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Meta-analysis of the association between common interleukin-1 polymorphisms and dental implant failure

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Abstract Interleukin-1 (IL) plays a pivotal role in immune–inflammatory response that maintains periodontal homeostasis. A number of epidemiological studies have been conducted to investigate the associations between common polymorphisms of *IL-1* (*IL-1A*, *IL-1B*) genes and risk of peri-implant disease, but the findings remain inconclusive. Thirteen studies evaluating the association between IL-1 polymorphisms and risk for peri-implant diseases (implant failure/loss, peri-implantitis) were included. Fixed model or random-effects models were applied to calculate overall and ethnicity-specific summary odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) as risk estimates for *IL-1* polymorphisms individually or in combination. Heterogeneity and publication bias were evaluated by Q-test, I^2 statistic, Begg's funnel plot and Egger's test accordingly. The composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) was associated with increased risk of implant failure/loss (OR 1.76, 95 % CI 1.21–2.57) and peri-implantitis (OR 2.34, 95 % CI 1.03–5.33). The significance was borderline in European descents (implant failure/loss: OR 1.48, 95 % CI 0.99–2.22; peri-implantitis: OR 1.65, 95 % CI 1.00–2.73). T allele of *IL-1B* (−511) was associated with increased risk of implant failure/loss (OR 1.28, 95 % CI 1.01–1.62), while the association was not significant in European descents (OR 1.12, 95 % CI 0.85–1.48). These findings support a potential role of *IL-1* polymorphisms, particularly the composite genotype of *IL-1A* (−889) and *IL-1B* (+3954), in peri-implant disease susceptibility. More studies with large sample size are needed to validate the associations.

Keywords IL-1 polymorphism · Genotype · Peri-implant disease · Peri-implantitis · Implant failure

Abbreviations

IL-1	Interleukin-1
CI	Confidence interval
HWE	Hardy–Weinberg equilibrium
OR	Odds ratio

Introduction

Use of dental implant has become popular since Branemark and his colleagues introduced the dental titanium implants in 1982. This trend is expected to continue at a rapid rate over the next decades. Dental implants are now the most chosen option for oral rehabilitation in edentulous and partially dentate patients because of its high predictability and success rate [1]. Nevertheless, failures do occur despite adequate surgical and medical treatment, with reported global failure rates of 1.9–3.6 % [2–4].

Osseointegration, referring to the process of direct anchorage of the implant surface to the surrounding host bone, is a prerequisite and an alternative term for clinical

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effectiveness of dental implant. Bone loss can occur with or without sign of infection, whereas peri-implantitis is an inflammatory lesion associated with loss of supporting bone around implant tooth [5]. Success of implant/osseointegration has been related to many systemic and local factors, including implant materials, bone quality, mechanical loading, bacterial infection, smoking, and several systematic diseases (osteoporosis, Crohn's disease, obesity) [2–4, 6, 7]. Other than these, the fact that implant failure/loss tends to cluster in subsets of individuals points to the potential role of host susceptibility factors [8]. So far the emphasis is on genes involved in immune-inflammatory response due to the inflammatory nature of osseointegration [6].

Peri-implantitis shares many clinicopathological features with periodontitis, and both are initiated by primarily gram negative anaerobic bacteria, while inflammatory process goes faster and deeper around implant teeth than around natural teeth and thus is a more significant problem for dental implant patients [9]. The reported prevalence of peri-implantitis in dental implant patients ranged from 8.9 to 47.1 % [10, 11]. Notably, genetic influence on peri-implantitis is likely to be significant because the twin study indicated that up to 50 % of the variation in periodontitis is genetically determined [12].

Interleukin-1 (IL-1) is the pivotal mediator of the immune-inflammatory response that acts both in response to bacterial infection and in bone metabolism [13, 14]. IL-1 family has at least 11 cytokines; clustered on chromosome 2q are three most studied members *IL-1A*, *IL-1B* and *IL-1RN*, which encode the agonistic proteins IL-1α and IL-1β, and their receptor antagonist IL-1Ra, respectively [15]. The effect of IL-1 is determined by the balance between IL-1α, IL-1β and IL-1Ra through competitive binding of IL-1Ra to the IL-1 receptor to block activity of IL-1α or IL-1β. IL-1 is strongly induced by lipopolysaccharide (LPS) from the cell walls of gram negative bacteria and act either directly or indirectly to initiate and amplify inflammatory responses, through inducing expression of a substrate of effectors including cytokines/chemokines and matrix metalloproteinases [13]. The ability of periodontopathic bacteria to stimulate IL-1 production, the overexpression of IL-1 in periodontal tissue, and the effect of IL-1 on periodontium are a plausible sequence of events in the pathogenesis of periodontal disease [14], and likely peri-implant disease as well. IL-1α and IL-1β expression has been found to increase in patients with peri-implantitis and implant failure/loss, regardless the time of failure [16–19].

