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META-ANALYSIS

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Association between Interleukin-1β Gene –511C>T/+3954C>T Polymorphisms and Aggressive Periodontitis Susceptibility: Evidence from a Meta-Analysis

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Data Interpretation D
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Background: Interleukin-1β (IL-1β) is an important inflammatory cytokine. The associations between IL-1β gene –511C>T/+3954C>T polymorphisms and aggressive periodontitis (AgP) susceptibility have been conflicting. We therefore conducted a meta-analysis to investigate the association of IL-1β genetic polymorphisms with susceptibility to AgP.

Material/Methods: PubMed and Embase electronic databases were searched for relevant studies. Odds ratios (ORs) with 95% confidence interval (CIs) were used to assess the association between IL-1β polymorphisms and AgP risk. Heterogeneity, publication bias, and sensitivity analysis were performed to guarantee the statistical power.

Results: Twenty published studies involving 965 patients and 1234 control subjects were included. No significant association between IL-1β polymorphisms and AgP was found. For –511C>T (T *vs.* C: OR=0.966, 95%CI=0.696–1.341, P=0.869; CT *vs.* CC: OR=0.936, 95%CI=0.761–1.151; TT *vs.* CC: OR=0.892, 95%CI=0.464–1.715, P=0.719; CT+TT *vs.* CC: OR=1.026, 95%CI=0.795–1.323; TT *vs.* CC+CT: OR=0.864, 95%CI=0.436–1.713). For +3954C>T (T *vs.* C: OR=1.069, 95%CI=0.901–1.268; CT *vs.* CC: OR=0.921, 95%CI=0.699–1.212; TT *vs.* CC: OR=1.064, 95%CI=0.747–1.515; CT+TT *vs.* CC: OR=0.990, 95%CI=0.764–1.283; TT *vs.* CC+CT: OR=1.229, 95%CI=0.919–1.643). Subgroup analyses were conducted with HWE, ethnicity, and study design, and no significant association was detected.

Conclusions: These results demonstrate that IL-1β –511C>T and +3954C>T polymorphisms are not the risk factors for developing AgP.

MeSH Keywords: Aggressive Periodontitis • Interleukin-1 • Polymorphism, Single Nucleotide

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Background

Aggressive periodontitis (AgP) is a complex multifactorial infectious disease of tooth-supporting tissues. It is characterized by rapid progressive damage of tooth-supporting tissues, such as alveolar bone loss with pocket formation, gingival inflammation, and recession [1]. This disease is the major cause of tooth loss in populations worldwide. Current evidence indicates that the interactions among different risk factors, such as microbiological factors, immunological factors, life habits, and genetic factors, are critical during periodontitis development [2].

Interleukin-1 (IL-1) is a critical cytokine involved in most inflammatory responses, and it has been implicated in mediating acute and serious inflammatory diseases [3]. The IL-1 gene family includes 2 functionally similar types (IL-1α and IL-1β), which are located in a cluster of human chromosome 2q13 [4]. IL-1β is produced by many cell types, including macrophages, monocytes, and T cells. Many recent studies have proven that high expression of IL-1β may be associated with inflammatory diseases, such as arthritis and bowel inflammation, and cancer conditions, such as gastric and oral cancers [5–7]. IL-1β has been reported to be a central pro-inflammatory cytokine of the immune system, as well as an important mediator during the pathogenesis of periodontal diseases [8,9]. A number of molecular studies proved that the IL-1β levels of gingival crevicular fluid and gingival tissue are significantly higher in AgP subjects [10–12].

Single-nucleotide polymorphism (SNP) is one of the most important types of gene mutation that influences gene transcription and translation, and it promotes the susceptibility of disease development [13,14]. IL-1β –511C>T and +3954C>T polymorphisms are the 2 most common *loci* that are thought to change the susceptibility of individuals to inflammation-induced periodontal diseases.

In 2002, Tai et al. [15] conducted the first study about the 2 polymorphisms of the IL-1β gene and AgP risk in a hospital-based Japanese study. As of this writing, several epidemiological studies have investigated the association between IL-1β –511C>T and +3954C>T polymorphisms and AgP susceptibility. In 2008, Nikolopoulos et al. [16] reported a recent meta-analysis that involved only 5–511C>T polymorphism and 16 +3954C>T polymorphism case-control studies. Several new studies had been published, but the results are still controversial. Considering the importance of IL-1β in the development of AgP, we conducted a meta-analysis of all relevant studies to clarify the association between IL-1β –511C>T and +3954C>T polymorphisms and AgP risk.

