



# The Association of Interleukin 1 Beta in Recurrent Aphthous Stomatitis – A Systematic Review

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## Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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## ABSTRACT

**Background:** Recurrent aphthous stomatitis (RAS) is a chronic ulcerative disease with a complex aetiology and a strong immunological basis. The prototypical pro-inflammatory cytokine is interleukin-1 (IL-1). IL-1alpha and IL-1beta are the two subtypes of IL-1. The proinflammatory cytokine interleukin-1beta is a key mediator of inflammation which affects cell proliferation and differentiation.

**Aim:** To systematically review the association of Interleukin 1 beta with the recurrent aphthous stomatitis.

**Methods:** A comprehensive search was done using electronic data bases such as PubMed Central, Google Scholar and direct web search. The title scan was used to find relevant articles, which were then read and appraised for inclusion. This review analysed all research that investigated the use of IL1 beta with RAS.

**Results:** Electronic database search identified 31 articles. After evaluating the title, abstract, and full text of these articles, only 2 were selected for the present systematic review. A final of 2 studies were included based on the inclusion criteria to meet the research question.

**Conclusion:** This current study shows that IL1 beta is not a significant reliable indication of RAS. The association of IL1 beta and RAS varies due to a variety of confounding variables.

**Keywords:** *Interleukin; Interleukin 1 beta; cytokines; inflammatory response; recurrent aphthous stomatitis.*

## 1. INTRODUCTION

A self-limiting oral ulcerative lesion is Recurrent Aphthous Stomatitis (RAS). RAS prevalence varies widely, ranging from 5% to 50% depending on the patient's demographic and economic circumstances [1]. Aphthous stomatitis can appear in the significantly in the 2<sup>nd</sup> decade of life and persist until maturity. Women noticeably have higher frequency of RAS (57.2%) than men (48.3%), while children had a 39% prevalence of RAS. Mostly commonly seen in the buccal mucosa, labial mucosa and tongue which are self limited to 7-14 days with frequent reoccurrences [2]. Patients with RAS often have a lot of pain, and the symptoms can have a big influence on their quality of life [3]. Since it is a self limiting condition, there is no definitive curative treatment to prevent the recurrence and also the etiopathogenesis of RAS is not known. RAS is a complex etiology that is still completely unclear. However, multiple investigations have revealed that immunologic, genetic, allergy, dietary, and microbiological variables all have a role. The role of genetic predisposition in the occurrence of RAS has recently been examined, as persons with a positive family history had a higher incidence of the condition [3]. Multifunctional cytokines that mediate the immune response and may be responsible for the formation of RAS ulcers are engaged in the inflammatory response. Interleukins (IL-1beta, IL-6, and IL-10), tumor necrosis factor-alpha (TNF-alpha), and interferon-gamma (IFN-gamma) [3, 4].

Interleukin 1 beta (IL-1) is a cytokine protein that has two genes: IL-1 alpha and IL-1 beta. IL-1 precursor is converted into mature IL-1 by cytosolic caspase 1 (interleukin 1 beta convertase [5]. Activated macrophages create this cytokine as a proprotein, which caspase 1 (CASP1/ICE) proteolytically converts to its active form. This cytokine plays a role in cell proliferation, differentiation, and apoptosis, and is a major modulator of the inflammatory response [6]. Immune and inflammatory responses to

infections are controlled by the IL-1 family of cytokines. B lymphocytes, NK cells, and epithelial cells all produce interleukin-1, which is also expressed by tissue macrophages, monocytes, fibroblasts, and dendritic cells. It promotes the development of endothelial cell adhesion molecules (ECAMs), which help leucocytes, migrate into tissues [7]. The role of genetic variability of the IL1 gene has been examined in RAS and it is known to have a hereditary basis, however illnesses may also be influenced by environmental factors, such as the ingestion of foods with an unbalanced nutritional profile.

Previous research has investigated at the ability of IL1 beta and its relationship with RAS, and a positive correlation between IL1 beta and RAS has been identified ([8,9]. Also there are contradicting result has been obtained for the same [10]. This current study aims on performing a systematic review to evaluate the association of IL1 beta and RAS.