The critical role of IL-1 in immune-inflammatory response has led to extensive studies of functional *IL-1* polymorphisms in related to dental implant disease including implant failure/loss and peri-implantitis, but results from different studies remain contradictory. A quantitative analysis of the combined data from the existing studies would be worthwhile to refine the possible associations because most of these studies have limited sample size and a single study might have been underpowered to detect the desired difference. The present study, therefore, reviewed the latest and relevant publications and applied a meta-analytic approach to better estimate the associations between *IL-1* polymorphisms and peri-implant diseases.

Materials and methods

Search strategy

A systematic literature search was performed on Pubmed, Embase, ISI Web of Science, and Cochrane Library databases. The search used combinations of the following key words: ("dental implant" or" oral implant" or "peri-implant disease" or "implant loss" or "implant failure" or "peri-implantitis") and ("interleukin-1" or "IL-1" or "interleukin") and ("polymorphism" or "SNP" or "genotype"). In addition, the reference lists of the retrieved research papers, reviews, comments, letters and other relevant publications were also hand-searched to identify all potential eligible published studies. The literature search was updated to January 2013.

Eligibility criteria

English language published studies were eligible for meta-analysis if they evaluated the association between *IL-1* polymorphisms and risk for dental implant disease in dental implant patients using unrelated case–control or cohort study design. The primary outcome of interest was implant failure/loss or peri-implantitis. All included studies provided sufficient data for calculation of odds ratio (OR) and corresponding 95 % confidence interval (95 % CI). For papers with overlapping study subjects the paper with smaller sample size was excluded. Data from review papers, abstracts and unpublished data were not included.

Data extraction

All data were reviewed and extracted in duplicate independently (JL and CL) and discrepancies were resolved through discussion. The following information was extracted from each study: (1) name of first author; (2) year of publication; (3) country/region of authors; (4) ethnicity of the study subjects; (5) sample size; (6) type of outcome measure; (7) numbers of alleles and/or genotypes in cases and controls.

Statistical analysis

Deviation from Hardy–Weinberg equilibrium (HWE) among controls was assessed, as appropriate, using a

χ^2-test and a $P < 0.05$ was accepted as significant disequilibrium. The association between *IL-1* genetic polymorphisms and implant outcome was measured by OR and 95 % CI, which was determined based on allele distribution or genotype distribution under dominant inheritance model. A fixed model (Mantel–Haenszel method) was used to calculate the summary ORs and 95 % CIs unless there was evidence of heterogeneity across studies, in which case a random-effects model (DerSimonian and Laird method) was employed [20]. Heterogeneity across studies was assessed using the Cochran's Q-test, and by the I^2 statistic which presents the proportion of total variation as a result of between-studies heterogeneity in the meta-analysis [21]. Heterogeneity was considered significant when the P for Q-test < 0.05 and/or $I^2 > 50$ %. Publication bias was evaluated by Begg's funnel plot, and Egger's linear regression test with $P < 0.10$ being accepted statistically significant due to the low power of the test [22, 23]. In addition, sensitivity analyses were performed by excluding studies in which there were departures from HWE in controls [24], and by removing each study in turn and analyzing the remaining studies. Stratification analysis was used to explore the heterogeneity across studies by categorizing subjects into different subgroups by ethnicity. All the P values were two sided, and data analyses were carried out using the Review Manager software (RevMan, version 5.1, the Cochrane Collaboration, Copenhagen, Denmark) and Stata (version 11.1, Stata Corp, College station, TX).