Material and Methods

All methods used in this meta-analysis were performed following the guidelines of Meta-analysis of Observational Studies in Epidemiology [17].

Search strategy

Two online electronic databases (PubMed and Embase) were searched using the terms "periodontitis," "aggressive periodontitis," "AgP," "Interleukin-1," "IL-1," "polymorphism," "variant," and their combined phrases for all studies on the association between IL-1β polymorphisms and AgP risk, up to February 1, 2015. All selected studies satisfied the following inclusion criteria: (1) case-control or cohort design study on IL-1β polymorphisms and AgP; (2) focus on IL-1β –511C>T and +3954C>T polymorphisms; and (3) sufficient genotype frequency to estimate the odds ratio (OR) and 95% confidence interval (CI). Exclusion criteria included review articles, case reports, and animal models. The largest or most recently published studies were selected when similar or overlapping data were present.

Data extraction

Two reviewers (Hu and Liu) independently extracted the following information from all collected studies: the first author's name, publication date, country and racial descent (categorized as either Asian or white), sources of controls, number of cases and controls with different genotypes, Hardy-Weinberg equilibrium (HWE), and minor allele frequency. A third reviewer (Niu) was introduced to adjudicate any discrepancies in each item for consistency.

Statistical analysis

ORs with 95% CIs were calculated to evaluate the strength of the association between the IL-1β polymorphisms and AgP risk. For IL-1β –511C>T and +3954C>T polymorphisms, the pooled ORs were obtained for allele contrast (T *vs.* C), co-dominant model (CT *vs.* CC and TT *vs.* CC), dominant model (CT+TT *vs.* CC), and recessive model (TT *vs.* CC+CT). In subgroup analysis, HWE, ethnicity, and study design were also analyzed statistically. Heterogeneity was calculated based on Cochran's Q and I^2 statistics [18]. ORs were estimated using a random-effects model (DerSimonian and Laird method) when I^2 was greater than 50%; otherwise, a fixed-effects model (Mantel-Haenszel method) was used [19]. Cumulative meta-analyses and sensitivity analysis were conducted to evaluate the stability of the results by sequentially removing each study in each model. Potential publication bias was analyzed by Egger's linear regression and Begg's funnel plot [20]. Statistical analysis was performed using STATA version 11.0 (Stata Corporation, College Station, TX, USA), with 2-sided *P* values. $P<0.05$ considered significant.

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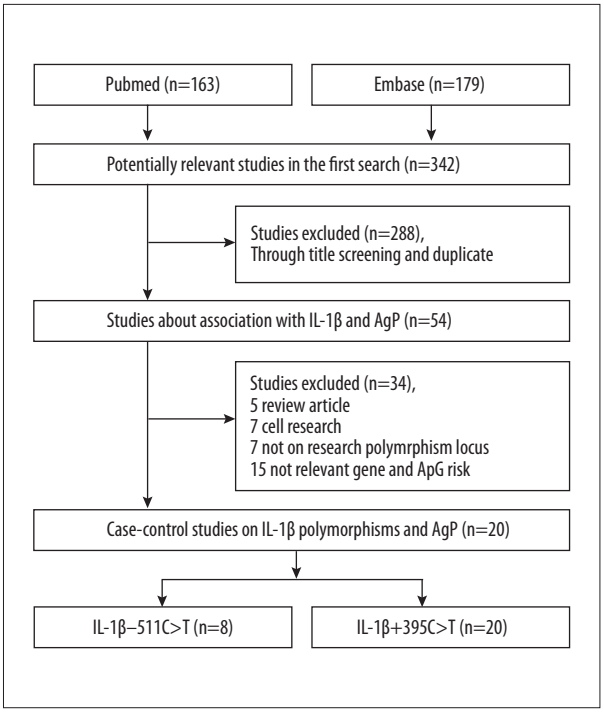

Figure 1. Flow diagram of the study selection process.

