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Association of IL-6-174 G/C and IL10-1082 G/A polymorphisms with recurrent aphthous stomatitis risk

A meta-analysis

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Abstract

Background: Recurrent aphthous stomatitis (RAS) is a common oral disease with unknown etiology. The association between IL-6-174 G/C and IL10-1082 G/A polymorphisms and the risk of RAS remains controversial. Therefore, we conducted this meta-analysis to gain more evidence-based information.

Methods: Four online databases, PubMed, Embase, Web of Science, and Cochrane Library, were searched, and the relevant publications were collected. An odds ratio (OR) with a 95% confidence interval (CI) was applied to assess the association of the IL-6-174 G/C and IL10-1082 G/A polymorphisms with RAS susceptibility.

Results: Nine published case–control studies with 779 patients and 1016 controls were collected. The overall analysis proved that the IL10-1082 G/A polymorphism was significantly associated with the risk of RAS in a dominant model (GG + AG vs AA: OR = 1.49, 95% CI = 1.10–2.01, $P = .01$). A subgroup analysis based on ethnicity revealed significant associations in Asian populations in allelic, heterozygote, and dominant models (G vs A: OR = 1.55, 95% CI = 1.04–2.31, $P = .03$; AG vs AA: OR = 1.76, 95% CI = 1.16–2.67, $P = .01$; GG + AG vs AA: OR = 2.04, 95% CI = 1.37–3.03, $P = .00$). The association in Caucasians and people of mixed ethnicity requires further study. No significant association was detected between the IL-6-174 G/C polymorphism and RAS in any of the genetic models. However, subgroup analysis by ethnicity revealed that the Caucasians were more likely to develop RAS in 4 genetic models (G vs C: OR = 2.36, 95% CI = 1.26–4.41, $P = .01$; GG vs CC: OR = 7.05, 95% CI = 3.50–14.18, $P = .00$; GG + CG vs CC: OR = 4.28, 95% CI = 2.17–8.45, $P = .00$; GG vs CG + CC: OR = 2.59, 95% CI = 1.05–6.41, $P = .04$). In addition, a significantly decreased risk of RAS susceptibility was found in Asians (CG vs CC: OR = 0.27, 95% CI = 0.07–0.99, $P = .049$; GG + CG vs CC: OR = 0.27, 95% CI = 0.07–0.98, $P = .047$).

Conclusion: Our meta-analysis indicated that the IL10-1082 G/A polymorphism is associated with RAS susceptibility, especially in Asians. In contrast, the IL-6-174 G/C polymorphism does not have a statistically significant association with RAS susceptibility. However, it may play a different role during the development of RAS in different ethnicities.

Abbreviations: CI = confidence interval, OR = odds ratio, RAS = recurrent aphthous stomatitis, SNPs = single nucleotide polymorphisms.

Keywords: gene polymorphism, interleukin-10, interleukin-6, meta-analysis, recurrent aphthous stomatitis

1. Introduction

As a common oral inflammatory disease, recurrent aphthous stomatitis (RAS) is characterized by recurrent episodes of oral ulceration.[1,2] Three different RAS types are usually seen in the clinic, including minor aphthous ulcers, major aphthous ulcers, and herpetiform ulcers.[3] An estimated 1 in 4 people in the population will suffer from RAS at some time in their life.[4] Several possible predisposing factors such as local trauma, psychological stress, viruses, bacteria, systematic disease, food hypersensitivity, and nutritional deficiencies have been reported in relation to RAS, while genetic and immunological factors may also play a role in the pathogenesis of RAS.[5–9] However, despite several studies focused on this field, the etiology of RAS has not been fully defined.

Among these predisposing factors, the immune factor is the most widely studied. The increased local expression of Th1 genes and the production of pro-inflammatory cytokines, such as IL-6, were observed in RAS patients.[10] In addition, normal oral mucosal keratinocytes from RAS patients were reported to express lower levels of IL-10 mRNA than that from normal controls, suggesting that the immune system failed to suppress the inflammatory reaction toward oral mucosa.[11]

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SY and BZ contributed equally to this work.

