

Association of Interferon-gamma Gene Polymorphism (+874 A/T) and Oral Lichen planus susceptibility: Systematic Review and Meta-Analysis

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Abstract

Background and objectives: Most studies have identified interferon-gamma (IFN- γ) as a key role in the pathogenesis of oral lichen planus (OLP). Recent studies have also shown a link between IFN- γ (+874 A/T) gene polymorphism and OLP. The purpose of the present meta-analysis is to investigate the relationship between IFN- γ (+874 A/T) gene polymorphism and susceptibility to OLP.

Methods: A systematic search of resources to investigate the association between IFN- γ and OLP from Google scholar, PubMed, Embase, Cochrane, Scopus, Proquest, Ovid and Web of science (from 2000 to April 2019) completed. Two individuals independently assessed the quality of the articles. Endnote X5 resource management software was used to organize, study titles and abstracts as well as identify duplicates. A random effect model was also used to perform the meta-analysis.

Results: Four IFN- γ (+874 A/T) polymorphism studies with 297 patients in the case group and 621 healthy controls in the 4 different countries were included. After meta-analysis, a significant association was found between IFN- γ polymorphism (+874 A/T) and OLP. (T vs A: odds ratio (OR) = 1.62; 95% CI = 1.28-2.04; TT vs AA: OR = 2.67; 95% CI = 1.6- 4.45; AT vs AA: OR = 1.56; 95% CI = 1.6- 4.45; TT vs AT + AA: OR = 1.73; 95% CI = 1.13-2.64; AT + TT vs AA: OR = 1.75; 95% CI = 1.28-2.43)

Conclusion: Based on this meta-analysis, there was a positive relationship between IFN- γ (+874 A/T) gene polymorphism and the risk of OLP. The findings showed that increasing TT genotypes significantly increased susceptibility to OLP in comparison with other genotypes.

Keywords: oral lichen planus, gene polymorphism, IFN- γ

Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease that affects 1-2% of adults (1). The results show OLP is reticular white lesions that are usually bilateral, seen in the oral mucosa and sometimes in the tongue. In some cases, these lesions are associated with mucosal ulcers (2-4). Although the mechanism of lichen planus pathogenesis is not completely clear, it is commonly known as an immunological disease. Microscopically, it is similar to T-cell hypersensitivity reaction (3). The role of cytokines associated with T cells has been studied in recent decades. Among these cytokines, interferon-gamma and interleukine-4 (IL-4) have been further investigated, because IFN- γ and IL-4 are specific cytokines for T helper (TH) 1 and T helper 2 cells, respectively (3,5). IFN- γ is a soluble cytokine, also known as a macrophage activating factor(6). This cytokine plays an important role in the immune process, especially against viral infection, intracellular bacteria and tumor control (7). Research has shown that Th1/Th2 imbalance is involved in the pathogenesis and development of many types of autoimmune diseases (8). Since OLP has an immunologic basis, it appears that cytokine proteins frequently change during this disorder (9). Therefore, achieving a coherent result helps us to understand the pathogenesis of this disease. Many studies have been done to evaluate the cytokines in Lichen planus. Among the masses of cytokines studied, IFN- γ was the target of our systematic study.

The IFN- γ coding gene is located on chromosome 24q12 and contains four exons and three introns. Polymorphisms at the site of the first intron in the +874 region (rs2430561) increase IFN- γ production (10,

11). Studies in China, Thailand, and Italy have shown a link between IFN- γ gene polymorphism and OLP (12-14). In some of these studies, no association was found between (+874 A/T) gene polymorphisms and autoimmune diseases (15, 16).

Due to the small volume of individual studies and other limitations, these studies have low statistical power and are poor in estimating disease risk, Also, due to inconsistent conclusions in this field, the aim of the present study was to identify and comprehensively analyze all relevant clinical studies to investigate the association of the IFN- γ gene polymorphism (+874 A/T) and susceptibility to oral lichen planus. These results may provide further evidence for understanding the pathogenesis and progression of OLP, as well as a pathological basis for physicians, for better treatment and for prognosis.

Materials and Methods

- Identify eligible studies

A systematic search of resources was conducted to investigate the association between IFN- γ gene polymorphism and susceptibility to OLP in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (17). The Google scholar, PubMed, Embase, Cochrane, Scopus, Proquest, Ovid and Web of science databases from January 2000 to April 2019 were used to search articles. From the combination of keywords; selected based on MESH and Embase (" Oral precancerous lesion (s) " OR " oral lichen planus" OR " oral premalignant lesion (s) " OR "OLP") AND (" Interferon gamma " OR " IFN " OR " IFN- γ " OR "Interferon γ ") AND (" polymorphism " OR " allele " OR " variant "

OR " single nucleotide polymorphism " OR " SNP " were used. In addition, the reference lists in related articles and reviews are also considered eligible studies. Data were extracted by two reviewers using data extraction form and according to the inclusion and exclusion criteria. In times of disagreement, a third reviewer was used.