Results

Study characteristics

A total of 342 articles were obtained through the literature search. The flow chart of study selection is shown in Figure 1. In the first step of title and duplicate screening, 288 studies were excluded. In the remaining 54 studies, 34 studies were excluded (5 were reviews, 7 focused on molecular research, 7 were about the research polymorphism locus, and 15 were not about the relevant gene and AgP risk). Twenty publications with sufficient data were collected in our meta-analysis [15,21–39]. Out of these 20 articles, 8 case-control studies with 522 cases and 683 controls described the association between IL-1β –511C>T polymorphism and AgP risk [15,23,25,27,30,32–34], and 22 case-control studies involving 965 cases and 1234 controls focused on the relationship of IL-1β +3954C>T polymorphism and AgP susceptibility [15, 21–39]. Only 2 studies deviated from the finding of HWE in IL-1β +3954C>T polymorphism [35,37]. The characteristics of the selected studies are summarized in Table 1.

Quantitative analysis

For IL-1β –511C>T polymorphism

Eight related publications (522 cases and 683 controls) reported on the association between IL-1β –511C>T polymorphism and AgP risk [15,23,25,27,30,32–34]. Three studies described Asian populations [15,25,32], and 5 studies described white populations [23,27,30,33,34]. Overall, no significant association between IL-1β –511C>T polymorphism and AgP risk was found in this meta-analysis [T *vs.* C: OR=1.069, 95% CI=0.901–1.268, P=0.443, I^2=0%; CT *vs.* CC: OR=0.921, 95% CI=0.699–1.212, P=0.556, I^2=8.9%; TT *vs.* CC: OR=1.064, 95% CI=0.747–1.515, P=0.732, I^2=5.6%; CT+TT *vs.* CC: OR=0.990, 95% CI=0.764–1.283, P=0.938, I^2=3.9%; TT *vs.* CC+CT: OR=1.229, 95% CI=0.919–1.643, P=0.164, I^2=0.0%]. In subsequent analysis without the 2 studies that deviated from the HWE, consistent results were found in all 5 genotype models. In the stratified analysis of ethnicity and study design, a similar lack of associations was found between IL-1β –511C>T polymorphism and AgP risk (Table 2).

Sensitivity and cumulative analyses showed that no single study qualitatively changed the pooled ORs, indicating that the results of this meta-analysis were highly stable. Funnel plot and Egger's test were performed to estimate publication bias, and no asymmetrical evidence was revealed. The results were further supported by data analysis using Egger's test [T *vs.* C: P=0.10; CT *vs.* CC: P=0.23; TT *vs.* CC: P=0.17; CT+TT *vs.* CC: P=0.61; TT *vs.* CC+CT: P=0.10].

For IL-1β +3954C>T polymorphism

The 20 articles included 22 case-control studies (965 cases and 1234 controls) focused on IL-1β +3954C>T polymorphism [15,21–39]. Five studies focused on Asian populations [15,22,25,32,36], and 15 studies described white populations [21,23,27–31,33–35,37–39], and 2 studies assessed mixed populations [24,26]. No significant associations were found in any of the 5 models [T *vs.* C: OR=0.966, 95% CI=0.696–1.341, P=0.836, I^2=72.8%; CT *vs.* CC: OR=0.936, 95% CI=0.761–1.151, P=0.531, I^2=24.4%; TT *vs.* CC: OR=0.892, 95% CI=0.464–1.715, P=0.732, I^2=54.0%; CT+TT *vs.* CC: OR=1.026, 95% CI=0.795–1.323, P=0.845, I^2=32.9% (Figure 2); TT *vs.* CC+CT: OR=0.864, 95% CI=0.436–1.713, P=0.675, I^2=60.9%] (Table 2). Further stratified and subgroup analyses according to ethnicity and control design were conducted, and no significant association was found. Heterogeneities were observed in the following 3 models: T *vs.* C, TT *vs.* CC, and TT *vs.* CC+CT. Meta-regression analyses were conducted, and no significant key factors for heterogeneity were identified. However, subgroup analysis by ethnicity and control design revealed the heterogeneities in some models.

Sensitivity and publication bias were also determined. No conspicuous changes in the pooled ORs (Figure 3 for CT+TT *vs.* CC model) were detected, and publication bias was not observed [T *vs.* C: P=0.96; CT *vs.* CC: P=0.90; TT *vs.* CC: P=0.96; CT+TT *vs.* CC: P=0.05 (Figure 4); TT *vs.* CC+CT: P=0.10].