## 2. MATERIALS & METHODS

### 2.1 Search Strategy for Identification of Studies

The search was conducted in accordance with the Cochrane guidelines for systematic reviews. Papers were gathered from PubMed Central and Google Scholar for the years 2017-2021. We also used the internet to identify articles pertaining to our areas of interest. This study comprised of articles that evaluated the strong association of IL1 beta with RAS. The articles were extracted and evaluated further.

### 2.2 Search Methodology

The search methodology applied was using the following keywords:

“Interleukin 1 Beta” AND “Recurrent aphthous stomatitis” Filters: published in the last 5 year.

To ensure that no relevant publications were ignored, the systematic search was confined to these two terms. Adding another term would have restricted the search, but it would have also increased the chances of missing significant titles. Following the removal of duplicates, titles

were reviewed separately by two researchers using established inclusion and exclusion criteria. The remaining papers were thoroughly examined, and a decision was reached based on the relevance of the abstracts and full contents.

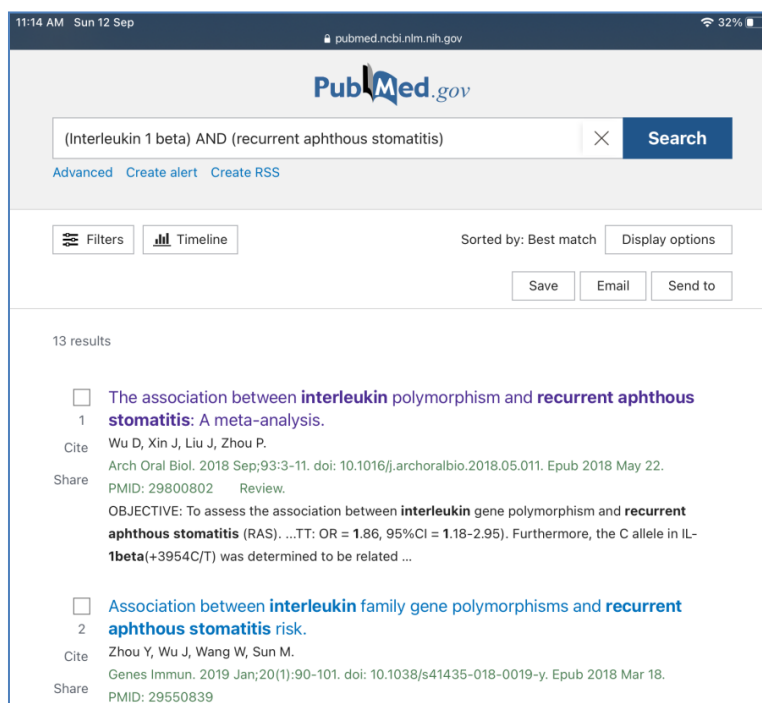


Fig. 1. Image showing the PubMed search strategy

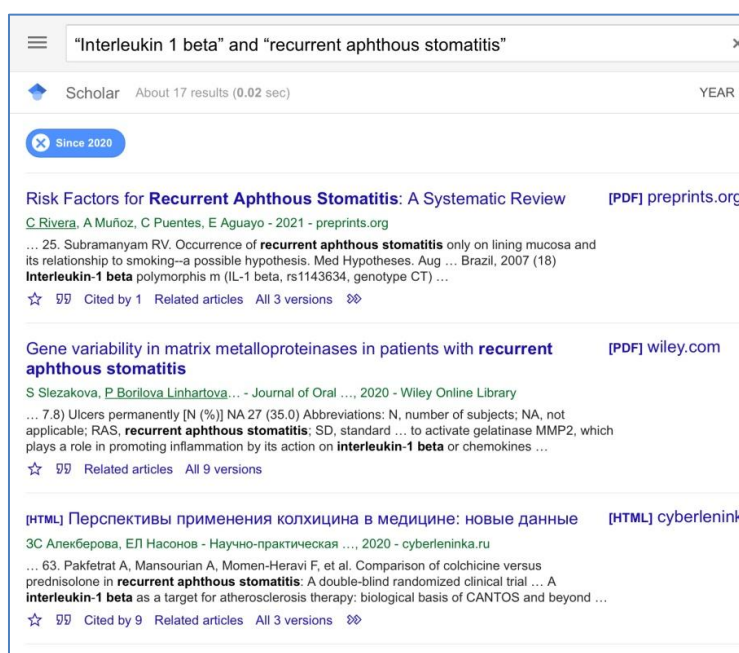


Fig. 2. Image showing the Google scholar search strategy

## 2.3 Selection of Studies

Inclusion criteria:

- Original research articles were included.
- Original research articles performed with IL1 beta studies were included.
- Articles published in English language were included in the review.
- Articles published in the last 5 years (2017-2021) were included.

