Original Article

Association between genetic polymorphisms and external apical root resorption: A systematic review and meta-analysis

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Objective: To date, only a few studies have investigated the relationships between genetic polymorphisms and external apical root resorption (EARR). Hence, the aim of this systematic review was to explore the relationship between different gene polymorphisms and their association with EARR. **Methods:** A complete literature search was conducted by two independent reviewers. The PubMed, Science Direct, and Scopus databases were searched. In addition, the bibliographies of all textbooks and relevant articles were searched manually. A meta-analysis was performed using data entered into the electronic databases until February 28, 2017. **Results:** On the basis of the search, we identified 17 and 7 publications for the systematic review and meta-analysis, respectively. Odds ratio (OR) was used to evaluate the association of the interleukin 1B (+3954) polymorphism and the risk of EARR. The overall OR from the studies was used to estimate the risk of EARR. However, no association was found and no publication bias was apparent for the risk of EARR in patients receiving orthodontic treatment. **Conclusions:** More research on the relationship between gene polymorphism and EARR is necessary to determine better specificity of possible interactions.
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Key words: Genetics, Root resorption, Tooth movement, Evidence-based orthodontics

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INTRODUCTION

External apical root resorption (EARR) is an adverse effect of orthodontic treatment in most of the patients, which results in the permanent loss of tooth structure from the root apex. Not only due to orthodontic treatment, the incidence of functional root resorption can also be found at the age of 32 to 50 years.[1] Few studies have documented extreme resorption sequelae that might negatively affect the patients.

Root resorption is considered an important adjunct effect of orthodontic treatment, which may start in any stage of treatment. Root resorption is usually initiated between the second and fifth weeks of orthodontic treatment, but it can only be identified on radiographs after 3 to 4 months.[2] Although many characteristics of root resorption remain unclear, it is considered a complicated biological process, which occurs when forces generated at the root apex surpass the resistance and reparative capability of the periapical tissues. The progress and severity of EARR are exaggerated by various risk factors.[3]

In 1997, Harris et al.[4] conducted the first study on the genetic influence on EARR. Thereafter, various genetic association studies have been conducted on the interrelationship between EARR and orthodontic treatment.[5-10]

A few studies documented the association of different genes, such as interleukin 1 (IL-1A, IL-1B, and IL-RN), vitamin D receptor, tumor necrosis factor-α, TNSALP, TNFRSF11A, and osteopontin, with EARR during orthodontic treatment.[5,6,10] Moreover, various studies have aimed to investigate the association between gene polymorphisms and the risk of EARR during orthodontic treatment. However, the outcomes of these studies have been contradictory.

Therefore, the aim of this systematic review and meta-analysis was to determine whether these gene polymorphisms are associated with EARR during orthodontic treatment.

MATERIALS AND METHODS

This systematic review adhered to the PRISMA guidelines (Figure 1). Moreover, to better outline the study, the participants, interventions, comparisons, outcomes, and study designs (PICOS) format was followed.[11] Literature search was conducted on the PubMed, Science Direct, and Scopus databases (studies included until February 28, 2017) by using the following key words: "Gene, Polymorphism, EARR, external apical root resorption, and orthodontic treatment." No restrictions were imposed on population, language, sample size, and treatment duration. All suitable articles were selected and their references were rechecked for any relevant articles overlooked during the electronic searches.