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Table 1. Characteristics of case-control studies on IL-1β –511C>T and +3954C>T polymorphisms and AgP risk included in the meta-analysis.

First author	Year	Country	Racial descent	Source of controls	Case	Control	Genotype distribution						P for HWE*	MAF
							Case			Control				
							C/C	C/T	T/T	C/C	C/T	T/T		
Tai	2002	Japan	Asian	Hospital control	47	97	13	25	9	31	51	15	0.425	0.418
Li	2004	China	Asian	Population controls	122	95	33	55	34	28	44	23	0.488	0.474
Scapoli	2005	Italian	Caucasians	Hospital control	39	96	13	23	3	38	51	7	0.068	0.339
Brett	2005	English	Caucasians	Population controls	50	100	23	21	6	51	39	10	0.533	0.295
Havemose-Poulsen	2007	Denmark.	Caucasians	Hospital control	44	25	15	19	11	11	13	1	0.233	0.300
Shete	2010	India	Asian	Population controls	54	101	9	15	30	9	43	49	0.921	0.698
Karasneh	2011	Jordan	Caucasian	Population controls	80	80	20	32	28	11	40	29	0.633	0.613
Schulz	2011	Germany	Caucasian	No available	86	89	37	36	13	36	40	13	0.728	0.371
							C/C	C/T	T/T	C/C	C/T	T/T		
Tai	2002	Japan	Asian	Hospital control	47	97	45	2	0	88	8	0	0.670	0.042
Gonzales1	2003	European	Caucasians	Hospital control	28	33	15	10	3	17	12	4	0.424	0.303
Gonzales2	2003	American	Caucasians	Hospital control	16	14	10	4	2	9	3	2	0.109	0.250
Anusaksathien	2003	Thai	Asian	Hospital control	26	43	24	2	0	42	1	0	0.939	0.012
Quappe	2004	Chile	Mixed	Population controls	36	75	25	11	0	63	10	2	0.066	0.093
Scapoli	2005	Italian	Caucasians	Hospital control	40	96	24	15	1	42	43	11	0.999	0.339
Li	2004	China	Asian	Population controls	122	95	114	7	1	93	2	0	0.917	0.011
Moreira	2005	Brazilian	Mixed	Hospital control	46	31	34	12	0	24	7	0	0.479	0.113
Brett	3005	English	Caucasians	Population controls	49	98	28	9	12	58	32	8	0.246	0.245
Sakellari	2006	Greek	Caucasians	Hospital control	46	90	26	16	4	50	35	5	0.725	0.250
Droździk	2006	Poland	Caucasians	No available	20	52	15	5	0	31	19	2	0.662	0.221
Havemose-Poulsen1	2007	Denmark.	Caucasians	Hospital control	18	25	9	7	2	16	9	0	0.272	0.180
Havemose-Poulsen2	2007	Denmark.	Caucasians	Hospital control	27	25	19	7	1	16	9	0	0.272	0.180
Guzeldemir	2008	Turkey	Caucasians	Population controls	31	31	19	11	1	0	7	24	0.479	0.887
Shete	2010	India	Asian	Population controls	54	101	41	13	0	75	25	1	0.489	0.134
Karasneh	2011	Jordan	Caucasian	Population controls	80	80	45	32	3	41	33	6	0.856	0.281
Schulz	2011	Germany	Caucasian	No available	82	88	51	25	6	50	33	5	0.884	0.244
Shibani	2011	Syria	Caucasian	Hospital control	32	35	15	14	3	22	8	5	0.017	0.257
Masamatti	2012	Indian	Asian	Hospital control	30	30	19	10	1	21	7	2	0.227	0.183
Yücel	2013	Turkish	Caucasian	Hospital control	56	47	29	19	8	32	9	6	0.002	0.223
Ayazi	2013	Iran	Caucasian	Population controls	26	25	10	0	16	14	7	4	0.096	0.300
Ebadian	2013	Iran	Caucasian	Hospital control	53	48	32	21	0	24	20	4	0.954	0.292

* HWE in control; MAF – minor allele frequency in control group.

