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Review

The association between interleukin polymorphism and recurrent aphthous stomatitis: A meta-analysis

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ABSTRACT

Objective: To assess the association between interleukin gene polymorphism and recurrent aphthous stomatitis (RAS).

Designs: Two electronic databases, PubMed and Embase, were utilized to assemble potentially relevant studies meeting the inclusion criteria. A meta-analysis was conducted using Revman 5.3 software (London, UK), and the pooled odds ratio (OR) and 95% confidence interval (CI) were then used to evaluate the strength of the relationship between the gene polymorphisms of IL-1beta(−511C/T), IL-1beta(+3954C/T), IL-6(−174G/C) and IL-10(−1082G/A) and the risk of RAS.

Results: Ten studies were included in the final meta-analysis, with 884 cases and 1104 controls participating. The results demonstrated that the polymorphism of IL-1beta(−511C/T) significantly increased the probability of the development of RAS in Europeans. (T *vs.* C: OR = 1.35, 95%CI = 1.09–1.67; CC *vs.* CT + TT: OR = 1.77, 95%CI = 1.24–2.53; CC *vs.* TT: OR = 1.86, 95%CI = 1.18–2.95). Furthermore, the C allele in IL-1beta (+3954C/T) was determined to be related to the risk of RAS in Americans (C *vs.* T: OR = 1.52, 95%CI = 1.07–2.17) and the presence of the C gene was considered a risk variant (CC + CT *vs.* TT: OR = 1.46, 95%CI = 1.01–2.11), but no relationship was found between the polymorphism of IL-10(−1082G/A) and the risk of RAS.

Conclusions: The meta-analysis suggested that the mutation of IL-1beta(−511C/T) in Europe and IL-1beta (+3954C/T) in America tend to increase the risk of RAS, but the polymorphism of IL-10(−1082G/A) appears to have no association with RAS risk in America. Further study is required to confirm the above conclusions.

1. Introduction

Recurrent aphthous stomatitis (RAS), one of the most common inflammatory diseases of the oral mucosa, is characterized by recurrent episodes of oral ulceration. The prevalence of RAS is between 5–20% in the general population (Izakovicova Holla et al., 2017). The clinical manifestations of RAS, frequently located in the buccal or labial mucosa and even on the tongue, are painful, round, shallow ulcers with a yellowish-gray pseudomembranous center surrounded by well-defined erythema. There are three main types of RAS, based on the clinical features, namely, minor (MiRAS), major (MaRAS) and herpetiform ulceration (HU) (Rogers, 1997).

Patients with RAS typically experience much pain and the symptoms can severely impact their quality of life (Cardoso et al., 2017). While the etiology of RAS is multifactorial and remains largely unknown, many studies have shown that immunologic, genetic, allergic, nutritional, and microbial factors show a close correlation. Recently, the role of genetic predisposition has been considered in the occurrence of RAS, since people with a positive family history had a higher incidence of the disease (Slebioda, Szponar, & Kowalska, 2014).

It has been demonstrated that immune disorders in the body should also be related to the mechanism of RAS pathogenesis. Multifunctional cytokines which are involved in the inflammatory response can also mediate the immune response and may be responsible for the formation of RAS ulcers (Chavan et al., 2012). The gene polymorphisms likely contribute to susceptibility to RAS by interfering with the metabolism of cytokines, such as the interleukins (IL-1beta, IL-6 and IL-10) (Najafi et al., 2015), tumor necrosis factor-alpha (TNF-alpha) (Guimaraes et al., 2007) and interferon-gamma (IFN-gamma) (Najafi et al., 2017).