Ethical approval and informed consent were not required for this study, as these studies were based on previously published articles.

- Inclusion and exclusion criteria

Inclusion criteria included: English language case-control study, cohort, and cross-sectional. Clinical studies focusing on the relationship between the IFN- γ gene and the risk of OLP, published between 2000 and April 2019. Also, patients in the patient group should have no other disease than lichen planus.

The number of studies for a single gene locus (SNP) should not be less than 3 studies. Exclusion criteria were as follows: animal studies, laboratory studies, systematic reviews, case reports, invalid theories, or studies without accurate genotype data to calculate odds ratios (ORs) and 95% confidence intervals (CIs) needed.

- Data mining and quality assessment

The articles were extracted from the databases using the mentioned keywords and were selected by the subject expert in three stages. First, the titles of all articles were reviewed, and articles that were incompatible with the study objectives were excluded. Abstracts and full texts of the articles were studied and studies with exclusion criteria with poor correlation with study objectives were identified and excluded. The studies selected

by the two reviewers were evaluated for risk of bias and in times of disagreement were referred to a third reviewer.

Required information extracted from the articles was summarized in Extraction form. Information extracted included: author's name, year of publication, individual characteristics (including number of patients in groups, age, and sex), country and genotyping method. Endnote X5 resource management software was used to organize, study titles and abstracts as well as identify duplicates. Quality assessment of obtained articles was performed according to the checklist which was provided by the Joanna Briggs Institute (18).

-Statistical analysis

The probability of each allele and genotype in the patient group was compared to the control group in the meta-analysis. Pooled ORs were calculated for allelic model (T vs A), homozygote model (AA vs TT), heterozygote model (AT vs AA), dominant model (TT+AT vs AA), and recessive model (TT vs AA+AT). Heterogeneity between studies was assessed by Cochran's statistics (Q) and I², which expressed the percentage of variation between studies. I² values 25%, 50% and 75% were considered to present low, moderate and high levels of heterogeneity, respectively. Statistical analysis was performed using CMA v.3.0 software and p-value less than 0.05 was considered as significant level.

Results

-Characteristics of included studies

A systematic search of sources identified 1022 articles. 484 articles were excluded due to duplication and 530 articles after reviewing

the title and review of the abstracts were excluded. After reviewing the full text articles, 4 articles were excluded from the study. Finally, 4 articles were included in this

meta-analysis study. The flow chart for the identified and imported articles is shown in Figure 1. The characteristics of the included studies and patients are shown in Table 1.