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IL-6 is mainly produced by peripheral blood mononuclear cells, including macrophages, T cells, and B cells, and plays important roles in immune regulation and immune cell activation.[12–14] IL-6 makes significant contributions to a variety of autoimmune diseases. Damaged cells can produce IL-6 during trauma, and the acute production of IL-6 stimulates various cell populations and induces acute-phase proteins.[14] IL-10, synthesized by Th2 cells, is a cytokine synthesis inhibitory factor and is essential for Th2 responses.[15,16] IL-10 plays a central role in immune regulation and anti-inflammation by downregulating the expression of Th1 cytokines.[17,18]

Genetic polymorphisms are prevalent and play an important role in human diseases. Studies have found that single nucleotide polymorphisms (SNPs) can control the production of IL-6 and IL-10.[13,19] Recently, the associations between specific IL-10 and IL-6 gene polymorphism and RAS susceptibility have been widely researched. Given the important role of gene polymorphisms in cytokine release, a better understanding of their function will strengthen the future of RAS therapeutics.

The polymorphisms of IL-6 at position -174G/C and IL-10 at position -1082G/A were studied in RAS patients and controls. The functional promoter polymorphism, -174G/C (rs1800795), is located in the IL-6 promoter region on chromosome 7p21.[20] Studies have shown that carriage of the IL-6-174 G allele is associated with a higher production of IL-6 than the C allele.[13] The polymorphism, -1082G/A, has been identified in the IL-10 promoter region, and studies have shown that a G allele at the -1082 position is related to higher IL-10 production than an A allele at the same position.[21]

To date, many epidemiological studies have focused on the association of the IL-6-174 G/C and IL10-1082 G/A polymorphisms with RAS susceptibility. However, the results remain ambiguous and inconclusive as a result of the reduced power of single studies. Therefore, we conducted this meta-analysis to gain more evidence-based information to strengthen the association.

2. Methods

2.1. Database search

PubMed, Embase, Web of Science, and Cochrane Library databases were searched in May 2017 by 2 independent reviewers without language or time restrictions. We used the following search terms: ("interleukin" or "IL") and ("genetic polymorphism" or "single nucleotide polymorphisms" or "SNP") and ("recurrent aphthous stomatitis" or "RAS" or "recurrent aphthous ulcer" or "RAU"). The cited references in eligible articles were hand searched to identify additional publications. Ethical approval and informed consent were not required, as this study was based on previously published studies and had no direct patient contact or influences on patient care.

2.2. Study selection

Two reviewers independently evaluated all of the search results. The inclusion criteria were as follows: case–control or cohort design studies investigating the association between the IL-6-174 G/C, IL10-1082 G/A polymorphisms, and RAS susceptibility; and studies with sufficiently available genotyping data for the calculation of the odds ratios (ORs), 95% confidence intervals (95% CIs), and the Hardy–Weinberg equilibrium (HWE). The exclusion criteria were not case–control or cohort design studies, studies without available data, studies with duplicate data, and case reports, reviews, or animal studies.

2.3. Data extraction

Two reviewers (S.Y and B.Z) independently extracted the following data from the included studies: surname of the first author and the year of publication, ethnicity, the study design, including number of cases and controls, type of controls, and genotyping type. Disagreements were solved by consulting with other authors.

2.4. Quality score assessment

The Newcastle–Ottawa scale was used to assess the quality of the eligible studies. Study selection, comparability, and outcome are used to assess the methodological quality of the included studies. Two investigators independently calculated the score of the included studies. The scores ranged from 0 to 9, and articles scored greater than 6 were considered high-quality studies, whereas others were considered of low quality. Discrepancies between the 2 investigators were solved by discussion to reach a consensus.