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Table 2. Summary ORs and 95% CI of IL-1β –511C>T and +3954 C>T polymorphism and AgP risk.

–511C>T	T *vs.* C					CT *vs.* CC				TT *vs.* CC				CT+TT *vs.* CC				TT *vs.* CC+CT			
	N*	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)	OR	95% CI	*P*	I^2 (%)
Total	8	1.069	0.901 –1.268	0.443	0.0	0.921	0.699 –1.212	0.556	8.9	1.064	0.747 –1.515	0.732	5.6	0.990	0.764 –1.283	0.938	3.9	1.229	0.919 –1.643	0.164	0.0
Ethnicity																					
Asian	3	1.101	0.850 –1.428	0.465	0.0	0.907	0.577 –1.425	0.672	43.4	1.080	0.644 –1.811	0.770	0.0	0.997	0.653 –1.522	0.987	17.8	1.268	0.847 –1.900	0.249	0.0
Caucasian	5	1.045	0.833 –1.311	0.705	20.7	0.929	0.656 –1.314	0.676	3.3	1.050	0.646 –1.706	0.845	30.8	0.986	0.710 –1.369	0.932	17.5	1.188	0.782 –1.804	0.419	0.0
Design																					
HB	3	1.299	0.937 –1.800	0.117	0.0	1.202	0.730 –1.979	0.470	0.0	1.926	0.904 –4.102	0.089	11.9	1.331	0.822 –2.154	0.245	0.0	1.723	0.880 –3.374	0.112	28.2
PB	4	1.004	0.802 –1.259	0.970	0.0	0.797	0.541 –1.174	0.251	49.5	0.882	0.562 –1.385	0.586	3.5	0.865	0.603 –1.242	0.432	40.7	1.157	0.816 –1.641	0.413	0.0
+3954 C>T	**T *vs.* C**					**CT *vs.* CC**				**TT *vs.* CC**				**CT+TT *vs.* CC**				**TT *vs.* CC+CT**			
Total	22	0.966	0.696 –1.341	0.836	72.8	0.936	0.761 –1.151	0.531	24.4	0.892	0.464 –1.715	0.732	54.0	1.026	0.795 –1.323	0.845	32.9	0.864	0.436 –1.713	0.675	60.9
HWE	20	0.922	0.643 –1.32	0.659	74.3	0.852	0.685 –1.509	0.149	8.2	0.818	0.378 –1.770	0.610	59.0	0.866	0.707 –1.060	0.162	27.9	0.843	0.377 –1.886	0.796	65.1
Ethnicity																					
Asian	5	1.118	0.702 –1.780	0.639	9.7	1.199	0.713 –2.015	0.494	0.0	0.877	0.183 –4.205	0.870	0.0	1.174	0.706 –1.952	0.536	0.5	0.816	0.172 –3.878	0.799	0.0
Caucasian	15	0.870	0.576 –1.314	0.508	80.1	0.823	0.648 –1.045	0.109	22.0	0.885	0.416– 1.883	0.752	63.5	0.931	0.686 –1.263	0.646	40.3	0.880	0.402 –1.927	0.749	68.9
Mixed	2	1.473	0.770 –2.818	0.242	0.0	1.875	0.911 –3.859	0.531	20.9	0.498	0.593 –1.179	0.656	NA	1.723	0.848 –3.501	0.133	0.0	0.403	0.019 –8.608	0.560	NA
Design																					
HB	13	0.971	0.777 –1.213	0.796	6.8	1.062	0.797 –1.415	0.681	0.0	0.843	0.495 –1.434	0.529	0.0	1.020	0.777 –1.339	0.886	0.0	0.795	0.471 –1.341	0.389	0.0
PB	7	0.966	0.386 –2.417	0.941	90.5	0.911	0.463 –1.792	0.787	59.6	0.678	0.129 –3.557	0.646	80.0	1.128	0.595 –2.137	0.712	66.4	0.764	0.136 –4.288	0.760	83.9
Other	2	0.798	0.510 –1.250	0.325	0.0	0.687	0.391 –1.210	0.194	24.4	0.981	0.318 –3.030	0.973	0.0	0.714	0.417 –1.225	0.221	0.0	1.117	0.367 –3.396	0.845	0.0

* Number of comparisons; PB – population based; HB – hospital based.