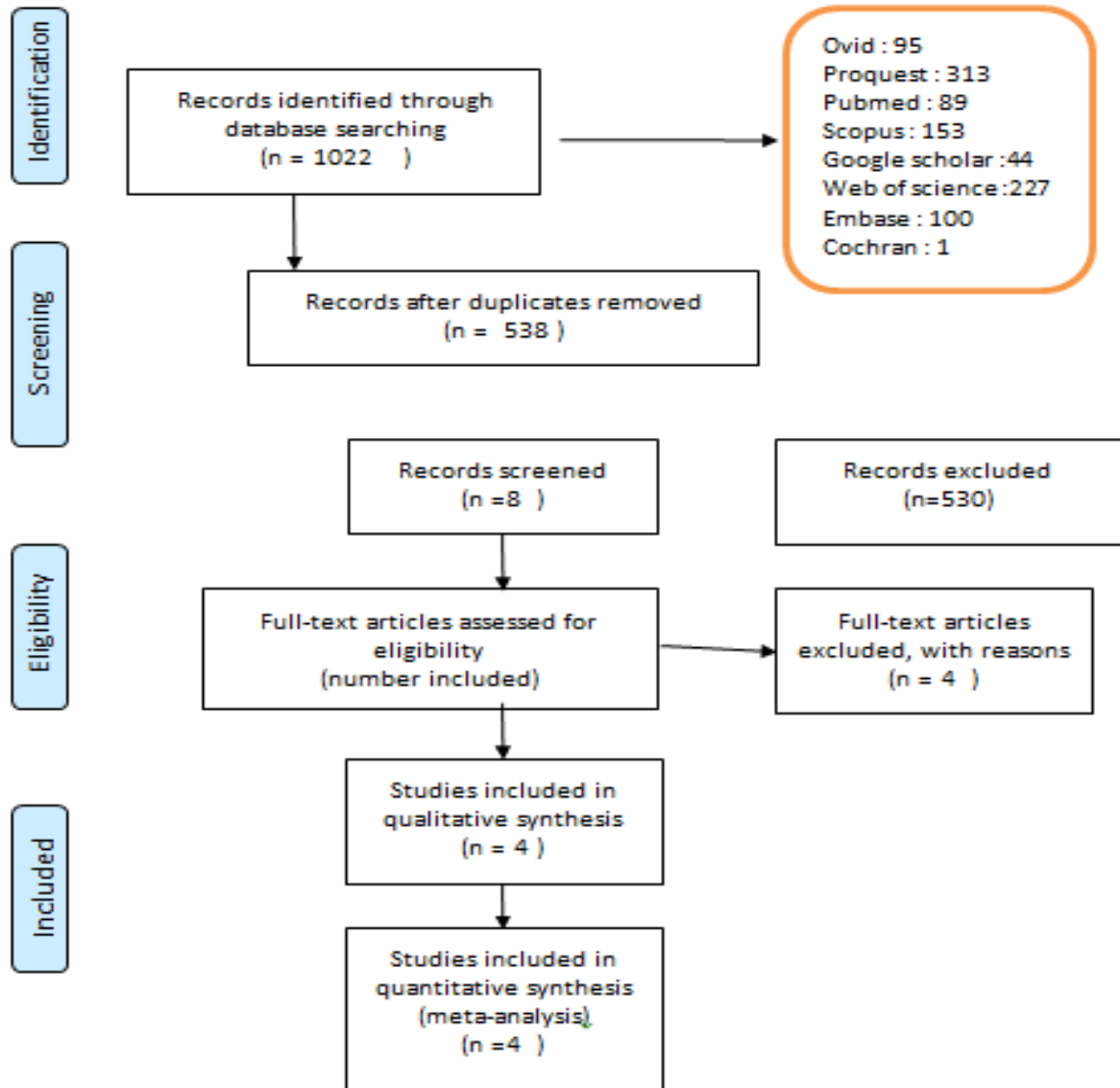


Fig. 1: The flowchart of searching strategy based on PRISMA guidelines.

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

Firs author	Year	Type of OLP E/NE	country	Genotyping method	Case		control	
					Number (male/female)	Age	Number (male/female)	Age
Azab NA (15)	2018	4/11	Egypt	Real time PCR	15 (-/-)	55.1 \pm 8.3	15 (-/-)	45 \pm 6.7
Al-Mohaya MA(24)	2016	-	Saudi Arabia	ARMS-PCR	42 (16/26)	27-72	195 (100/95)	20-65
Kimkong I (14)	2012	17/57	Thailand	PCR-SSP	74 (14/60)	53.3 \pm 13	268 (101/167)	29 \pm 9.1
Bai J (12)	2008	81/70	China	PCR-SSP	151 (86/65)	45	143 (79/64)	45.8

E=erosive, NE= non erosive, ARMS-PCR=amplification refractory mutation system-polymerase chain reaction, PCR-SSP= polymerase chain reaction sequence-specific primer

-Meta-analysis results:

Allelic model (T vs A):

Four articles reported the frequency of alleles observed in the case and control groups. There were 214 T alleles in patients with Lichen planus and 408 T alleles in control group. Heterogeneity between studies was not significant (Q-value = 0.98, df = 3, I² = 0.00, p-value = 0.80). Based on the results of the meta-analysis using fixed effects model it was observed that the odds of T vs A allele were 1.62 times higher than that of the control group. This value was statistically significant (OR = 1.62; 95% CI = 1.28-2.04, p-value

<0.001). Figure 2 shows the forest diagrams related to the meta-analysis.