The inclusion criteria for the published articles were as
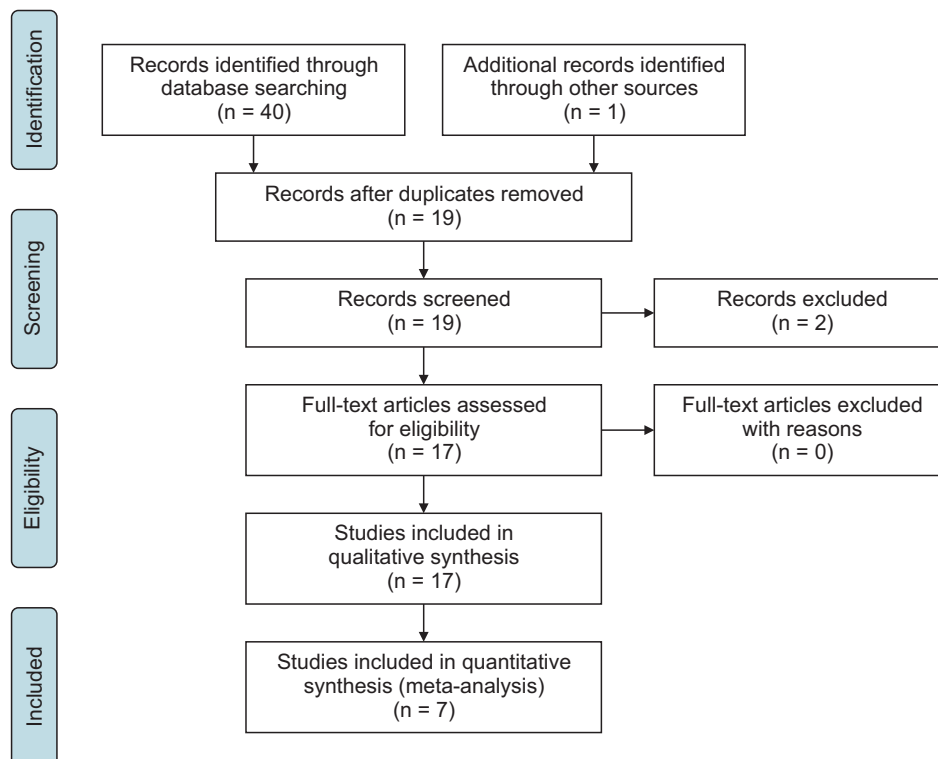
Figure 1. Flow chart of the PRISMA guidelines for study selection.

Table 1. Main characteristics of the included studies

No	Study (year)	Country	Ethnicity	Sample size (n)	Radiographs used	Genotype method	Biological marker	Outcome
1	Fontana et al. (2012)[6]	Brazil	White	377	Peri-apical	TaqI	VDR	Vitamin D receptor TaqI polymorphism were associated with EARR in orthodontic patients.
2	Guo et al. (2016)[16]	China	Chinese	174	CBCT	Taq-man	IL-6 and IL-RN	IL-6 SNP GC is a risk factor for EARR.
3	Al-Qawasmi et al. (2003)[30]	USA	Caucasian	38 families total 79 siblings	Lateral cephalogram and OPG	Not specified	TNF-α, TNFRSF11A, and TNSALP	TNFRSF11A locus, or another tightly linked gene, is associated with EARR.
4	Al-Qawasmi et al. (2003)[5]	USA	Caucasian	118 subjects from 35 families	Lateral cephalogram and OPG	Ncoi and TaqI	IL-1A and IL-1B	IL-1B gene, known to decrease the production of IL-1 cytokine in vivo, significantly increases the risk of EARR.
5	Bastos Lages et al. (2009)[17]	Brazil	White Brazilian	61	Periapical	TaqI	IL-1B	The polymorphism of the IL-1B gene is associated with root resorption.
6	Linhartova et al. (2017)[31]	Czech Republic	Caucasian children of Czech origin	99	Lateral cephalogram and OPG	Taq-man	IL-17, SPP1, P2RX7, and TNFRSF11B	Effect of IL-17, P2RX7, SPP1, or TNFRSF11B SNPs themselves on the development of EARR was not confirmed in the Czech population.
7	Iglesias-Linares et al. (2012)[18]	Spain	White	93	Lateral cephalogram and OPG	HotStar Taq polymerase	IL-1A and IL-1B	The development of EARR in subjects with root-filled teeth who undergo orthodontic treatment might be attributable to genetic variations in the IL-1B gene.
8	Iglesias-Linares et al. (2012)[8]	Spain	Not mentioned	146	Lateral cephalogram and OPG	HotStar Taq polymerase	IL-1A and IL-1B	Genetic inheritance of IL-1B gene, in homozygous subjects is associated with a two times increased predisposition to have EARR secondary to orthodontic tooth movement in endodontically treated teeth.
9	Iglesias-Linares et al. (2013)[20]	Spain	Caucasian	93	Lateral cephalogram and OPG	HotStar Taq polymerase	IL-1RN	IL1RN gene associated with an increased risk of suffering post-orthodontic EARR in root-filled teeth.
10	Iglesias-Linares et al. (2014)[9]	Spain	Caucasian	87	Lateral cephalogram and OPG	Not mentioned	Osteopontin	Variations in the osteopontin gene are determinants of a genetic predisposition to suffer EARR secondary to orthodontic treatment.
11	Iglesias-Linares et al. (2012)[19]	Spain	White	54	Lateral cephalogram and OPG	HotStar Taq polymerase	IL-1A, IL-1B, and IL-1RN	Not only in the IL-1B gene are determinants of a predisposition to postorthodontic EARR.