Exclusion criteria:

- Case reports and review articles were excluded.
- Studies published in other languages were excluded.
- Studies that used other variables of IL1 beta were excluded.

## 2.4 Data Extraction

Once the articles to be reviewed were finalized, data were collected from each article, tabulated and was verified and interpreted.

## 3. RESULTS

### 3.1 Study Selection

A search of the PubMed electronic database revealed 13 papers, a search of Google Scholar yielded 17 papers, and a web search yielded 1 item. After the duplicates were deleted, there were just 27 studies left. After title and abstract scanning, 25 articles were removed because they did not meet the inclusion and exclusion criteria. The bibliographies of these full-text papers were checked for studies not located in electronic databases. There were no relevant studies found in the cross-reference. 2 studies met the inclusion and exclusion criteria for the targeted study. The PRISMA flowchart depicting the study selection approach is shown in Fig. 3.

### 3.2 Study Characteristics

The study characteristics of the included articles are summarized in Table 1. The studies included in this review have shown association of IL1 beta with the RAS.

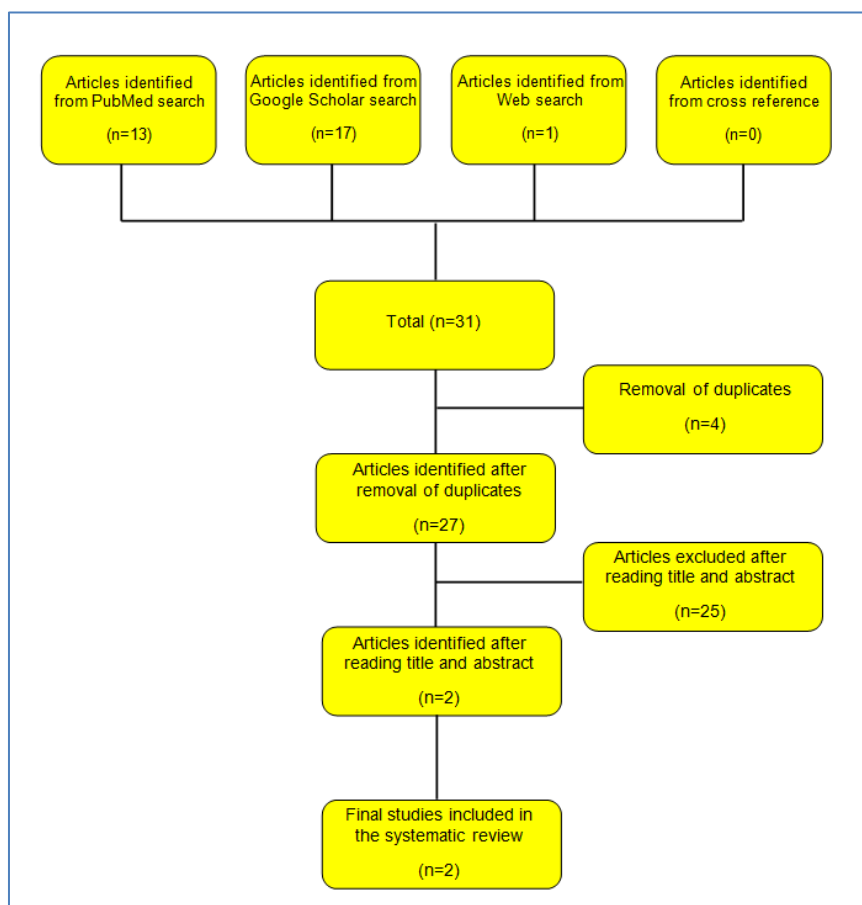


Fig. 3. Image showing the PRISMA flowchart

**Table 1. Study characteristics of the articles included in this review**

S. no	Authors	Year	Sample size	Study design	Method	Results	Conclusion
1.	Ślebioda Z, et al.	2017	140	Case control study	Restriction endonuclease fragment length polymorphism (RFLP) analysis and polymerase chain reaction (PCR)[PCR-RFLP].	There were no statistically significant differences in the genotype distribution for the IL-1 $\beta$ C[+3954]T polymorphism between the RAS and control groups but the frequency of IL-1 $\beta$ *T[-511]/*T[-511] homozygotes Among the patients was significantly higher when compared to our study control (p < 0.0347).	The genetic association between the Studied SNPs of the IL-1 $\beta$ gene and RAS still remain controversial.
2.	Tekcan A, et al.	2021	169	Case control study	Polymerase chain reaction (Conventional PCR)	No statistically significant difference was found in the genotype distributions and allele frequencies of IL-1 VNTR variant between RAS patients and healthy controls.	Lack of association between IL-1 VNTR variant and RAS could indicate that IL-1Ra has no significant role in the pathophysiology of RAS.

2 studies have performed analysis with IL1 beta with a case control study design. The study sample sizes were almost similar in both the studies with 140 & 169 respectively. One study used Restriction endonuclease fragment length polymorphism (RFLP) analysis and polymerase chain reaction (PCR)[PCR-RFLP] and other study used PCR[Conventional PCR]. The results from 2 articles showed that association of IL1 beta with RAS is always controversial. Slebioda Z, et al. [10] and Tekcan A, et al. [11] found negative association of IL1 beta and RAS.

#### 4. DISCUSSION

Previous research done by Slebioda z, et al was unable to find a link between the IL-1 C/T polymorphism and the risk of RAS. The frequency of the 2/2 genotype was not substantially greater in RAS patients. However, the allele distribution in that study differed [10]. Based on their findings, the genetic link between the examined IL-1 beta and RAS was still contentious. Another study included in this review performed by Tekcan A, et al. also found lack of link between the IL-1 VNTR variation and RAS could mean that IL-1 plays no function in RAS pathogenesis [11].

