys/19 girls) 69 unrelated controls (26 boys/43 girls)	No statistical association	[53]
4q22.1	*Osteopontin* (*OPN*) Aliases: bone sialoprotein I (BSP-1/BNSP), secreted phosphoprotein 1 (SPP1, OMIM #166490)	rs9138 (+1239A/C)	3′ UTR	87 Caucasian orthodontic patients from Seville, Spain 37 with EARR (>2 mm) 50 controls Mean length of orthodontic treatment 27.5 ± 8.3 months (stdev); EARR measured at the completion of orthodontic treatment	Allele-2/allele-2 [CC] at increased risk of post-orthodontic EARR (OR 4.10; $p = 0.045$; 95 % CI = 1.03–16.35) Allele-1 [T] is protective for EARR (OR 0.035; $p = 0.035$' 95 % CI = 0.062–0.90)	[55]
4q22.1	*Osteopontin* (*OPN*) also known as bone sialoprotein I (BSP-1 or BNSP), secreted phosphoprotein 1	rs9138 (+1239 A/C)	3′ UTR	Case-control retrospective study 99 Caucasian children of Czech origin 15.0 ± 4.7 (mean age ± standard deviation)	No statistical association	[53]

Table 1 (continued)

Single nucleotide polymorphisms studied in conjunction with EARR						
	(SPP1, OMIM #166490)			30 individuals with EARR of maxillary incisors (11 boys/19 girls) 69 unrelated controls (26 boys/43 girls)		
12q13.11	*Vitamin D receptor* (*VDR*; OMIM #601769)	rs731236 (C/T; also termed TaqI)	Synonymous variant in exon 1 AAT → ATC Ile → Ile	377 Brazilian orthodontic patients diagnosed with class II Div 1 160 individuals with EARR ≤ 1.43 179 individuals with EARR > 1.43 38 untreated individuals Mean age, 14.9 years (range, 8–21 years); EARR measured after the first 6 months of treatment	CC + CT versus TT C allele was protective for EARR ($p = 0.091$; OR = 0.29, 95 % CI = 0.07–1.23)	[40]

[a] Reference related to rs1143634 influencing IL-1B production: Pociot F, Molvig J, Wogensen LW, Orsaae H, Nerup J. A Taq I polymorphism in the human interleukin-1 (IL-1) gene correlates with IL-1 secretion in vitro. Eur J Clin Invest 1992; 22:396–402

[b] Reference related to rs1143634 influencing IL-1B production: Iwasaki LR, Gibson CS, Crouch LD, Marx DB, Pandey JP, Nickel JC. Speed of tooth movement is related to stress and IL-1 gene polymorphisms. Am J Orthod Dentofacial Orthop 2006; 130. 698.e1–9

[c] Reference related to rs1143634 influencing IL-1B production: Latkovski G, Licis N, Kalnins U. C-reactive protein levels and common polymorphism of the interleukin-1 gene cluster and interleukin-6 gene in patients with coronary heart disease. Eur J Immunogenet 2004; 31:207–13

OR odds ratio, *CI* confidence interval

Likewise, in a study already mentioned for its association with *P2RX7* in the previous section, treatment factors such as the influence of treatment duration, numerous cephalometric measurements (pretreatment values and posttreatment change in values), extraction of maxillary premolars, as well as genotypes for multiple DNA polymorphisms were investigated for their influence on EARR. It was found that a longer length of treatment and specific genotypes for *P2RX7* SNP rs208294 together explained 25 % of the total variation associated with EARR concurrent with orthodontics in a North American Caucasian sample [36••]. The genetic findings in this study and the one from Portugal are particularly interesting since the protein products of the *P2RX7* and *IRAK* genes are involved in the IL1B pathway.

Osteoporosis, Tooth Movement, and EARR in Orthodontics

Transient or chronic imbalances in bone remodeling, caused by cellular over-activation or inhibition of the effector cells, osteoclasts, or osteoblasts, respectively, affect alveolar bone density in the case of the long bones. In this respect, the sex hormones act as potent regulators of bone metabolism, to the extent that the balance and rate of bone remodeling are even affected by an estrus cycle-dependent variation described in orthodontic tooth movement [60]. Tooth movement was described to be some 30 % greater in estrus than in pro-estrus ($p < 0.05$), with a negative correlation observed between estradiol levels and pyridinoline, TRAP activity, and also IL-1 and interleukin-6 (IL-6), which suggests that estrus cycle-dependent variations in tooth movement occur through their effects on bone resorption [61, 62].