Table 1. Continued

No	Study (year)	Country	Ethnicity	Sample size (n)	Radiographs used	Genotype method	Biological marker	Outcome
12	Linhartova et al. (2013)[24]	Czech Republic	Not mentioned	106	Lateral cephalogram and OPG	Ncoi, TaqI and VNTR-PCR	IL-1A, IL-1B, and IL-1RN	No significant role of IL-1A and IL1B variants in EARR was confirmed, IL-1RN VNTR may be associated with EARR, especially in girls.
13	Pereira et al. (2014)[21]	Portugal	Portuguese Caucasian	195	OPG	AseI, TaqI and Taq-man	P2RX7, IL-1B, TNFRSF11B, OPG, and TNFRSF11A, RANK	This study highlights the P2RX7 gene as a possible factor of susceptibility to EARR.
14	Pereira et al. (2016)[22]	Portugal	Portuguese Caucasian	195	OPG	TaqI and Taq-man	IL-1B, IL-1RN and IRAK1	IRAK1 polymorphism is proposed as a protective variant for EARR.
15	Sharab et al. (2015)[23]	USA	Caucasian	460	Lateral cephalogram, OPG and occlusal	Not mentioned	P2RX7, CASP1, IL-1B, IL-1A and IL-1RN	EARR occurrence was associated with both genetic and treatment-related variables, which together explained 25% of the total variation associated with EARR in the sample tested.
16	Tomoyasu et al. (2009)[10]	Japan	Japanese	54	Cephalometric radiographs	Sequence	IL-1B	No significant difference in the frequency of the IL-1B polymorphism between EARR cases and controls in the Japanese population.
17	Gülden et al. (2009)[7]	German	Not mentioned	258	OPG	Ncoi and TaqI	IL-1A and IL-1B	IL-1A polymorphism point to an association of the genotype 2-2 with EARR and IL-1B polymorphism in patients revealed no indication of a predisposition of EARR.

VDR, Vitamin D receptor; EARR, external apical root resorption; CBCT, cone-beam computed tomography; IL, interleukin; SNP, single nucleotide polymorphism; OPG, osteoprotegerin; TNF, tumor necrosis factor; VNTR, variable number tandem repeat.

follows: 1) association between genetic polymorphisms and the risk of EARR and 2) genotypes determined by calculating the odds ratios (ORs). Moreover, 1) studies with duplication of data, 2) review articles, and 3) studies with insufficient data were excluded. Two reviewers independently reviewed all the articles and selected the studies on the basis of the inclusion and exclusion criteria. No disagreement occurred between the two reviewers. The studies were selected for the systematic review when they fulfilled the appropriate criteria.

For quality evaluation, the strengthening the reporting of genetic association (STREGA) statement and checklist were followed.[12] Methodologic quality scores were calculated and ranged from 0 (lowest) to 20 (highest). Studies with scores < 10 were considered low-quality studies and those with scores ≥ 10 were considered high-quality studies.

A meta-analysis was performed on the basis of the association of a similar gene (IL-1B [+3954]) with the EARR outcomes of selected studies.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Co., Armonk, NY, USA) and Comprehensive Meta-Analysis (CMA) Software version 3 (Biostat, Englewood, NJ, USA). To assess the interobserver agreement of the grading qualities of the studies, Cohen's kappa analysis was performed to identify the quality of the studies. The level of agreement was graded according to the kappa scores, with 0.81–1, 0.61–0.80, 0.41–0.60, 0.21–0.40, and < 0.20 indicating near perfect, substantial, moderate, fair, and poor agreement, respectively.[13]

ORs with corresponding 95% confidence intervals were used to estimate the power of the association between EARR and gene polymorphisms. A dominant model (CC + CT vs. TT), co-dominant model (CC vs. TT or CT vs. TT), and recessive model (CC vs. CT + TT) were

used to obtain the pooled OR. Residuals were checked for suspected outliers in each study. Heterogeneity was tested using Q statistics and I^2 statistics. $I^2 < 50\%$ and a p-value of Q statistics > 0.10 indicated a lack of heterogeneity across the studies.