2.5. Statistical analysis

Statistical analyses were performed using the Stata 12.0 software (Stata Corporation, College Station, TX). The OR and 95% CIs were determined to measure the strength of the association between the IL-6-174 G/C and IL10-1082 G/A polymorphisms and RAS susceptibility. Pooled ORs were performed for allelic comparison (IL-6-174 G/C: G vs C; IL10-1082 G/A: G vs A), the homozygote (IL-6-174 G/C: GG vs CC; IL10-1082 G/A: GG vs AA), heterozygote (IL-6-174 G/C: CG vs CC; IL10-1082 G/A: AG vs AA), dominant (IL-6-174 G/C: GG + CG vs CC; IL10-1082 G/A: GG + AG vs AA), and recessive models (IL-6-174 G/C: GG vs CG + CC; IL10-1082 G/A: GG vs AG + AA), respectively. The HWE was calculated in the control group using the χ^2 test to ensure that the controls represented normal and healthy people; $P < .05$ was considered a significant departure from HWE. The I^2 statistic was used to test the statistical heterogeneity between studies. Values of 25%, 50%, and 75% corresponded to low, moderate, and high heterogeneity, respectively. The fixed effects model was used if $I^2 < 50\%$, and the random effects model was used when $I^2 > 50\%$.

3. Results

3.1. Study selection and characteristics

A total of 41 published articles were identified through database searches, and additional studies were found in the reference lists of relevant studies. The flow chart of the search process is shown in Fig. 1. Of the 41 articles, 28 articles were excluded as a result of duplication, and 4 articles were excluded because they were not relevant to our study. After reading the full text, 9 articles that met all of the inclusion criteria and were enrolled in the meta-analysis,[22–30] 8 of which were in English[23–30] and 1 in Chinese.[22] Among them, 1 article[28] provided data regarding both IL-6-174 G/C and IL10-1082 G/A polymorphisms and their associations with RAS susceptibility; therefore, we considered this article to be 2 studies. In total, 10 studies from 9 articles containing 779 cases and 1016 controls investigating the association among IL-6-174 G/C and IL10-1082 G/A polymorphisms and RAS susceptibility were included in the meta-analysis.

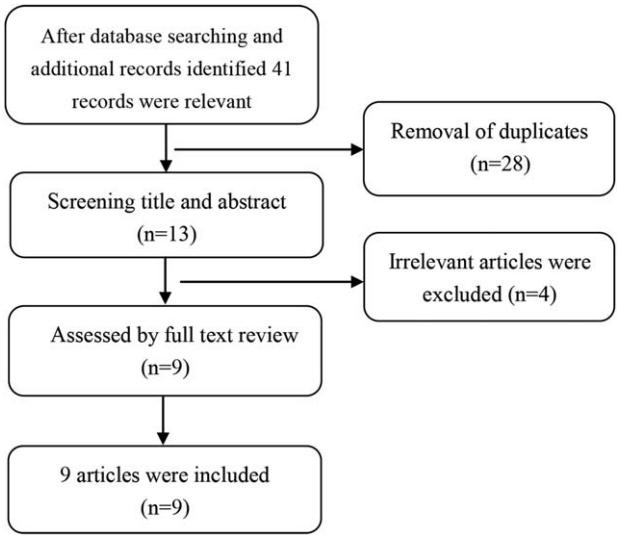

Figure 1. Study flow diagram.

The characteristics of the included studies are listed in Tables 1 to 3. Three different ethnicities, Asian, Caucasian, and Mixed, were studied in these articles. There were 4 articles[22–24,27] about Asians and 4[24,26,29,30] about Caucasians but only 1[28] about mixed ethnicity. Regarding experimental controls, only 1[24] of the studies included patients without RAS as controls. The other studies used healthy controls or ethnicity-matched healthy controls. Three studies[22,23,25] adopted PCR-SSP for genotyping, whereas 2 studies[24,26] used PCR-RFLP, and 4[27–30] used other genotyping methods. The HWE was calculated in the control groups, and 2 studies[23,25] were tested inconsistently.

