Journal of Craniomaxillofacial Research

Vol. 10, No. 1 Winter 2023

# A review of the effect of genetic factors on recurrent aphthous in articles published from 2010-2021: A review

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**ARTICLE INFO**

*Article Type:*
**Review Article**

*Received:* 8 Sep. 2022
*Revised:* 5 Oct. 2022
*Accepted:* 19 Dec. 2022

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**ABSTRACT**

**Introduction:** The main known factors for causing recurrent oral aphthous are genetics and heredity, hematological defects, and immunological disorders. This study was conducted to review the effect of genetic factors on recurrent oral aphthous.

**Materials and Methods:** This study is a literature review that examines the findings derived from existing research articles investigating the influence of genetic factors on the development of recurrent oral aphthous ulcers. The articles on the same topic were selected from available studies on the web, PubMed ISI, Science, Scopus, and Google Scholar, in 10 years from 2013 to 2022. Articles were chosen and assessed based on specific inclusion and exclusion criteria, employing keywords such as genome, oral, recurrent aphthous, and genetic factor as part of the selection process.

**Findings:** 31 studies were selected after screening and based on the inclusion and exclusion criteria. Among them, 1, 2, 3, 2, 5, 5, 6, 3, 3, 1 studies which were done subsequently in the years 2022, 2021, 2020, 2019, 2018, 2017, 2016, 2015, 2014, and 2013, were selected. Among them, 9 studies showed no correlation between genetic factors and RAS incidence, and in the 22 remaining studies, a significant correlation was observed between genetic factors and gene expression in RAS patients compared to healthy people.

**Conclusion:** Genetic factors are effective in the occurrence of recurrent oral aphthous in people.

**Keywords:** Recurrent oral aphthous; Genetic factors; Genome.

## Introduction

Despite the significant advancement and rapid ongoing research in the field of medical science and medical technology, there are still a wide array of diseases that medical science has not effectively treated. The recurrent oral aphthous ulcer is a specific and bothersome instance of such a disease [1]. Recurrent oral aphthous is the most common inflammatory disease of the oral mucosa. The incidence of oral aphthous among the general population has been reported 5% to 50 % depending on the ethnic and socioeconomic groups [2]. RAS presents as recurrent round or oval painful oral ulcers with well-defined borders [3], ulcers can interfere with eating

swallowing, and speaking [4]. Despite the numerous studies, the exact etiology and pathogenesis of RAS are still unknown [5]. The main known factors causing recurrent oral aphthous are heredity, hematological defects, and immunological disorders. Other factors include trauma, stress, hormonal changes, and food allergies which can directly or indirectly change the body's oxidant/antioxidant balance and accelerate producing free radicals [6]. A free radical is an unstable molecule that has one or more unpaired electrons in its structure. Some of the most important free radicals in the biological system are derived from oxygen [7].

Some studies indicate that Immune deficiency is involved in the development of recurrent oral aphthous [8], recent evidence has shown that RAS could be the result of an abnormal cytokine storm. This process leads to increased Cell-mediated immunity response against localized areas of the mucosa [9]. These changes are related to cell-mediated immunity and local secretion of proactive cytokines such as TNF, IL-2, and IFN-y. One crucial point to highlight is that the circulating leukocytes of patients with recurrent oral aphthous, secrete high levels of TNF compared to healthy people [10]. TH1 activates cell-mediated immunity and the secretion of the mentioned cytokines [11]. IL-17 Is a protein with a molecular mass of 32KDa and belongs to the family with the same name, which includes 6 Cytokine (IL-17-A-F).

Cell receptor IL-17 (IL-17R) secrets from endothelial cells of T cells, B cells, fibroblasts, lung cells, myelomonocytic cells, and stem cells of bone marrow. These cytokines work synergistically with TNF-α and IL-1, which are secreted in response to extracellular pathogens and destroy their cellular matrix [12,13]. Several roles have been considered for these cytokines due to the numerous reactions of these Cytokines with different molecules. However, its primary function lies in facilitating pro-inflammatory processes. Another very important role of this cytokine is its effect on a specific subset of $CD4^+$ called T helper 17, which has an important role in autoimmune diseases such as anti-tumor immunity, Ra, Asthma, and Allograft rejection [14]. Considering the importance of recurring oral aphthous in patients and the high frequency of this disease, and the lack of studies about the exact relation between the genetic factors and its occurrence, this study aims to investigate the effect of genetic factors on recurrent oral aphthous.