Results

Characteristics of included studies

Figure 1 is the flowchart of study selection process [25]. The initial search of the three electronic databases yielded a total of 90 records. After screening titles and abstracts, 18 studies were eligible for full text review after excluding overlapping publications, non-English publications, abstracts, reviewer papers and studies that were not dental implant-related or IL-1-related. During screening titles and abstracts, six were found to be review papers which were also searched for possible eligible studies and then excluded from meta-analysis. Of the 18 studies, five were excluded after full-text

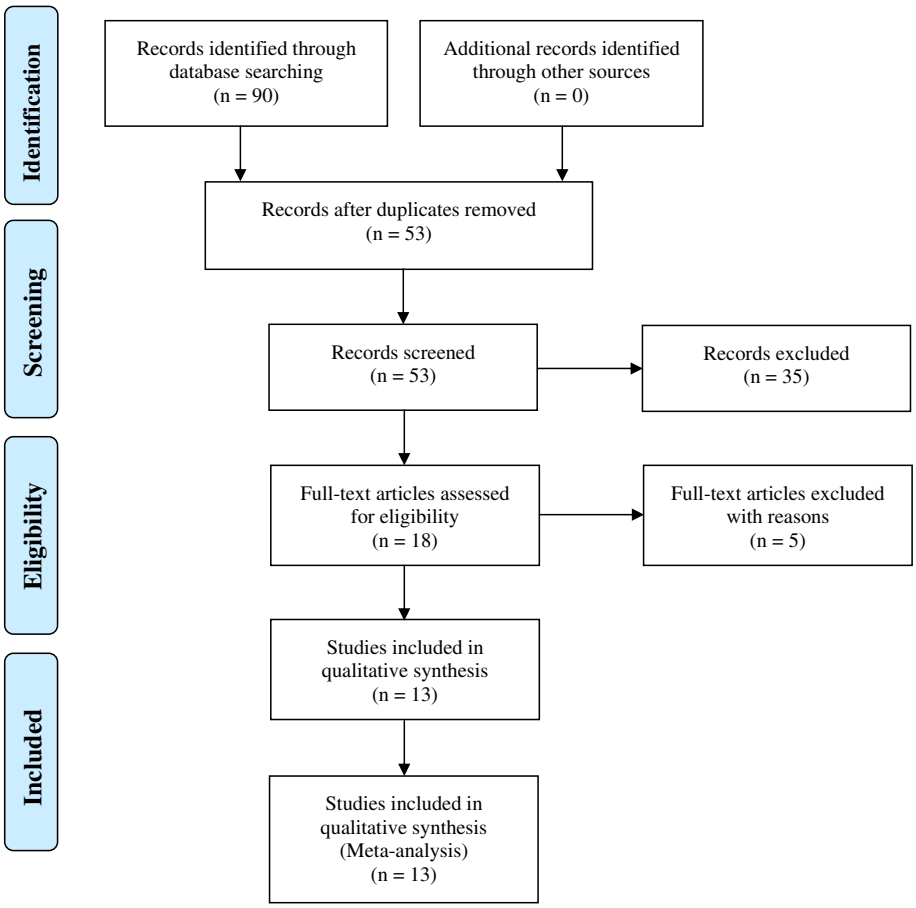

Fig. 1 PRISMA [25] flow chart of selection process to identify eligible studies for meta-analysis

Table 1 Characteristics of the eligible studies included in the meta-analysis

Study	Country origin	Ethnicity	Genetic variants	Cases (n)	Controls (n)	Outcome
Campos [46]	Brazil	Caucasian	IL-1A (−889) IL-1B (−511) (+3953) IL-1RN (VNTR)	28	34	Early implant failures
Vaz [49]	Portugal	Caucasian	IL-1A (−889) IL-1B (+3953)	55	100	Implant loss or biological complications
Laine [50]	Sweden	NS	IL-1A (−889) IL-1B (−511) (+3953) IL-1RN (VNTR)	71	49	Peri-implantitis
Lachmann [56]	German	NS	IL-1A (−889) IL-1B (+3953)	11	18	Peri-implantitis
Melo [47]	Brazil	Mixed	IL-1B (−511) (+3954)	16	31	Peri-implantitis
Hamdy [34]	Egypt	NS	IL-1A (−889) IL-1B (+3953)	25	25	Peri-implantitis
Roger [55]	Australia	Caucasian	IL-1A (−889) IL-1B (+3953)	19	31	Implant failure
Dirschnabe [31]	Brazil	Mixed (>98 % Caucasian)	IL-1B (−511)	92	185	Implant loss
De Boever [45]	Belgium	NS	IL-1A (−889) IL-1B (+3953)	2	20	Implant loss
Jacobi-Gresser [19]	German	Caucasian	IL-1A (−889) IL-1B (+3953) IL-1RN (+2018)	41	68	Implant loss
Montes [32]	Brazil	Mixed (>95 % Caucasian)	IL-1B (+3953) IL-1RN (VNTR)	90	176	Implant loss
Lin [33]	China	Asian	IL-1A (−889) IL-1B (−511) (+3953)	29	30	Marginal bone loss
Shimpuku [48]	Japan	Asian	IL-1A (−889) IL-1B (−511) (+3953)	17	22	Marginal bone loss