3.2. Study quality assessment

The score of the NOS assessment is summarized in Table 1. Eight articles scored more than 6 points and were considered high quality. One study[24] scored 6 point and was considered low quality.

3.3. Meta-analysis

The meta-analysis results are summarized in Table 4. The results of a pooled analysis did not find any statistical significance of the

Table 1

Characteristics of included studies.

Study	Country	Ethnicity	Design	Case/Control	Type of controls	Genotyping type	*P* for HWE	NOS score
Jing et al[22]	China	Asian	C-C	138/124	Healthy controls	PCR-SSP	.25	7
Najafi et al[23]	Iran	Asian	C-C	64/140	Ethnicity-matched controls	PCR-SSP	<.05	7
Yakar et al[24]	Turkey	Caucasian	C-C	36/130	Patients without RAS	PCR-RFLP	.37	6
Najafi et al[25]	Iran	Asian	C-C	60/140	Ethnicity-matched controls	PCR-SSP	.04	7
Karakus et al[26]	Turkey	Caucasian	C-C	184/150	Healthy controls	PCR-RFLP	.59	8
Sun et al[27]	China	Asian	C-C	42/86	Healthy controls	PCR	.29	7
Guimarães et al[28]	Brazil	Mixed	C-C	64/64	Ethnicity-matched controls	PCR	.06	8
Bazrafshani et al[29]	UK	Caucasian	C-C	100/91	Healthy controls	PCR	.72	7
Bazrafshani et al[30]	UK	Caucasian	C-C	91/91	Ethnicity-matched controls	PCR	.33	8

HWE = Hardy–Weinberg equilibrium in control, NOS = Newcastle–Ottawa Scale, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, PCR-SSCP = polymerase chain reaction-single strand conformation polymorphism, RAS = recurrent aphthous stomatitis.

Table 2

Distribution of IL-6-174G/C polymorphism in RAS patients and controls.

	Case (n)			Control (n)			Case (n)		Control (n)	
Study	CC	CG	GG	CC	CG	GG	C	G	C	G
Najafi et al[23]	6	37	17	4	93	42	49	71	101	177
Yakar et al[24]	0	15	21	9	43	78	15	57	61	199
Karakus et al[26]	7	38	139	24	68	58	52	316	116	184
Guimarães et al[28]	1	25	38	0	24	40	27	101	24	104
Bazrafshani et al[30]	4	29	58	12	48	31	37	145	72	110

Table 3

Distribution of IL10-1082G/A polymorphism in RAS patients and controls.

	Case (n)			Control (n)			Case (n)		Control (n)	
Study	GG	AG	AA	GG	AG	AA	A	G	A	G
Jing et al[22]	36	47	55	11	43	70	157	119	183	65
Najafi et al[25]	1	45	14	12	75	53	73	47	181	99
Sun et al[27]	23	19	0	42	39	5	19	65	49	123
Guimarães et al[28]	7	26	31	10	23	31	88	40	85	43
Bazrafshani et al[29]	32	44	24	25	47	19	92	108	85	97

Table 4

Meta-analysis results of the association between IL-6-174 G/C and IL-10-1082 G/A polymorphisms and RAS risk.