Publication bias was estimated using the funnel plot, wherein an asymmetric plot indicated possible bias. Begg's[14] and Egger's test[15] methods were used for assessing the funnel plot. A p-value < 0.05 was considered to indicate the presence of bias among the studies, and a p-value > 0.05 was considered to indicate the opposite.

RESULTS

The PRISMA guidelines were strictly followed to select the articles as presented in Figure 1. The total number of articles identified for this study was 40: 14 from PubMed, 14 from Scopus, and 12 from Science Direct, after being confirmed by the two independent reviewers. One article was included after manually searching the bibliographies of all the relevant articles. After removing duplicates, 19 publications were selected for the current study. Two studies were further excluded as they did not meet the inclusion criteria. After excluding the duplicates and including the manually searched article, a total of 17 articles were finally included in the systematic review (Table 1) and 7 were included in the meta-analysis (Table 2).

Quality assessment of the selected studies for this systematic review according to the STREGA guidelines[14,15] was performed by two independent reviewers. Among the 17 selected studies, 11 were classified as high-quality studies (≥ 10) and 6 as low-quality studies (< 10) (Table 3). Inter-rater reliability for these five criteria was 0.728, which represented a substantial level of agreement. Cohen's kappa score for most of the criteria showed the absolute level of inter-rater agreement (Table 4).

Table 2. Characteristics of the studies included in the meta-analysis

No	Author (year)	Country	Case/Control	EARR (> 2 mm)			Control (< 2 mm)		
				CC	CT	TT	CC	CT	TT
1	Bastos Lages et al. (2009)[17]	Brazil	23/38	11 (18.0)	7 (11.5)	5 (8.2)	6 (9.8)	12 (19.7)	20 (32.8)
2	Iglesias-Linares et al. (2012)[8]	Spain	30/43	24 (32.9)	5 (6.8)	1 (1.4)	19 (26.0)	17 (23.3)	7 (9.6)
3	Iglesias-Linares et al. (2012)[18]	Spain	39/54	28 (71.8)	4 (10.3)	7 (17.9)	27 (50.0)	26 (48.1)	1 (1.9)
4	Linhartova et al. (2013)[24]	Czech Republic	32/74	18 (56.3)	12 (37.5)	2 (6.3)	38 (51.4)	32 (43.2)	4 (5.4)
5	Sharab et al. (2015)[23]	USA	67/67	37 (55.2)	26 (38.8)	4 (6.0)	44 (65.7)	21 (31.3)	2 (3.0)
6	Gülden et al. (2009)[7]	German	45/49	17 (37.8)	26 (57.8)	2 (4.4)	28 (57.1)	16 (36.4)	5 (10.2)
7	Iglesias-Linares et al. (2012)[19]	Spain	25/29	17 (31.8)	8 (14.8)	0 (0)	11 (20.4)	16 (29.6)	2 (3.7)

Values are presented as number only or number (%).
EARR, External apical root resorption.

Table 3. Quality assessment of the included studies

No	Author (year)	Selection	Comparability	Exposure	Study methodologies	Genetic analysis	Score
1	Fontana et al. (2012)[6]	** (2)	* (1)	* (1)	** (2)	***** (5)	12
2	Guo et al. (2016)[16]	** (2)	0	* (1)	** (2)	**** (4)	9
3	Al-Qawasmi et al. (2003)[30]	* (1)	0	0	* (1)	***** (5)	7
4	Al-Qawasmi et al. (2003)[5]	* (1)	0	0	* (1)	***** (5)	7
5	Bastos Lages et al. (2009)[17]	*** (3)	* (1)	** (2)	* (1)	***** (5)	12
6	Linhartova et al. (2017)[31]	*** (3)	* (1)	** (2)	** (2)	****** (6)	14
7	Iglesias-Linares et al. (2012)[18]	**** (4)	* (1)	* (1)	** (2)	***** (5)	13
8	Iglesias-Linares et al. (2012)[8]	**** (4)	* (1)	* (1)	** (2)	***** (5)	13
9	Iglesias-Linares et al. (2013)[20]	**** (4)	* (1)	** (2)	** (2)	****** (6)	15
10	Iglesias-Linares et al. (2014)[9]	**** (4)	* (1)	** (2)	** (2)	****** (6)	15
11	Iglesias-Linares et al. (2012)[19]	**** (4)	* (1)	* (2)	** (2)	***** (4)	13
12	Linhartova et al. (2013)[24]	**** (4)	* (1)	** (2)	** (2)	****** (6)	15
13	Pereira et al. (2014)[21]	* (1)	0	0	* (1)	****** (6)	8
14	Pereira et al. (2016)[22]	* (1)	0	0	* (1)	****** (6)	8
15	Sharab et al. (2015)[23]	**** (4)	* (1)	** (2)	* (1)	****** (6)	14
16	Tomoyasu et al. (2009)[10]	*** (3)	0	0	** (2)	***** (5)	10
17	Gülden et al. (2009)[7]	** (2)	0	0	* (1)	*****(5)	8