NS not specified

review because that two studies used continuous outcome measures and did not define success of dental implant [26, 27], two study did not provide sufficient data for risk association analysis [28, 29], and one study did not have control group for risk association analysis [30]. Finally, 13 studies were included in the meta-analysis. Two of the 13 studies were in the same population but investigated different *IL-1* polymorphisms [31, 32].

Table 1 shows the detailed characteristics of the studies included in the meta-analysis. All of these studies were hospital-based as both cases and controls were dental implant patients. Although the included studies were conducted in a wide range of geographical locations, most studies were on European descent population. Ten of the 13 included studies used epithelial buccal cells for DNA extraction, and the left three also used peripheral blood samples. SNPs among controls in all studies did not deviate from HWE except *IL-1A* (−889) in one study [33].

We did not restrict out search to any specific *IL-1* gene, but only genetic effect of *IL-1A*, *IL-1B*, and *IL-1RN* on dental implants have been reported so far, and the investigated genetic variations were *IL-1A* (−889), *IL-1B* (−511) and (+3954) and *IL-1RN* (VNTR) and *IL-1RN* (+2018) in one study. Finally, six, six, and eight included studies were on the association between implant failure/loss and *IL-1A* (−889), *IL-1B* (−511) and (+3954), respectively. As shown in Table 1, *IL-1B* (+3953) appeared in some studies, but it has been renamed and is now referred to as *IL-1B* (+3954). We will use this term in the present study. Meta-analysis of *IL-1RN* (VNTR) was not conducted because only three studies have been published. Other than these, a composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) was studied as well; the simultaneous presence of allele T at *IL-1A* (−889) and *IL-1B* (+3954) was termed as genotype-positive, and the other combinations as genotype-negative in most studies.

Quantitative data synthesis

Rather than using the ORs adjusted by covariates from each study, risk estimates were calculated according to the raw data in this study. Results of pooled analysis on the associations between individual *IL-1* polymorphism and risk for implant failure/loss using allele frequency and a fixed model are shown in Fig. 2. A significant association between T allele of *IL-1B* (−511) and increased risk of implant failure/loss was observed (OR 1.28, 95 % CI 1.01–1.62; $P_{heterogeneity} = 0.26$, $I^2 = 24$ %). Under dominant inheritance model, however, no significant association was found for *IL-1B* (−511) (data not shown). Positive composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) was associated with increased risk of implant failure/loss (OR 1.76, 95 % CI 1.21–2.57; $P_{heterogeneity} = 0.17$, $I^2 = 34$ %) (Fig. 3).

In the stratification analyses by ethnicity, we grouped studies that were conducted on European/Caucasian population with two studies in Brazilian mixed population for majority of the subjects (>95 %) were European descent [31, 32]. The results revealed that no significant association with implant failure/loss was observed in European descents for *IL-1A* (−889), *IL-1B* (−511) or *IL-1B* (+3954), using allele frequency and a fixed model (Table 2). Similar, no significant result was observed for these