		Allelic model		Homozygote model		Heterozygote model		Dominant model		Recessive model	
	N	OR/95%CI	P	OR/95%CI	P	OR/95%CI	P	OR/95%CI	P	OR/95% CI	P
IL-6-174 G/C		G vs C		GG vs CC		CG vs CC		GG+CG vs CC		GG vs CG+CC	
Asian	1	0.83 (0.53–1.28)	.39	0.27 (0.07–1.08)	.06	0.27 (0.07–0.99)	<.05	0.27 (0.07–0.98)	<.05	0.91 (0.47–1.78)	.79
Caucasian	3	2.36 (1.26–4.41)	.01	7.05 (3.50–14.18)	.00	2.03 (0.99–4.16)	>.05	4.28 (2.17–8.45)	.00	2.59 (1.05–6.41)	.04
Mixed	1	0.86 (0.47–1.60)	.64	0.32 (0.01–8.02)	.49	0.35 (0.01–8.93)	.52	0.33 (0.01–8.21)	.50	0.88 (0.43–1.78)	.72
Total	5	1.55 (0.80–3.02)	.20	2.11 (0.45–10.01)	.35	1.14 (0.41–3.16)	.80	1.66 (0.43–6.41)	.46	1.70 (0.78–3.73)	.18
IL-10-1082 G/A		G vs A		GG vs AA		AG vs AA		GG+AG vs AA		GG vs AG+AA	
Asian	3	1.55 (1.04–2.31)	.03	2.09 (0.37–11.88)	.41	1.76 (1.16–2.67)	.01	2.04 (1.37–3.03)	.00	1.30 (0.38–4.49)	.68
Caucasian	1	1.03 (0.69–1.54)	.89	1.01 (0.46–2.25)	.97	0.74 (0.36–1.54)	.42	0.84 (0.42–1.65)	.61	1.24 (0.67–2.32)	.50
Mixed	1	0.90 (0.53–1.52)	.69	0.70 (0.24–2.07)	.52	1.13 (0.53–2.39)	.75	1.00 (0.50–2.00)	1.00	0.38 (0.13–1.10)	.07
Total	5	1.28 (0.92–1.78)	.14	1.37 (0.52–3.61)	.52	1.36 (0.98–1.88)	.06	1.49 (1.10–2.01)	.01	1.05 (0.47–2.36)	.90

CI = confidence interval, OR = odds ratio.

association between the IL-6-174 G/C polymorphisms and RAS susceptibility (G vs C: OR = 1.55, 95% CI = 0.80–3.02, $P = .20$, $I^2 = 89.3\%$; GG vs CC: OR = 2.11, 95% CI = 0.45–10.01, $P = .35$, $I^2 = 79.4\%$; CG vs CC: OR = 1.14, 95% CI = 0.41–3.16, $P = .80$, $I^2 = 52.4\%$; GG + CG vs CC: OR = 1.66, 95% CI = 0.43–6.41, $P = .46$, $I^2 = 74.0\%$; GG vs CG + CC: OR = 1.70, 95% CI = 0.78–3.73, $P = .18$, $I^2 = 87.2\%$; Table 4). An additional aspect of the IL10–1082 G/A polymorphism was a significantly increased risk, observed only in the dominant model (GG + AG vs AA: OR = 1.49, 95% CI = 1.10–2.01, $P = .10$, $I^2 = 40.5\%$; Fig. 2). In the subgroup analysis categorized by ethnicities, a significant association between the IL-6-174 G/C polymorphisms and RAS susceptibility was found in Asians (CG vs CC: OR = 0.27, 95% CI = 0.07–0.99, $P = .049$; GG + CG vs CC: OR = 0.27, 95% CI = 0.07–0.98, $P = .047$; Table 4) and Caucasians (G vs C: OR = 2.36, 95% CI = 1.26–4.41, $P = .01$; GG vs CC: OR = 7.05, 95% CI = 3.50–14.18, $P = .00$; GG + CG vs CC: OR = 4.28, 95% CI = 2.17–8.45, $P = .00$; GG vs CG + CC: OR = 2.59, 95% CI = 1.05–6.41, $P = .04$; Table 4). Interestingly, a significantly decreased risk of RAS susceptibility was found in Asians (CG vs CC: OR = 0.27, 95% CI = 0.07–0.99, $P = .049$; GG + CG vs CC: OR = 0.27, 95% CI = 0.07–0.98, $P = .047$; Table 4), whereas a significant risk increase was detected in Caucasians (G vs C: OR = 2.36, 95% CI = 1.26–4.41, $P = .01$; GG vs CC: OR = 7.05, 95% CI = 3.50–14.18, $P = .00$; GG + CG vs CC: OR = 4.28, 95% CI = 2.17–8.45, $P = .00$; GG vs CG + CC: OR = 2.59, 95% CI = 1.05–6.41, $P = .04$; Table 4). Subgroup analysis revealed that Asians with the IL10-1082 G/A polymorphism were more likely to develop RAS (G vs A: OR = 1.55, 95% CI = 1.04–2.31, $P = .03$; AG vs AA: OR = 1.76, 95% CI = 1.16–2.67, $P = .01$; GG + AG vs AA: OR = 2.04, 95% CI = 1.37–3.03, $P = .00$; Table 4). However, significant heterogeneity existed among the data from studies on the IL-6-174 G/C and IL10-1082 G/A polymorphisms. Only the heterozygote and dominant models of the IL10-1082 G/A polymorphism were considered to have low heterogeneity (Figs. 2 and 3). Subgroup analyses based on ethnicity did not