A previous literature has also found a positive association of IL1 beta with RAS where there was link between the IL-1 CT and CC genotype and RAS vulnerability particularly in Brazilian population [8] whereas they found no association with homozygote genotype (TT). Also another research found to have very similar results with a positive association of f IL-1 $\beta$  and RAS. They found that the Inheritance of the G allele of the IL-1B was strongly associated with RAS along with increased numbers of G/G homozygotes [9].The genetic association was not confirmed by another author as well [12]. In another research the patients with RAS exhibited C allele at the same location as in healthy controls and the difference is not statistically significant. Also on comparison with other similar researches they have found that G allele is much more associated with RAS that the C allele, particularly in – 511 polymorphisms [13].

This discrepancy in results could be because to variances in the RAS population's IL-1 genotype distribution. Differences in genotype distribution can also be attributed to population and environmental factors [14,15]. Ethnicity has a big impact on cytokine gene polymorphisms. The

frequency and distribution of gene polymorphisms in India are widely documented to differ significantly from that of other populations and ethnic groups [16]. The role of genetic variables, particularly those associated to immune system function is the key for the development of RAS [17, 18]. According to the findings, there is an equal chance of IL1 beta association and disassociation with the occurrence of the RAS. The clinical occurrence of RAS is highly variable depending on multiple factors and this variability could also indicate a polygenic inheritance pattern. This review is consistent with earlier studies that found the relationship between these two factors to be in a constant state of change. Current human genetics research appears to be focused on identifying genes and variants implicated in illness etiopathogenesis. The identification of a direct genetic etiologic component in RAS opens the door to future development of personalized treatment options for high-risk groups [8,19,20]. Furthermore researches should be performed specifically for each genotype in different polymorphisms associated with IL1 beta to get specific reliable results.

The authors do note the limitations of this review. This study was limited to studies performed in the last 5 years to evaluate the recent outcomes. Only 2 articles were included which makes it questionable evidence. We skipped the ethnicity subgroup analysis. Furthermore, the combined conclusion does not account for potential confounding factors because several studies looked at the relationship between cytokine gene polymorphism and RAS without taking into consideration of demographic characteristics in patients as well as healthy controls.

#### 5. CONCLUSION

This current study shows that IL1 beta is not a significant reliable indication of RAS because of the fluctuating results according to the genotypes. Also the association of IL1 beta and RAS varies due to a variety of confounding variables.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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