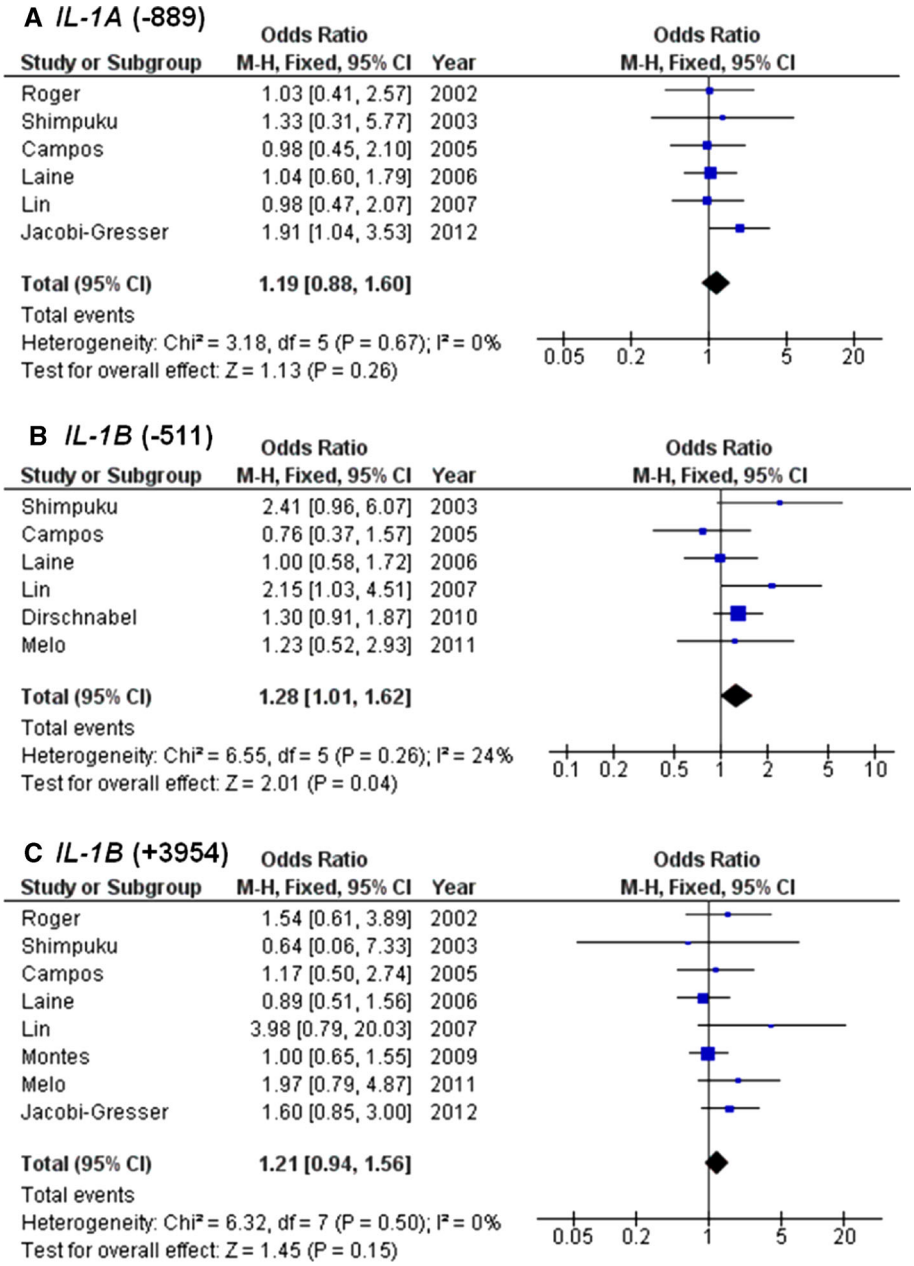

Fig. 2 Forest plot of meta-analysis on the association between (**a**) *IL-1A* (−889), (**b**) *IL-1B* (−511), (**c**) *IL-1B* (+3954) and risk for implant failure using allele frequency model (allele T vs. allele C)

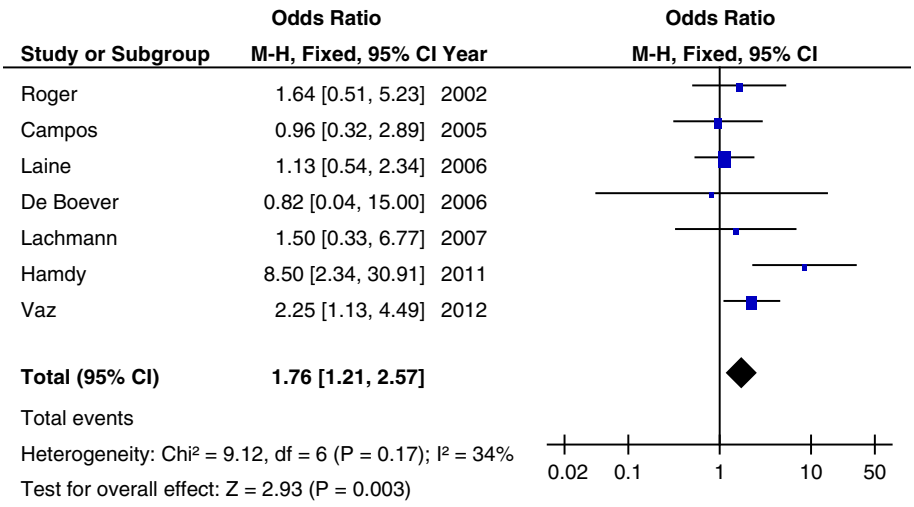

Fig. 3 Forest plot of meta-analysis on the association between the composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) and risk for implant failure (genotype-positive vs. genotype-negative)