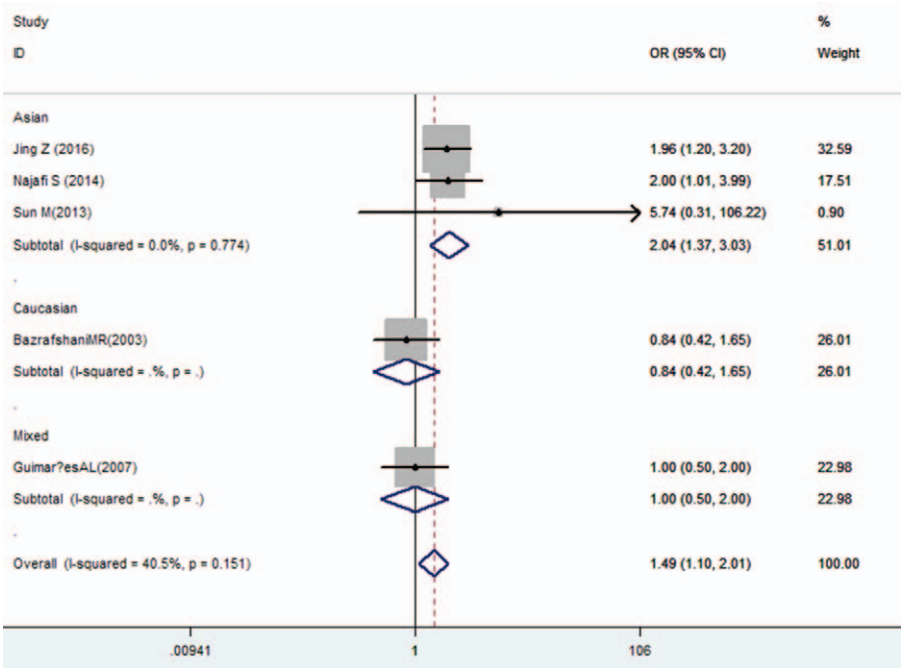

Figure 2. Forest plot of RAS risk associated with IL10-1082 G/A (Dominant model: GG + AG vs AA) polymorphism stratified by ethnicity.