In this respect, the effect of osteoporosis on orthodontic tooth movement has been extensively described in the literature at different levels. Estrogen withdrawal plays a critical role in the pathogenesis of post-menopausal osteoporosis, accelerating bone remodeling with a completely negative calcium balance [63, 64]. Diminished levels of estrogen correlate with unbalanced production of tumor necrosis factor α (TNF-α), receptor activator of RANKL, and IL-6. The cellular effects of estrogen are triggered by α and β estrogen receptors (Erα, ERβ), localized in osteoblasts and osteoclasts [64, 65]. Selective deletion of osteoclast-α receptors results in the increased proliferation and rate of survival of osteoclasts, leading to a dramatic loss of trabecular bone mass, while the constitutively active ERα in osteoblasts has the opposite effect, inducing the upregulation of osteoprotegerin (OPG) and IL-6 subsequently increasing bone mineral density in the femur [65, 66].

The knockout mouse model of ERα (ERKOα) showed a critical reduction in bone volume fraction and bone density irrespective of sex, indicating that ERα plays a central role in

controlling bone turnover [66]. Erα-deficient animals exhibit clearly impaired cellular apoptosis processes, with a simultaneous increase/decrease in osteoclast/osteoblast numbers, which leads to an uncoupled bone remodeling process favoring catabolic activity [67–69]. Moreover, the pro-resorptive phenotype observed in homozygous specimens with selective deletion of Erα has been associated with increased production of IL-33 as an ineffective counter-regulatory effect and increased levels of TNF-α and IL-1β in the periodontium [70]. Similarly, under OTM, ERαKO mice show an increase in the RANKL/OPG ratio, RANK, IL-6, and ST2, as well as decreased expression of dentin matrix acidic phosphoprotein and alkaline phosphatase in periodontal tissue [71]. Estrogen deficiency affects the rate of alveolar bone remodeling overall and secondarily the rate of experimental tooth movement, as shown in ovariectomized (OVX) rats undergoing lateral orthodontic tooth movement, where OVX specimens showed significantly ($p < 0.001$) increased rates of experimental tooth movement [64, 72].

The occurrence and severity of root resorption during orthodontic tooth movement in experimentally induced osteoporosis were also evaluated by some authors after 28 days of force application, analyzing root resorption craters, depth, and volume by using electron and laser scanning microscopes. Specifically, and most importantly, distal roots, those on the opposite side of the direction of tooth movement, were found to have resorption craters that were deeper and of greater volume than those observed in control animals in the cervical, middle, and apical thirds. The tooth movement was therefore not only faster in the experimentally induced osteoporosis group, but the severity of the root resorption was also found to be greater compared to the control group in those roots [73]. These results have however been questioned by other studies, which reported a similar acceleration in the tooth movement rate during orthodontic loading but found a reduced incidence of root resorption when assessed by histomorphometry in the roots near the alveolar bone and in the direction of the tooth movement [74].

Conclusion

Although EARR concurrent with orthodontic force is a complex trait, with multiple factors involving the reaction of the dental root, PDL, and alveolar bone to the force-induced strain on the root, it is clear that how all of these factors affect alveolar bone density has an effect on the degree and duration of strain on the dental root, leading to a cascade of resorption of the dental root. The combination of factors that may result in this complex trait appear to vary sample to sample and likely vary individual to individual, making a precise prediction of the occurrence of EARR unlikely, although with sufficient study, a relatively qualitative high, medium, or low risk may someday be possible to determine, although these would not be absolutes.

Acknowledgments • This study PI13/00310 was supported by the Instituto de Salud Carlos III (Plan Estatal de I+D+i 2013–2016) and co-financed by the European Development Regional Fund "A way to achieve Europe" (ERDF)

• USA NIH P30GM110788 COBRE III (LAM, JKH) and the University of Kentucky E. Preston Hicks Endowed Professorship (JKH).

Compliance with Ethical Standards

Conflict of Interest Alejandro Iglesias-Linares reports grants from Instituto de Salud Carlos III and ERDF during the conduct of the study. Lorri Morford reports grants from National Institutes of Health, during the conduct of the study. Jim Hartsfield reports grants from National Institutes of Health, during the conduct of the study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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