Table 2 Results of the pooled OR with 95 % CI in the meta-analysis stratified by ethnicity

Genotype	OR (95 % CI)	$P_{heterogeneity}$	I^2 (%)
European descents, implant failure/loss			
IL-1A (−889), allele T vs. C	1.23 (0.88–1.71)	0.41	0
IL-1B (−511), allele T vs. C	1.12 (0.85–1.48)	0.37	0
IL-1B (+3954), allele T vs. C	1.12 (0.85–1.47)	0.64	0
IL-1A (−889) and *IL-1B* (+3954), positive vs. negative genotype	1.48 (0.99–2.22)	0.74	0
Asian, marginal implant loss			
IL-1A (−889), allele T vs. C	1.05 (0.54–2.03)	0.72	0
IL-1B (−511), allele T vs. C	2.25 (1.27–4.01)	0.85	0
IL-1B (+3954), allele T vs. C	2.33 (0.67–8.05)	0.22	34

polymorphisms in European descents under dominant model (data not shown). Regarding the composite genotype of *IL-1A* (−889) and *IL-1B* (+3954), the positive composite genotype was associated with increased risk for implant failure/loss in European descent population, showing marginally significant (Table 2).Two studies in Asian evaluated the genetic effect of *IL-1A* (−889), *IL-1B* (−511) and (+3954) on marginal implant loss and revealed a significant effect of *IL-1B* (−511) (Table 2).

As the composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) has been associated with chronic periodontitis and was hypothesized to be related to peri-implantitis as well [34], we then conducted meta-analysis on the association between the composite genotype and this specific peri-implant disease. Four studies using peri-implantitis as outcome provided sufficient data for risk association analysis. The results revealed that having T allele at both *IL-1A* (−889) and *IL-1B* (+3954) was significantly associated with 2.09-fold (95 % CI 1.32–3.30; $P_{heterogeneity} = 0.05$, $I^2 = 62$ %) and 2.34-fold (95 % CI 1.03–5.33) increase of risk for peri-implantitis, using a fixed model and a random model, respectively. The composite genotype remained significantly associated with peri-implantitis in European descents (OR = 1.65, 95 % CI 1.00–2.73; $P_{heterogeneity} = 0.28$, $I^2 = 22$ %).

Heterogeneity and sensitivity analysis

The between-study heterogeneity was only significant for the association analysis between the composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) and risk of peri-implantitis ($P_{heterogeneity} = 0.05$, $I^2 = 62$ %). To explore the source of heterogeneity, we conducted a stratification analysis by ethnicity and found that heterogeneity in the subgroup of European descents was much lower ($P_{heterogeneity} = 0.28$, $I^2 = 22$ %), indicating that ethnicity might be a source of heterogeneity. Sensitivity analysis found that the significant association of the composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) with implant failure/loss and peri-implantitis, respectively, was ascribed to the study in Egyptian population [34] (data not shown). With regard to *IL-1A* (−889), the sensitivity analysis found no significant change by removing the study not in HWE [33].

Publication bias analysis

Begg's funnel plots were generated to evaluate publication bias. Figure 4 shows the funnel plot of the meta-analysis of the association between *IL-1B* (+3954) and risk of implant failure/loss. The shape of the funnel plot seemed