Table 4. Inter-rater agreement of quality assessment by using Cohen's kappa analysis

Quality assessment	Measure of agreement between raters
Selection	1
Comparability	0.876
Exposure	0.825
Study methodologies	1
Genetic analysis	1

Kappa score = 0.728.

The analysis of the association of EARR risk with the IL-1B (+3954) polymorphism showed that none of the dominant, co-dominant, and recessive models were associated with the risk of EARR. Moreover, although a less-expected frequency residual was detected because of a sampling error, it could still be included in the meta-analysis in the random-effect model without heavily influencing the outcome (Figures 2–5 and Table 5).

Both clinical and statistical heterogeneity were observed among the studies in the dominant, co-dominant, and recessive models (Table 6). Sensitivity analysis was performed after omitting one study at each step to observe the influence of each study on the pooled OR. However, the heterogeneity persisted irrespective of which study was omitted.

No evidence of publication bias was observed while comparing the IL-1B (+3954) polymorphism with the overall risk of EARR included in the meta-analysis (Figure 6 and Table 7).

DISCUSSION

In this systematic review, 11 of the 17 studies were classified as high-quality studies and 6 as low-quality studies. Many studies suggested that genetic polymorphisms may be associated with EARR.[6,8,16-23] However, few studies opposed this association.[7,10,24] The STREGA guidelines were formulated for conducting genetic-association studies to ensure they could attain a score of 20 regardless of the outcome.[12] However, in the current systematic review, none of the 11 studies classified as high-quality studies (score ≥ 10) could attain a score of 20. In contrast, the low-quality studies (score < 10) failed to fulfill the minimum categories of the STREGA guidelines, which might lead to a biased outcome in genetic-association studies. Most of the genetic studies associated with orthodontic treatment rarely comply with the STREGA or any other genetic guidelines. Therefore, specific studies may introduce bias owing to methodological inaccuracies.

A previous study revealed that under the same mechanical stress during orthodontic treatment, many subjects showed a low resistance to EARR, whereas