## Materials and Methods

This study is conducted through a comprehensive review of existing articles focused on investigating the impact of genetic factors on recurrent oral aphthous ulcers. Articles with a similar subject matter within the 10 years from 2013 to 2022 were selected from various internet databases such as Google Scholar, Scopus, PubMed, Web of Science, and ISI. The selection process was based on the following exclusion and inclusion criteria. Inclusion criteria were defined as studies done between 2013-2022 which were written in English and falling into the categories of clinical trials, prospective studies, or case reports. Conversely, the exclusion criteria were defined as studies that were not indexed in any of the mentioned databases, or their complete scripts were not available, animal studies, and meta-analyses. The search was conducted using specific keywords, which are listed in Table 1. Following the article review, the selected studies were translated. Table 2 was completed based on the examined variables in the present study, after careful evaluation of the articles and analysis of the results, interpretations were made. The obtained results from the research were subsequently compared as outlined below.

## Results

Based on the conducted searches, 31 studies were selected after screening and according to the inclusion and exclusion criteria. Out of these, 1 study was from 2022, 2 studies were from 2021, 3 studies were from 2015, 3 studies were from 2016, 5 studies were from 2017, 5 studies were from 2018, 2 studies were from 2019, 3 studies from 2020, 1 study from 2014, and 1 study from 2013 were reviewed.

*Table 1.* Keywords.

| Genetic factors | Recurrent aphthous | Oral | Genome |
|---|---|---|---|

*Table 2.*

| Row | Name of the author | Gene type | Related | Not related |
|---|---|---|---|---|
| 1 | Bartakova and colleagues (15) | ACE | * | |
| 2 | Girardelli and Colleagues (16) | genes panel-17 | * | |
| 3 | Shabana and collegues (17) | Poly morphism Genes IL-6-174G\C | | * |
| 4 | eny and colleagues (18) | IL-6 | * | |
| 5 | Sanchez and colleagues (19) | different Polymorphism of DNA | * | |
| 6 | Slezakova and colleagues (20) | 17 Poly Morphism in MMPsGenes | | * |
| 7 | zhou and Colleagues (21) | Polymorphism genes Family Interleukin | * | |
| 8 | Kowalska Colleagues (22) | β-gene Defensin - and 20G>A -44C>G | | * |
| 9 | Najafi and Colleagues (23) | IL-4 | * | |
| 10 | Najafi and Colleagues (24) | Alleles L/S and duplication HTTPPR-5 | * | |
| 11 | Najafi, Bidoki and Colleagues (25) | IL-17 | * | |
| 12 | Borilova Linhartova and colleagues (26) | Interleukin IL 2, 4) IL (and its receptor IL 13 and IL10) IL4Rα, α | * | |
| 13 | Slezakova and colleagues (27) | NLRP3 | * | |
| 14 | Najafi and Colleagues (28) | 2, - interferon-gamma | * | |
| 15 | Yousefi, Najafi and colleagues (29) | TGF-β ئ | * | |
| 16 | slebioda and Colleagues (30) | IL-β1 | | * |
| 17 | Izakovic a and colleagues (31) | 6-interleukin, 1- interleukin in | | * |
| 18 | Yigti And Colleagues (32) | rs1883832, rs4810485 (CD40) | | * |
| 19 | Najafi and Colleagues (33) | TAS, GSHP, SOD | * | |
| 20 | Bidoki Najafi and Colleagues (34) | NLRP3 | * | |
| 21 | Isaac Najafi and Colleagues (35) | IL-12 | | * |
| 22 | najafi and Colleagues (36) | HLA-DQB, HLA-DRB | * | |
| 23 | Manchanda and colleagues (37) | Serotonin transporter gene morphism | | * |
| 24 | Jing And Colleagues (38) | Transforming growth factor-β1 and Interleukin-1 | * | |
| 25 | Najafi and Colleagues (39) | IL-6, IL-1 | * | |
| 26 | Karasnneh and Colleagues (40) | CD86,TLR4, TLR2 | | * |
| 27 | Zare Bidoki and Colleagues (41) | NLRP3 | * | |
| 28 | Ślebioda (42) | Different Polymorphism of DNA | * | |
| 29 | Karakus and Colleagues (43) | IL-6 | * | |
| 30 | Najafi and Colleagues (44) | IL-10 | * | |
| 31 | AlkhateebAnd Colleagues (45) | SNPs | * | |

## Discussion

Recurrent aphthous ulcers are considered the most common oral cavity lesions [46]. The exact cause of these lesions is not well understood; however, the humoral immune system is believed to play an important role in the immunopathogenesis of aphthous ulcers [47]. Cytokines, including IL-8, a class of recently discovered molecules, can play an important role in the pathogenesis and treatment of important diseases such as cancers, inflammatory and autoimmune diseases, especially oral ulcers [48] [49]. Enhancing serum interleukin levels through the use of monoclonal antibodies and immune-modulating drugs can be employed as a potential treatment for inflammatory lesions. However, further investigation is needed to better understand the connection between serum interleukin levels and other genetic factors in inflammatory lesions, includ-

ing ulcers. Interleukins are produced by macrophages, stimulated T lymphocytes, monocytes, fibroblasts, and hepatocytes. The interleukin-producing gene is located on chromosome 40. This cytokine exerts its influence on target cells by binding to specific receptors, leading to specific biological changes within the cells. Numerous inflammatory lesions and diseases, including ulcers, can be attributed to the overproduction of inflammatory cytokines like IL-8 and IL-6. For instance, elevated levels of IL-8 have been identified in psoriasis lesions, gout, and synovial fluid in rheumatoid arthritis. Consequently, targeting and inhibiting these cytokines hold promise as a potential avenue for treating and improving the symptoms of these diseases.