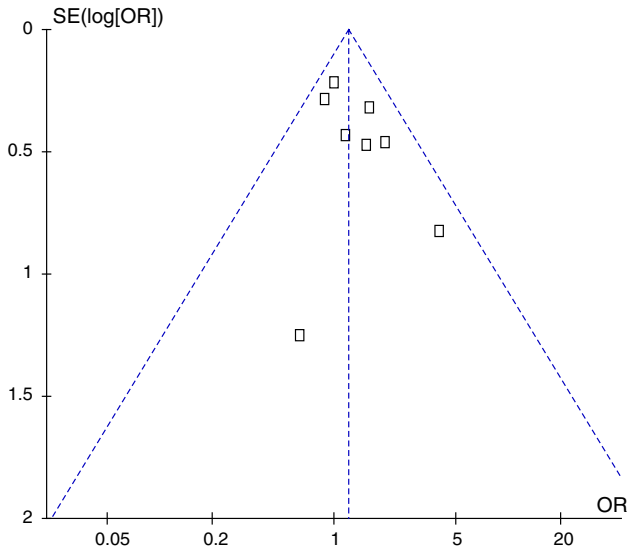

Fig. 4 Begg's funnel plot of publication bias for association analysis of *IL-1B* (+3954) with implant failure. LogOR is plotted versus standard error of LogOR. Each *dot* represents one included study and the *broken lines* represent the respective 95 % CI

symmetrical and none of the studies lie outside the limits of the 95 % CI, and similar symmetry was observed in other meta-analyses (data not shown). Egger's regression test reached no significance for all comparisons ($P > 0.10$).

Discussion

We reviewed the literature and conducted meta-analyses of *IL-1A* (−889), *IL-1B* (−511) and (+3954) in association with dental implant failure/loss and peri-implantitis. The polymorphic *IL-1A* (−889) (rs1800587) is located in the promote region of *IL-1A*, and the T allele has been shown to increase the transcriptional activity of the gene [35]. *IL-1B* (+3954) (rs1143634) is located in exon five and the C to T substitution leads to a synonymous change (Phe105-Phe). In vitro study have found *IL-1B* (+3954) allele T up-regulates the production of IL-1β significantly [36]. *IL-1B* (−511) (rs16944) is located in the promote region and is in near complete linkage disequilibrium with *IL-1B* (−31), which is at TATA box and markedly affect DNA–protein interaction in vitro, thus modifying expression of IL-1β [37]. In the present study, while there was no significant effect of *IL-1A* (−889) or *IL-1B* (+3954) individually, the positive composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) was associated with increased risk for implant failure/loss and peri-implantitis as well, and such accumulating genetic effect was also found in subgroup of European descents. Meanwhile, our results showed that *IL-1B* (−511) allele T carriers had increased risk for peri-implant disease, though such genetic effect was not found in subgroup of European descents.

Three literature reviews and one meta-analysis evaluated the role of *IL-1* genetic variations in peri-implant disease [38–41]. Differences exist between these reviews regarding searching strategies and inclusion criteria. One of the reviews was on implant biological complications including implant loss and peri-implantitis, and the other three including the meta-analysis focused on peri-implantitis only. The review on implant biological complications concluded that there was no obvious association between *IL-1* polymorphisms and implant failure [41]. The other two reviews on peri-implantitis only concluded that the evidence was insufficient regarding the association between *IL-1* polymorphisms and peri-implantitis, while some evidence supported the association, especially in combination with smoking [38, 39]. The only meta-analysis was based on two studies and found no significant association between the composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) and annual bone loss, a surrogate biomarker of peri-implantitis [40]. The two studies included in the above mentioned meta-analysis had no control group for comparison to estimate risk association [26, 27], and were excluded from our meta-analysis.

The composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) was first described as a genetic susceptibility marker associated with increased risk for severe chronic periodontitis by Kornman et al. [42]. While some subsequent studies have found controversial results, a recent meta-analysis of 10 studies reported a significantly increased risk for chronic periodontitis in association with the composite genotype in whites, and the magnitude (OR = 1.51, 95 % CI 1.13–2.02) is similar to that observed in our results [43]. Significant effects of individual *IL-1A* (−889) and *IL-1B* (+3954) on periodontitis were also observed in the meta-analysis, but we were unable to detect such significant genetic effect in association with peri-implantitis in our analysis.