CC vs. TT

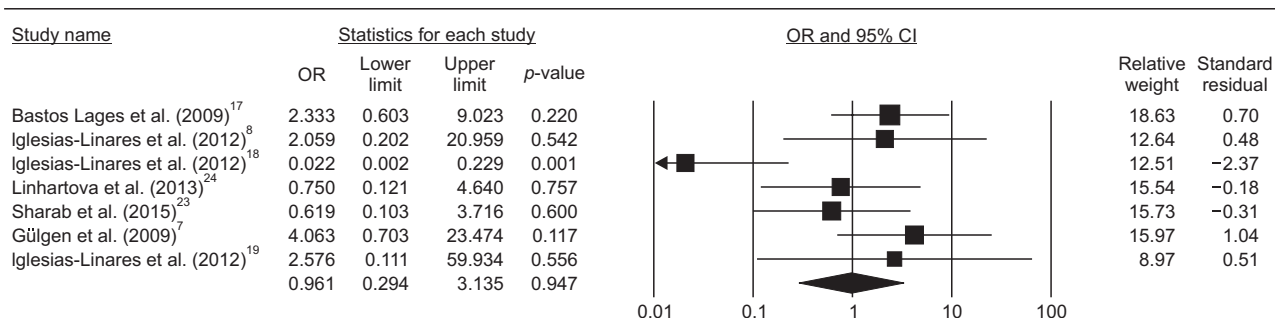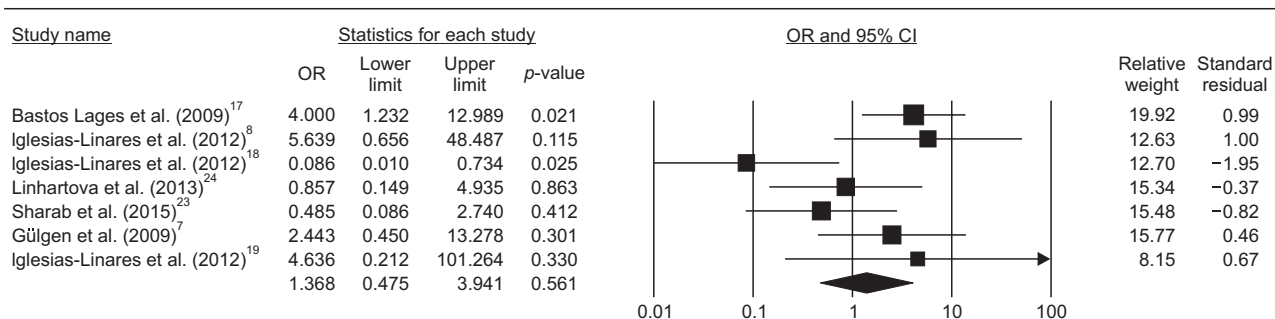| Study name	Statistics for each study				OR and 95% CI	Relative weight	Standard residual
	OR	Lower limit	Upper limit	p-value			
Bastos Lages et al. (2009)[17]	7.333	1.815	29.630	0.005		18.07	1.20
Iglesias-Linares et al. (2012)[8]	8.842	1.000	78.221	0.050		13.09	1.11
Iglesias-Linares et al. (2012)[18]	0.148	0.017	1.286	0.083		13.20	−1.59
Linhartova et al. (2013)[24]	0.947	0.159	5.661	0.953		15.46	−0.40
Sharab et al. (2015)[23]	0.420	0.073	2.426	0.333		15.68	−1.00
Gülgen et al. (2009)[7]	1.518	0.265	8.709	0.640		15.72	−0.06
Iglesias-Linares et al. (2012)[19]	7.609	0.334	173.379	0.203		8.77	0.81
	1.637	0.516	5.191	0.403			

0.01 0.1 1 10 100

Figure 2. Forest plots of external apical root resorption risk associated with the interleukin-1B polymorphism (CC vs. TT). OR, Odds ratio; 95% CI, 95% confidence interval.

CT vs. TT

Study name	Statistics for each study				OR and 95% CI	Relative weight	Standard residual
	OR	Lower limit	Upper limit	p-value			
Bastos Lages et al. (2009)[17]	2.333	0.603	9.023	0.220		18.63	0.70
Iglesias-Linares et al. (2012)[8]	2.059	0.202	20.959	0.542		12.64	0.48
Iglesias-Linares et al. (2012)[18]	0.022	0.002	0.229	0.001		12.51	−2.37
Linhartova et al. (2013)[24]	0.750	0.121	4.640	0.757		15.54	−0.18
Sharab et al. (2015)[23]	0.619	0.103	3.716	0.600		15.73	−0.31
Gülgen et al. (2009)[7]	4.063	0.703	23.474	0.117		15.97	1.04
Iglesias-Linares et al. (2012)[19]	2.576	0.111	59.934	0.556		8.97	0.51
	0.961	0.294	3.135	0.947			

0.01 0.1 1 10 100

Figure 3. Forest plots of external apical root resorption risk associated with the interleukin-1B polymorphism (CT vs. TT). OR, Odds ratio; 95% CI, 95% confidence interval.

CC + CT vs. TT

Study name	Statistics for each study				OR and 95% CI	Relative weight	Standard residual
	OR	Lower limit	Upper limit	p-value			
Bastos Lages et al. (2009)[17]	4.000	1.232	12.989	0.021		19.92	0.99
Iglesias-Linares et al. (2012)[8]	5.639	0.656	48.487	0.115		12.63	1.00
Iglesias-Linares et al. (2012)[18]	0.086	0.010	0.734	0.025		12.70	−1.95
Linhartova et al. (2013)[24]	0.857	0.149	4.935	0.863		15.34	−0.37
Sharab et al. (2015)[23]	0.485	0.086	2.740	0.412		15.48	−0.82
Gülgen et al. (2009)[7]	2.443	0.450	13.278	0.301		15.77	0.46
Iglesias-Linares et al. (2012)[19]	4.636	0.212	101.264	0.330		8.15	0.67
	1.368	0.475	3.941	0.561			