In this study, a total of 31 research articles were examined. Among these, 9 studies did not find any association between genetic factors and the occurrence of aphthous oral lesions. However, in the remaining 22 studies, a noteworthy correlation was observed between genetic factors and gene expression in patients with aphthous lesions compared to healthy individuals. Additionally, 10 studies investigated the relationship between interleukins and oral lesions, out of which 6 studies reported a positive and significant impact of interleukin expression in patients with recurrent aphthous stomatitis (RAS) when compared to healthy individuals [44,43,39,25,23,18]. Also, in two studies that investigated the relationship between β1-IL and 12-IL and oral lesions in patients with RAS compared to healthy individuals, no significant difference was observed in terms of gene expression between the two groups [35,30]. The findings from the studies conducted by Ślebioda et al. [30] and Isaac, Najafi et al. [35], which found no correlation between genetic factors and oral lesions, are not conflicting with other research. The reason for this lack of contradiction lies in the fact that the other studies investigating the significant relationship between interleukin expression and oral lesions in patients compared to healthy individuals focused on different types of interleukins. Specifically, the mentioned studies centered on β1-IL and 12-IL, which differ from the interleukins examined in similar research studies. However, in other studies, positive and significant results were observed regarding changes in interleukin expression in RAS patients compared to healthy individuals. For example, Aeny et al. [18] reported a significant difference in the levels of IL-6 and ROS in all groups, and a significant correlation between cortisol and ROS in the RAS group, suggesting that serum levels of IL-6 and ROS could be used for diagnosis of RAS. RAS was identified as being caused by malnutrition or atopy with cortisol for patients without psychological stress, which is consistent with a very strong correlation between cortisol and ROS levels in RAS without atopy. Najafi et al. [23] stated that there was no significant difference in the frequency of the IL-4 allele between RAS patients and the control group; however, the patient group showed a higher frequency of CC genotype and a lower percentage of TC genotype of IL-4 590 and significantly more haplotypes of TCT, GTT, GCT, and GTC of the IL-4 gene, while GCC and TTT haplotypes were more common in healthy individuals. Moreover, there was no significant difference in the polymorphism of the IL-4Rα gene between the two groups. They concluded that specific polymorphisms of the IL-4 gene could predispose individuals to RAS. In another study conducted by Bidoki et al. [78], it was shown that mutations in the IL-17F gene were associated with susceptibility to RAS. Additionally, Najafi et al. [28] reported in 2017 that certain SNPs of the IL-2 and γ-IFN genes were associated with the susceptibility of individuals to RAS.

In 2015, Najafi and colleagues [39] reported that specific SNPs of the IL-6 gene at position 174, located in the promoter region, are associated with susceptibility to RAS. Karakus and colleagues also reported a significant association between the RAS and the sensitivity to both C572>G and C174>G polymorphisms of the IL-6 gene. Considering the results of previous studies, it can be concluded that interleukins are significantly higher in patients with oral lesions compared to healthy individuals. However, further studies are needed among different populations to confirm these findings [23,25,28].

In studies that investigated various DNA polymorphisms, the results indicated a significant effect of interleukins and interferons, especially interferon alpha and gamma. Ślebioda (1995) stated that various genetic factors affect an individual's susceptibility to RAS, including different DNA polymorphisms that have occurred in the human genome, especially those related to interleukins (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12), interferon gamma (γ-IFN), and tumor necrosis factor alpha (TNF-α). Additionally, the role of DNA polymorphisms in the serotonin transporter gene, nitric oxide synthase gene, and cell adhesion molecule genes are also effective in the occurrence of RAS. Sánchez et al. (2002) also reported that the incidence of human leukocyte antigen (HLA) A33, B35-HLA, B81-HLA, B12-HLA, and DR5-HLA in patients with RAS was higher than in healthy individuals, while HLA-DR7 and HLA-B51 were higher in healthy indi-

viduals. Moreover, genetic risk factors increase an individual's susceptibility to this disease. These risk factors include interleukins (IL-6, IL-5, IL-4, IL-2, IL-ß, IL-12, IL-10), interferon gamma, and tumor necrosis factor (TNF-α). According to the results, it can be stated that the expression of interleukins and interferons is higher in patients with oral ulcers compared to healthy individuals. In numerous studies, the serum levels of interleukins have been investigated in patients with oral lichen planus, and the reason for this investigation has been explained as follows: many inflammatory diseases and lesions, including lichen planus, can be caused by the production and various effects of inflammatory cytokines such as IL-8 and IL-6. For example, high levels of IL-8 have been found in psoriatic lesions, gout, and synovial fluid in rheumatoid arthritis [48].