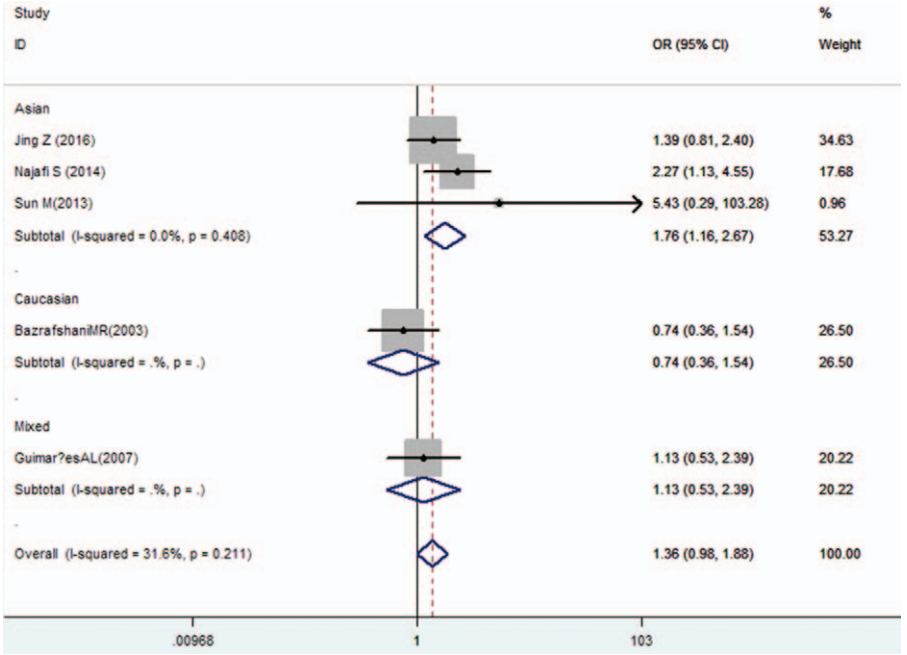

Figure 3. Forest plot of RAS risk associated with IL10-1082 G/A (Heterozygote model: AG vs AA) polymorphism stratified by ethnicity.

reveal the sources of heterogeneity. The sources of heterogeneity may be due to study design; thus, further investigation is required.

4. Discussion

RAS is a very common oral disease with unknown etiology. Many factors such as immunological, genetic, psychological, and microbiological factors are associated with this condition.[5,31] An abnormal cytokine cascade in the region of oral mucosa is thought to enhance the cell-mediated immune response, eventually leading to the development of RAS.[10] Evidence has shown the association of IL-6 and IL-10 levels with RAS.[32,33] For example, although high levels of interleukin (IL)-6 were not detected in the serum of RAS patients,[34] high levels of IL-6 have been observed in the circulation of ulcer tissue.[35,36] It is recognized that cytokine gene polymorphisms can influence cytokine production, particularly those within the promoter region of the gene.[13,37,38] Both the IL-6-174 G/C and IL10-1082 G/A polymorphisms are located in the promoter region,[20,21] and the association between the IL-6-174 G/C and IL10-1082 G/A polymorphisms and RAS susceptibility has been widely studied. A study by Bazrafshani et al[30] found that in the IL-6-174 G/C polymorphism, the G allele occurred with a significantly higher frequency in patients ($P < .05$) than healthy controls, and the greatest risk was associated with G/G homozygosity (OR = 3.4; 95% CI = 1.9–6.2; $P < .05$). Karakus et al[26] also found statistically significant differences between patient with the IL-6-174 G/C polymorphism and healthy controls ($P < .0001$). The GG genotype and G allele of the -174 G/C polymorphism were found more frequently in RAS patients (OR = 4.87, 95% CI = 3.06–7.85, $P < .0001$; OR = 3.82, 95% CI = 2.64–5.59, $P < .0001$, respectively). In contrast, Yakar et al[24] and Guimarães et al[28] found that the IL-6-174 G/C polymorphism was not associated with RAS. One article published by Najafi et al[23] showed a higher significantly frequency of the C/C homozygosity genotype among patients ($P = .044$). Nevertheless, no significant differences were found for patients with the G/G homozygosity genotype. This finding was consistent with Guimaraes et al[28] but contrasted with that of Bazrafshani et al. [30]

Controversies also exist in the study of the IL10-1082 G/A polymorphism. Najafi et al[25] reported that the heterozygote GA genotype was significantly higher in the RAS patient group (OR = 2.27; 95% CI 1.13–4.55; $P < .05$). Jing et al[22] also found that the GA genotype, GG genotype, and G allele at the IL-10-1082A/G site exhibited an increased risk of RAS (OR = 1.391, 95% CI = 0.808–2.396, $P < .05$; OR = 4.165, 95%CI = 1.944–8.924, $P < .05$; OR = 2.134, 95% CI = 1.474–3.089, $P < .05$, respectively). However, these findings were in contrast to previous studies by Bazrafshani et al[29] and Guimaraes et al.[28] To address these controversies and draw more comprehensive conclusions, we conducted this meta-analysis.