0.01 0.1 1 10 100

Figure 4. Forest plots of external apical root resorption risk associated with the interleukin-1B polymorphism (CC+CT vs. TT). OR, Odds ratio; 95% CI, 95% confidence interval.
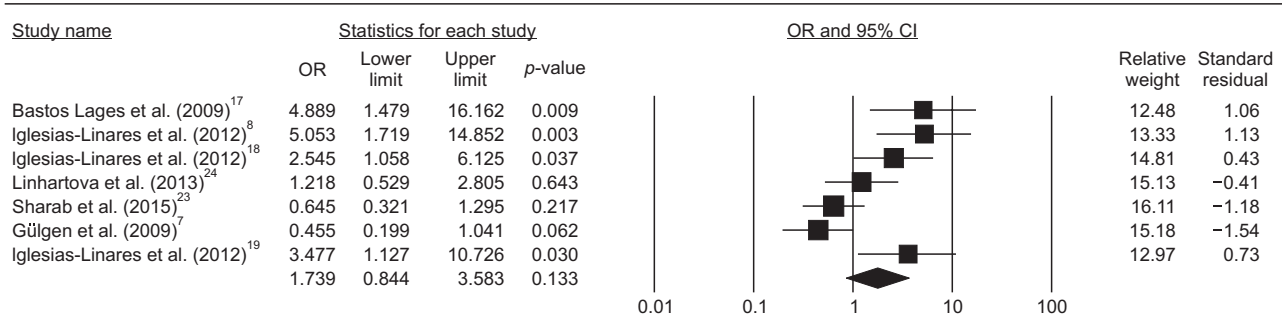
others experienced severe EARR.[4] In this respect, many researchers investigated a possible link between polymorphic targets in different genes and the association of EARR with orthodontic treatment.[7-9] The current systematic review showed that 15 of the 17 studies aimed to determine the association of IL-1 cluster genes with EARR.

Cytokines have been revealed to disturb bone remodeling and are presently assumed to play a vigorous role in both physiological and pathological bone regulation. Many cells are involved in bone resorption and formation, including osteoclasts, osteoblasts, and bone marrow cells.[25,26] IL-1 is one of the most important monocyte-macrophage-derived cytokines that acts as a potent stimulator of bone resorption in organ culture.[27] IL-1 has been verified to stimulate bone resorption both *in vitro* and *in vivo*.

At present, the IL-1B (+3954) gene polymorphism

CC vs. CT + TT

Study name	OR	Lower limit	Upper limit	p-value	OR and 95% CI	Relative weight	Standard residual
Bastos Lages et al. (2009)[17]	4.889	1.479	16.162	0.009		12.48	1.06
Iglesias-Linares et al. (2012)[8]	5.053	1.719	14.852	0.003		13.33	1.13
Iglesias-Linares et al. (2012)[18]	2.545	1.058	6.125	0.037		14.81	0.43
Linhartova et al. (2013)[24]	1.218	0.529	2.805	0.643		15.13	−0.41
Sharab et al. (2015)[23]	0.645	0.321	1.295	0.217		16.11	−1.18
Gülgen et al. (2009)[7]	0.455	0.199	1.041	0.062		15.18	−1.54
Iglesias-Linares et al. (2012)[19]	3.477	1.127	10.726	0.030		12.97	0.73
	1.739	0.844	3.583	0.133			

Figure 5. Forest plots of external apical root resorption risk associated with the interleukin–1B polymorphism (CC vs. CT+TT). OR, Odds ratio; 95% CI, 95% confidence interval.

Table 5. Association of the risk of external apical root resorption with the interleukin 1B (+3954) polymorphism

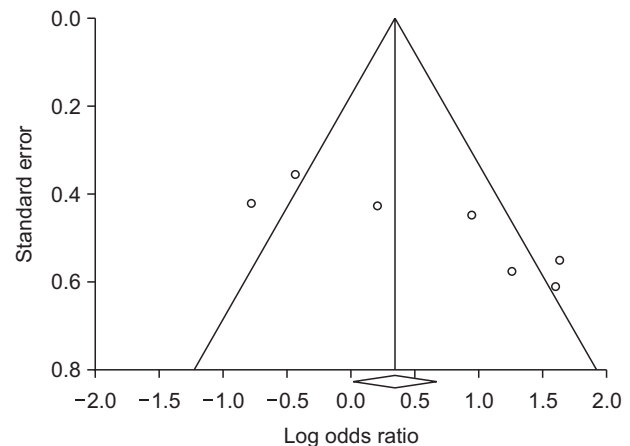| Genotype	OR	95% CI	p-value
CC vs. TT	1.637	0.516–5.191	0.403
CT vs. TT	0.961	0.294–3.135	0.947
CC + CT vs. TT	1.368	0.475–3.941	0.561
CC vs. CT + TT	1.739	0.844–3.583	0.133

OR, Odds ratio; 95% CI, 95% confidence interval.