In the present study, the ORs were not derived from multivariable models, but from the raw data only considering *IL-1* polymorphisms and peri-implant disease. A recent systematic review concluded that a history of periodontitis and smoking are risk factors associated with increased risk of peri-implantitis, and diabetes emerged as a potential risk factor as well, though evidence is still limited [44]. In the present study, however, these factors were not used in stratification analysis, given lack of adequate data for meta-analysis. Most included studies did not report periodontitis history in patients, while one study included only patients with a history of advanced aggressive periodontitis and observed similar frequency of positive composite genotype in patients with and without implant loss [45]. Regarding smoking status, most studies considered this potential confounding factor; of the 13 included studies, three included only patients who were

non-smokers [34, 46, 47], two studies were matched by smoking status [31, 32], and five included both smoker and non-smoker patients but had comparable frequency distributions of smoking habits between cases and controls [19, 33, 45, 48, 49]. In one study that smokers were more frequently in cases than in controls, the association of *IL-1A* (−889), *IL-1B* (−511) and (+3954) with peri-implantitis did not change substantially after adjustment of smoking status [50]. The study by Vaz et al. failed to detect any joint effect of smoking habits with the *IL-1* composite genotype on risk for peri-implant disease [49]. As a matter of fact, the possible synergistic effect of smoking with *IL-1* polymorphisms was based on three studies that were excluded in our analysis because of lack of healthy control group [26, 27, 30].

Our results show that ethnicity was a significant source of heterogeneity in this meta-analysis. The between-study heterogeneity in pooled analysis of the composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) and risk for implant failure/loss and peri-implantitis was dramatically reduced in stratification analysis by ethnicity. The significant association between *IL-1A* (−511) and implant failure/loss disappeared in subgroup of European descents. Interethnic differences in genotype frequencies of *IL-1* polymorphisms have been found, including *IL-1A* (−889) (allele T frequency: 25.2 % in HapMap-CEU, 46.0 % in HapMap-YRI, and 7.3 % in HapMap-CHB), *IL-1B* (+3954) (allele T frequency: 20.8 % in HapMap-CEU, 9.3 % in HapMap-YRI, and 3.7 % in HapMap-CHB), and *IL-1B* (−511) (allele T frequency: 35.8 % in HapMap-CEU, 58.0 % in HapMap-YRI, and 46.3 % in HapMap-CHB). Consistently, the prevalence of positive composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) has been reported in 28–38 % of Caucasian patients with periodontitis [42, 51, 52]. The prevalence was significantly lower in a Chinese population (2.3 %), and interestingly, all of the subjects carrying the positive *IL-1* composite genotype had chronic periodontitis, suggesting a potential genetic effect in this ethnic group [53]. However, so far, two studies in Chinese and Japanese populations failed to detect any significant association of marginal implant loss with *IL-1A* (−889) and *IL-1B* (+3954) [33, 48]. More studies are expected to ascertain the role of *IL-1* polymorphisms in modulating susceptibility to peri-implantitis, especially in Asians.

Limitations of this meta-analysis should be addressed when interpreting the results. The term implant failure/loss indicates a heterogeneous condition which has variable clinical and radiographic outcome measurements, so did the definition of peri-implantitis. This is still an unsolved issue in this new research area, as described by Needleman et al. [54]. So it is possible that if *IL-1* polymorphisms only affect susceptibility to a specific subset of peri-implant disease, failure to detect significant associations in individual studies and the pooled analysis may be explained by lack of appropriately selected endpoints. Besides, misclassification bias could be substantial in some studies given the lack of clear and consistent classification system and may contribute to the heterogeneity of our meta-analysis. Importantly, the quality of meta-analysis is limited by the quality of data in individual studies. In the present study, the quality of individual studies included was not the optimal, regarding the fact that all controls were hospital-based, one study did not clearly defined inclusion/exclusion criteria [55], and some studies did not clearly described the ethnicity of subjects [34, 45, 50, 56]. In addition, the included studies vary in confounders such as age, sex, ethnicity, and smoking, while in the pooled analysis we used only the raw data and therefore were not able to control these potential confounders or evaluate the potential gene-environment interactions. All these factors may have contributed to heterogeneity, though the overall heterogeneity in the present study was not significant and reduced after stratification analysis by ethnicity. Another primary limitation of our study is the small sample size. Because of the rarity of the disease, small numbers of studies and individual sample sizes limited our ability to conduct more meaningful stratification analyses to explore the source of heterogeneity and limited our ability to draw any definite conclusions. Finally, although no any publication bias was detected in the funnel plot and Egger's tests, English language selection bias cannot be excluded.

Overall, our findings provide evidence of genetic effect of the composite genotype of *IL-1A* (−889) and *IL-1B* (+3954) on risk for implant failure/loss and peri-implantitis. Larger studies in population with different ethnic background and with detailed individual information, such as smoking habits and periodontitis history, are needed to confirm our findings.

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Conflict of Interests The authors have declared that no competing interests exist.

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