Discussion

In 1999, the new criteria for classification of periodontal disease were published. AgP is a type of periodontal disease that includes 2 severe subvarieties: generalized aggressive periodontitis and localized aggressive periodontitis. Sometimes, AgP exhibits the following features: patients are always young people with rapid loss of attachment and bone destruction, and familial association. A number of etiology studies have shown that the occurrence of AgP mainly includes 2 aspects: (1) microbial factors, particularly *Actinobacillus actinomycetemcomitans* infection, which is a critical pathogen in AgP patients; and (2) human immunity defects, which are often associated with AgP risk. In past years, the differences in periodontitis among individuals were not always interpreted to oral hygiene status. Currently, genetic factors are considered strong determinants of this disease. Gene mutation, particularly SNPs, may change the expression level of a protein and then alter the immune response, thereby influencing patients' susceptibility to AgP development.

IL-1, with its proinflammatory properties, has been implicated in the pathogenesis of periodontitis. Moreover, it is involved in inflammation during AgP development. In 2002, Tai et al. [15] reported the first negative result about the association between IL-1β –511C>T or +3954C>T polymorphism and AgP risk. Since then, a substantial number of studies on the association between IL-1β –511C>T or +3954C>T polymorphism and AgP

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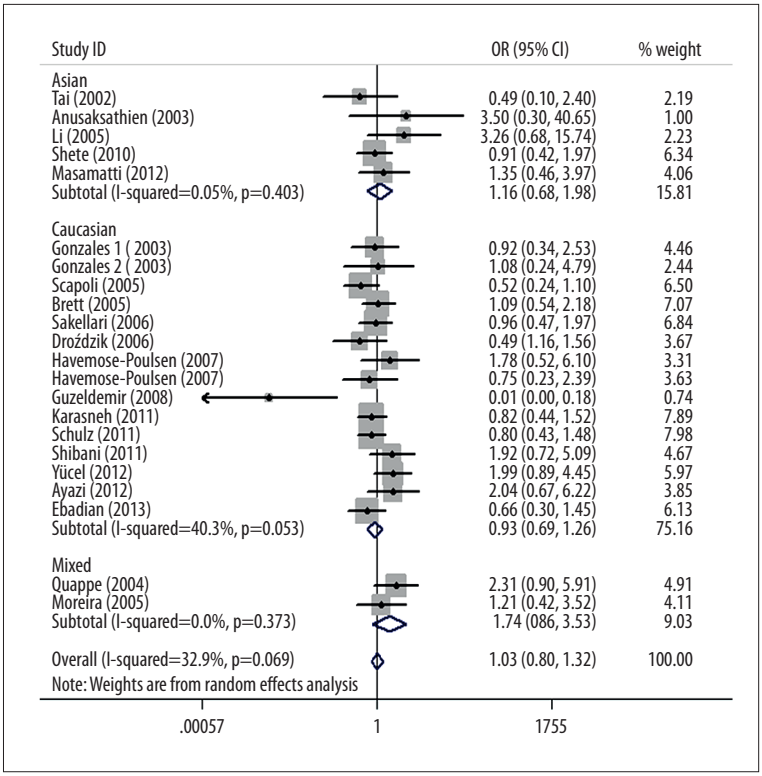

Figure 2. OR and 95% CIs for the association between IL-1β +3954 C>T polymorphism and AgP risk in CT+TT *vs.* CC model.