Table 6. Test of heterogeneity among the studies

Model	Q statistics	p-value*	I² statistics (%)
CC vs. TT	15.051	0.020	60.136
CT vs. TT	15.140	0.019	60.371
CC + CT vs TT	13.799	0.032	56.520
CC vs. CT + TT	25.881	0.000	76.917

*p-value for Q statistics.

Figure 6. Funnel plot for the publication bias test (CT vs. TT).

Table 7. Publication bias among the studies

Genotype	Begg's test	Egger's test
CC vs. TT	0.326	0.401
CT vs. TT	0.146	0.231
CC + CT vs. TT	0.326	0.269
CC vs. CT + TT	0.060	0.135

has been documented as a high-risk factor associated with EARR.[5] Patients who are homozygous for the IL-1B (+3954) allele 1 have a 95% probability of developing root resorption of more than 2 mm.[28] Among the 17 articles selected for this systematic review, 14 were conducted to determine the association between IL-1 and IL-1B (+3954) polymorphisms and EARR. Owing to their similar methodology, 7 studies were selected for this meta-analysis to determine the relationship between the IL-1B (+3954) gene polymorphism and EARR. The pooled result showed a negative association between EARR and the IL-1B (+3954) gene polymorphism. A small sample size, inclusion of different ethnic groups, and other confounding factors might be the reasons behind this insignificant association. The studies included in this meta-analysis had sample sizes less than 100, except for 2 studies. Moreover, 5 of 7 studies were conducted in different ethnic groups, and the frequency of geno-

types varied among ethnicities. In addition, confounding factors such as sex, treatment modalities, duration of treatment, smoking, diabetes, and body mass index may influence the occurrence of EARR, but these were not considered in this study; therefore, the outcome may be inaccurate. In addition, different radiography techniques, such as lateral cephalography, orthopantomography, and cone beam computed tomography, were used for measuring the EARR in different studies. The different precisions of these different radiography techniques may affect the outcome of the analyses. Iglesias-Linares et al.[8] conducted three different studies using IL-1B (+3954) and EARR aiming to obtain different outcomes.

Although the ethnic groups, genotyping methods, and biological markers were identical in the aforementioned studies, the sample sizes and objectives were different, and this resulted in the different outcomes.[8,22,23]

Although only some studies found a positive association between IL-1B gene polymorphisms and EARR, the negative result of this meta-analysis will be a matter of argument. Therefore, we conducted statistical heterogeneity tests by using I^2 and Q statistics, which indicated that the significant heterogeneity observed in the current meta-analysis may alternatively suggest a bias in the design of some of the analyzed studies.[29] Nevertheless, clinical heterogeneity is always present in a meta-analysis and is based on the sample size, study design, intervention, and outcomes. The current meta-analysis also represented clinical heterogeneity based on the ethnic background, sample size, genotyping methods, and outcomes.

EARR is a common phenomenon after orthodontic treatment.[23,30,31] Therefore, assessing the risk of developing EARR after orthodontic treatment is an important factor for successful treatment. Progression of EARR is a multifactorial event. The results of the current systematic review and meta-analysis may, together with further research, support that several genes are closely associated with EARR. Monitoring and screening for EARR risk in patients receiving orthodontic treatment are valuable components for ensuring more effective control and prevention of EARR.

CONCLUSION

- The outcome of this systematic review shows that different gene polymorphisms may indicate the occurrence of EARR in some individuals undergoing orthodontic treatment.
- The present study also proposes certain recommendations for prospective researchers assessing gene polymorphisms in patients receiving orthodontic treatment.
- The meta-analysis suggested that the IL-1B polymorphism is not associated with a predisposition to EARR, but there was significant heterogeneity among the study results. However, the heterogeneity among the published studies remains inexplicable.
- Although IL-1B is considered a promising gene for predicting EARR in patients receiving orthodontic treatment, further better-controlled studies are warranted to verify this association.

CONFLICTS OF INTEREST

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

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