To our knowledge, this is the first meta-analysis conducted to evaluate the association between the IL-6-174 G/C and IL10-1082 G/A polymorphisms and RAS susceptibility. The pooled analysis showed that there was no statistically significant association between the IL-6-174 G/C polymorphisms and RAS susceptibility. The dominant model of IL10-1082 G/A polymorphism (GG + AG vs AA: OR = 1.49, 95% CI = 1.10–2.01, $P = .01$, $I^2 = 40.5\%$) appeared to be a risk factor for RAS. However, the heterogeneity among the studies was quite large. A subgroup analysis was conducted to evaluate the relationship between ethnicities. However, only 1 Asian study and 1 mixed ethnicity study were enrolled in the IL-6-174 G/C polymorphism analysis, while 1 Caucasian study and 1 mixed ethnicity study were enrolled in the IL10-1082 G/A analysis. Therefore, the pooled effect sizes could not be calculated; more studies are needed. The subgroup analysis revealed that the same genetic polymorphism may have varying effects on RAS among different ethnicities. For example, Asians with the IL10-1082 G/A polymorphisms were more likely to develop RAS (G vs A: OR = 1.55, 95% CI = 1.04–2.31, $P = .03$; AG vs AA: OR = 1.76,

95% CI = 1.16–2.67, $P = .01$; GG + AG vs AA: OR = 2.04, 95% CI = 1.37–3.03, $P = .00$). Possible explanations may be the differences in habits, genetic background, and environmental exposure among ethnicities.

Immunological pathway, especially cell-mediated immune response, was one of the main interests of researchers as underlying pathophysiology for RAS. Polymorphisms associated with cytokines have been widely used to investigate the pathogenesis of oral mucosal disease. In this study, we evaluated the association between IL-6-174 G/C and IL10-1082 G/A polymorphisms and the risk of RAS. IL-6 is a multifunctional cytokine that participates in inflammatory response; it is especially important for the acute phase response.[14] However, we failed to find the association between IL-6-174 G/C polymorphisms and RAS risk. This result may be caused by the population heterogeneity. IL-10, also known as cytokine synthesis inhibitory factor, has important effects on immune regulation. Lacking IL-10 production following mild trauma could lead to failure to suppress the subsequent inflammatory response and increase the chance of a local cell mediated immune response developing against the oral mucosa.[15,18] We found a significant relationship between IL10-1082 G/A polymorphisms and the risk of RAS. Nevertheless, depending on subgroup analysis, the association was significant in Asians, while no association was observed in other races. These findings may provide more information for understanding the pathogenesis of RAS, as well as provide a basis for clinicians in the determination of further treatment and prognosis.

There are some specific limitations in this meta-analysis. First, the limited number of eligible studies and small number of cases and control subjects in the study may influence the power of this meta-analysis. Second, the source of heterogeneity was not revealed by subgroup analysis, suggesting that other factors, such as the differences in studies, gender, and lifestyle factors, may have resulted in heterogeneity. Third, more ethnicity based studies are required to strengthen the conclusions of the subgroup analysis. Fourth, data from 2 of the studies[23,25] included in this analysis were inconsistent with HWE and will influence the accuracy of the results. Finally, the conclusions were only depended on the ORs, which may lead to confounding bias.

5. Conclusion

Our meta-analysis indicated that the IL10-1082 G/A polymorphism is associated with RAS susceptibility, especially in Asians. In contrast, the IL-6-174 G/C polymorphism did not have a statistically significance association with RAS susceptibility. However, considering the limitations of this study, additional ethnicity-based studies that are carefully designed with large sample sizes are required to assess the association between the IL-6-174 G/C and IL10-1082 G/A polymorphisms and RAS risk.

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