IL-1beta, a proinflammatory cytokine, has two main polymorphisms

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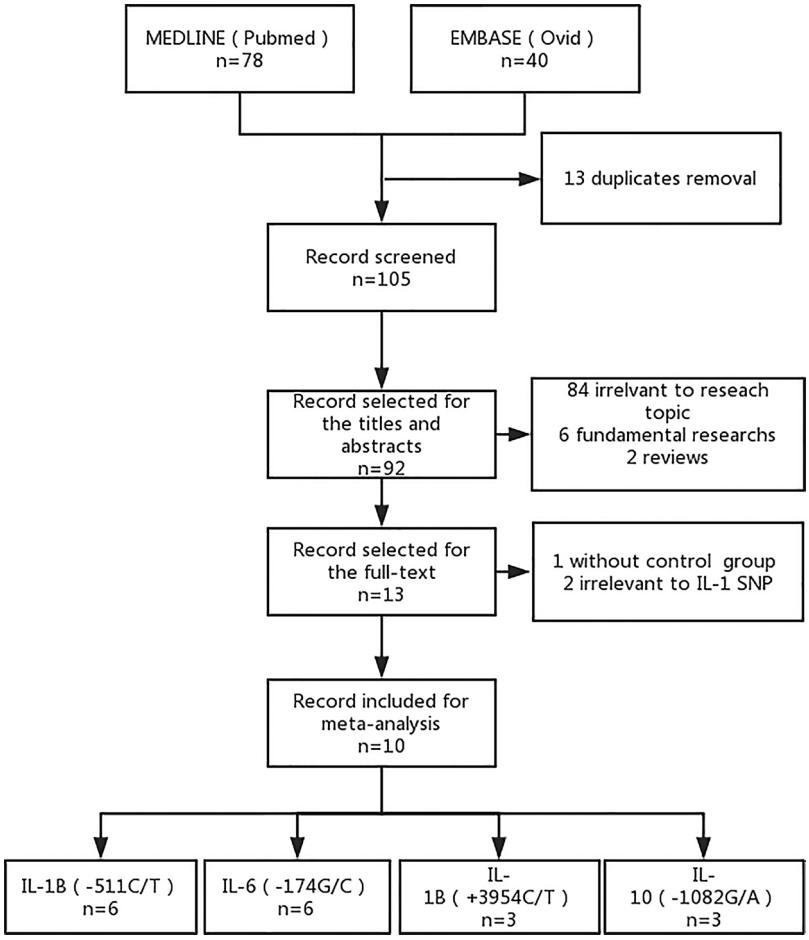

Fig. 1. Flowchart of the inclusion process of studies for meta-analysis.

Table 1
Characteristics of the studies included in the meta-analysis(1).

Study ID	Year	Country	Region distribution	Age, (years, mean ± SD)		Sex		Sample size		Study design
				Cases	controls	Cases	Controls	Cases	Controls	
Slebioda	2017	Poland	Europe	35.1 ± 16.9	34.2 ± 16.4	F = 65 M = 39	F = 55 M = 20	104	75	case-control
Izakovicova Holla	2017	Czech	Europe	40.2 ± 15.0	46.5 ± 11.8	F = 28 M = 35	F = 92 M = 92	64	184	case-control
Zhang	2016	China	Asia	43.5 ± 31.3	44.0 ± 28.5	F = 66 M = 72	F = 62 M = 60	138	124	case-control
Yakar	2015	Turkey	Europe	40.0 (18–70)[#]	50 (18–84)[#]	F = 21 M = 15	F = 71 M = 59	36	130	case-control
Najafi	2015	Iran	Europe	36.6	NA	F = 24 M = 40	NA	60	139	case-control
Karakus	2014	Turkey	Europe	36.0 ± 11.9	37.28 ± 13.09	F = 118 M = 66	F = 88 M = 62	184	150	case-control
Akman	2008	Turkey	Europe	32.8 ± 13.4	33.4 ± 12.9	F = 24 M = 17	F = 35 M = 22	41	56	case-control
Guimaraes	2006	Brazil	America	31.7 ± 14.3	36.9 ± 16.5	F = 36 M = 28	NA	64	64	case-control
Bazrafshani	2003	USA	America	34.3 ± 24.6	NA	F = 64 M = 36	F = 58 M = 33	100	91	case-control
Bazrafshani	2002	USA	America	37.3 ± 24.6	NA	F = 61 M = 30	NA	91	91	case-control

"NA" = not available; F = female, M = male; [#]year(min-max).

due to the transpositions between C and T at positions -511(C → T) and +3954(C → T) (Huang, He, Shao, Jia, & Yuan, 2017) base pairs (bp) from the transcriptional site. Moreover, the IL-6 gene, which contains five exons and four introns, maps to human chromosome 7p21, where many types of single-strand conformational polymorphisms (SNPs) have been found in the promoter region (Biffl, Moore, Moore, & Peterson, 1996). The IL-6 − 174 G > C variant, one of the most common loci in IL-6, is located immediately upstream of a multi-response element at position -173 to -151 and affects IL-6 transcription (Fishman et al., 1998). In addition, two other functional SNPs, at