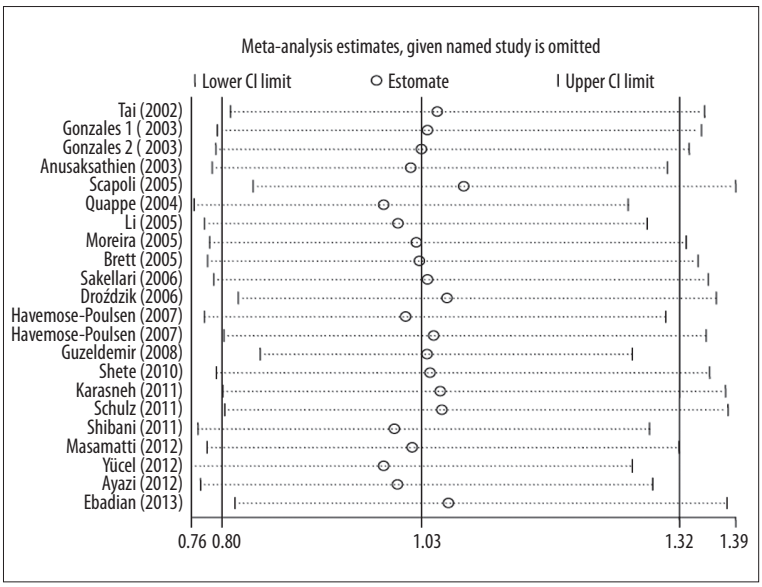

Figure 3. Sensitivity analysis through deleting each study to reflect the influence of the individual dataset to the pooled ORs in CT+TT *vs.* CC model of IL-1β +3954 C>T polymorphism and AgP risk.

risk have been published, but the results were inconsistent. Quappe et al. [24] found that the T allele of IL-1β +3954C>T polymorphism is significantly associated with AgP in Chilean patients (OR=2.86, 95% CI=1.06–7.71, *P*=0.03). Similar results were also revealed in English patients with IL-1β +3954C>T polymorphism[23]. Furthermore, the IL-1β -511 CT heterozygote exhibited a significantly positive association in a male Chinese AgP group (OR=3.16, 95% CI=1.01–9.89, *P*=0.048) [25]. However, numerous studies obtained negative results.

In our meta-analysis, no significant association between IL-1β –511C>T or +3954C>T polymorphism and AgP risk was found in overall pools. Further analyses on gene models and groups stratified by ethnicity and control design were conducted to obtain more precise results. This investigation could provide a useful summary of the relationship between IL-1β –511C>T or +3954C>T polymorphism and AgP risk, and help improve clinical understanding needed to construct a molecular basis for the diagnosis and treatment of AgP.

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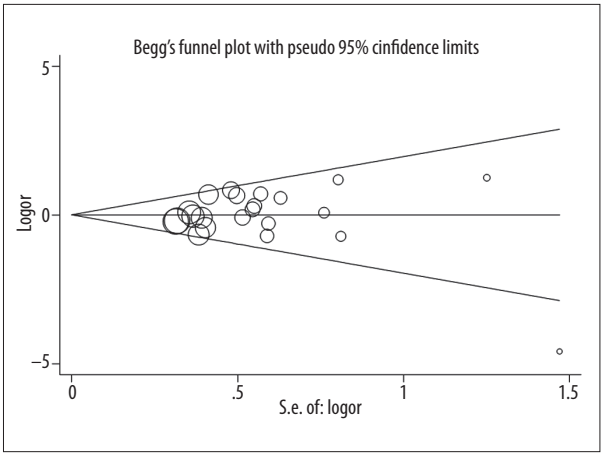

Figure 4. Funnel plot analysis to detect publication bias for CT+TT *vs.* CC model of IL-1β +3954 C>T polymorphism and AgP risk.

However, some limitations should be addressed. First, the sample size was still relatively small for each polymorphism, particularly for IL-1β –511C>T locus, which decreased the statistical power of results or resulted in a different conclusion. Second, a certain degree of heterogeneity existed in the IL-1β +3954C>T locus in the 4 genetic models. Subgroup analyses indicated that this heterogeneity could be explained by ethnicity and control design. Other factors, such as environment, living habits, and age, might contribute to heterogeneity, but these interactions were not investigated in this study because of unavailable data. Third, only 2 polymorphisms were analyzed in our meta-analysis. Haplotype analyses of the 2 polymorphisms were not conducted because of insufficient haplotype data from the included reports, although haplotype analysis may be more precise and credible. Despite these limitations, no qualitative changes were found in sensitivity and publication bias in this meta-analysis, thereby indicating that the results on the possible association between IL-1β –511C>T or +3954C>T polymorphism and AgP risk were statistically robust.

Conclusions

The results of this meta-analysis suggest that IL-1β –511C>T and +3954C>T polymorphisms are not key factors in AgP development. Considering the importance of IL-1β during AgP progression, more large-scale case-control studies are necessary to explore the association and potential haplotype and gene – environment interactions between IL-1β polymorphisms and AgP risk.

Conflicts of interest

No additional external funding was received for this study. No competing financial interests exist.

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