Therefore, inhibiting these cytokines could be a considered for the treatment and improvement of disease symptoms [50]. This is because employing particular cytokines that counteract the effects of other cytokines can be beneficial in this context [51]. Sirajedin et al. have shown the presence of IL-2 receptors in stomatitis and described IL-2 itself as a stimulant for the secretion of IL-8 by the action of macrophage mediators, endothelial cells, and fibroblasts, leading to increased levels of IL-8 in these patients [48]. Sirajedin also observed elevated TNFα levels in stomatitis patients, wherein IL-8 levels were boosted due to macrophage stimulation and TNFα mediators [52] Studies have shown that many parasitic, bacterial, and viral infections result in IL-8 production [53]. Lin et al. in 2005 linked viral infections to increased levels of IL-8 and IL-6 in patients with recurrent stomatitis. The serum levels of these two cytokines were significantly increased [54].

Despite the high expression of interleukins in patients with oral lichen planus, other studies that have investigated other genes have also shown that the expression of ACE, 17-panel genes, L/S alleles, 5-HTTLPR, TLR2, HLA-DQB and HLA-DRB, NLRP3, TAS and GSHP, SOD, gamma-interferon, TLR4, CD86, SNPs, and NLRP3 is also associated with the disease in affected individuals, and the expression of these genes is increased in individuals with oral lichen planus compared to healthy individuals. For example, Bartakova et al. [15] reported that while AGTGD and TGD haplotypes are associated with an increased risk of RAS occurrence, CGI haplotype may be a protective factor against RAS susceptibility in individuals. Girardelli et al. [16] also reported that although oral lichen planus associated with systemic inflammation may lead to the clinical diagnosis of BD or SLE.

Individuals experiencing the early onset of the disease during childhood might benefit from genetic testing to identify potential rare monogenic disorders. Najafi and colleagues [24] stated that there was no significant difference in the frequency of genotypes LL and LS between the patient and control groups, but the frequency of the SS genotype was significantly higher in the patient group compared to the control group. They concluded that the S allele can almost double the risk of developing RAS. Yousefi, Najafi, and colleagues [29] stated that single nucleotide polymorphisms of the β-TGF gene can play a role in the pathogenesis of RAS. Therefore, specific SNPs of the β-TGF gene are associated with RAS pathogenesis. Najafi and colleagues [33] stated in their study in 2016 that patients with recurrent aphthous stomatitis have higher levels of SOD and GPX, which are indirectly related to each other, meaning lower levels of GPX and higher levels of SOD are associated with more injury and pain.

However, the TAS level remains stable. Bidoki, Najafi, and colleagues [34] stated that due to the high frequency of the TT genotype of rs3806265 NLRP3 gene in patients with RAS, it seems that this gene polymorphism can make individuals more susceptible to RAS. The same author also stated in 2016 that HLA genes play a role in the occurrence of RAS and different DRB-HLA and DQB1-HLA alleles and related haplotypes are the three main factors in RAS susceptibility in this population. Bidoki, Zare and colleagues [41] also stated that considering the high frequency of the TT genotype of rs3806265 NLRP3 gene in patients with RAS, it seems that this polymorphism can affect individual susceptibility to RAS. Additionally, Alkhateeb and colleagues [45] considered the inheritance of A and AA alleles and the AC genotype of rs5361 selectin-E polymorphism to be associated with increased risk of RAS. However, in contrast to the reported results, Karasneh et al. [40] found a significant increase in A and AA alleles of rs10759931 TLR4 genotype in patients. The C and CC alleles of TLR4rs1927911 genotype were also increased in patients compared to the control group but did not lead to a significant difference. TLR2 and CD86 were not associated with the occurrence of oral lesions.

## Conclusions

Since some genes' expression in patients with oral aphthae can be significantly higher than in healthy individuals, genetic testing can be used to determine the predisposition of individuals to oral aphthae. Therefore, genetic factors are an effective factor in the inci

dence of oral aphthae in individuals.

## Conflict of Interest

There is no conflict of interest to declare.

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*Please cite this paper as:*
Najafi Sh, Pourheydar P, Taheri L, Goudarzi M. A review of the effect of genetic factors on recurrent aphthous in articles published from 2010-2021: A review. J Craniomax Res 2023; 10(1): 1-8