Homozygote model (TT vs AA):

Four articles reported the frequency of alleles observed in patients in the control and case groups. Heterogeneity between studies was not significant (Q-value = 1.77, df = 3, I² = 0.00, p-value = 0.62). Based on the results of meta-analysis using fixed effects model, it was observed that TT vs AA genotype was 2.67 times higher than control group. This value was statistically significant (OR = 2.67; 95% CI = 1.6- 4.45; p-value = <0.001). Figure 3 shows the forest diagrams related to the meta-analysis

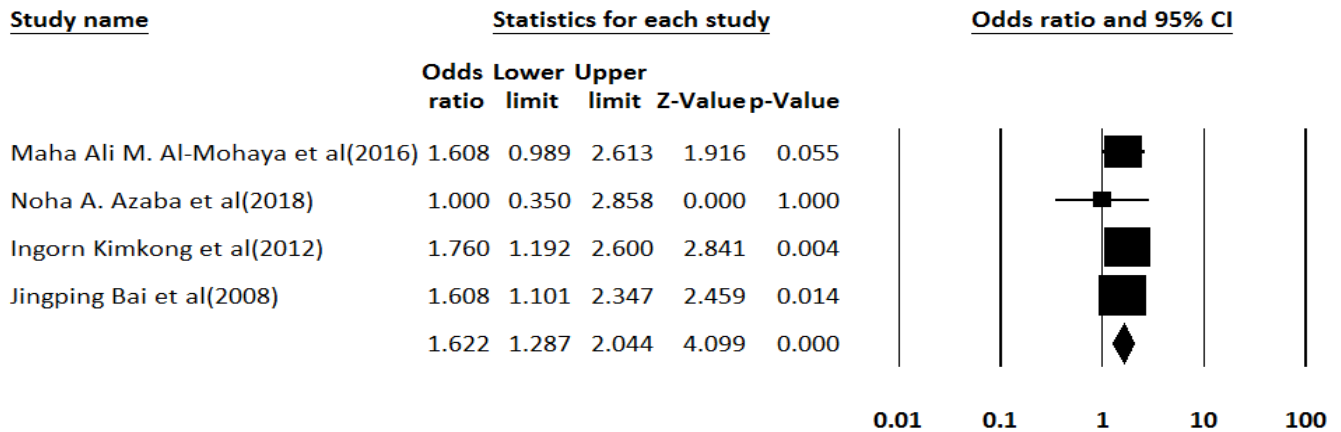


Figure 2. Forest plot of the IFN- γ +874A/T polymorphism and OLP susceptibility in allelic model (T vs A). CI=confidence interval, OR=odds ratio.

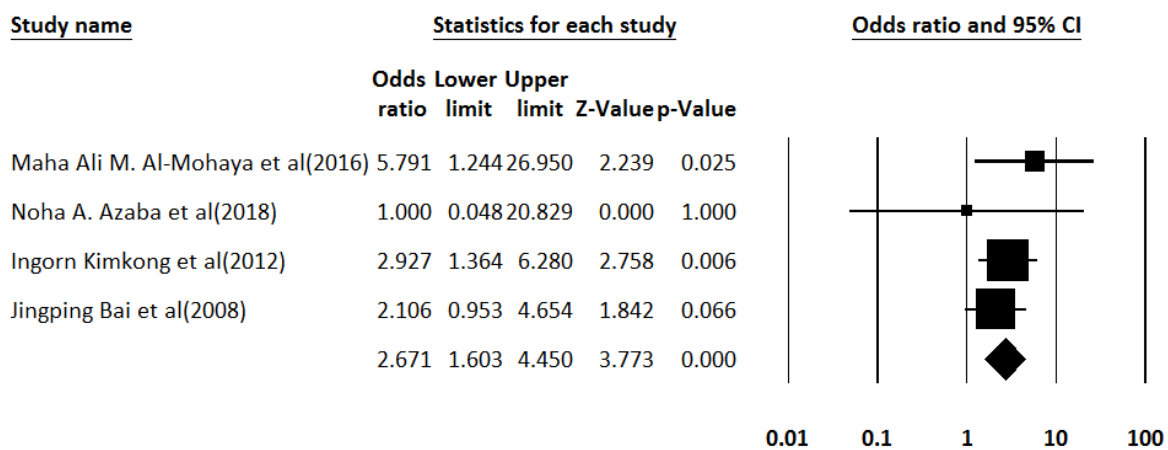


Figure 3. Forest plot of the IFN- γ +874A/T polymorphism and OLP susceptibility in homozygote model (TT vs AA). CI=confidence interval OR=odds ratio

Heterozygote model (AT vs AA):

Four articles reported the frequency of alleles observed in patients in the control and case groups. Heterogeneity between studies was not significant (Q-value = 4.72, df = 3, I² = 36.47, p-value = 0.19). Based on the results of the meta-analysis using fixed effects model, it

was observed that the odds of AT vs AA genotype in Lichen planus patients were 2.67 times higher than the control group. This value was statistically significant (OR = 1.56; 95% CI = 1.08-2.25, p-value = 0.01). Figure 4 shows the forest diagrams related to the meta-analysis.

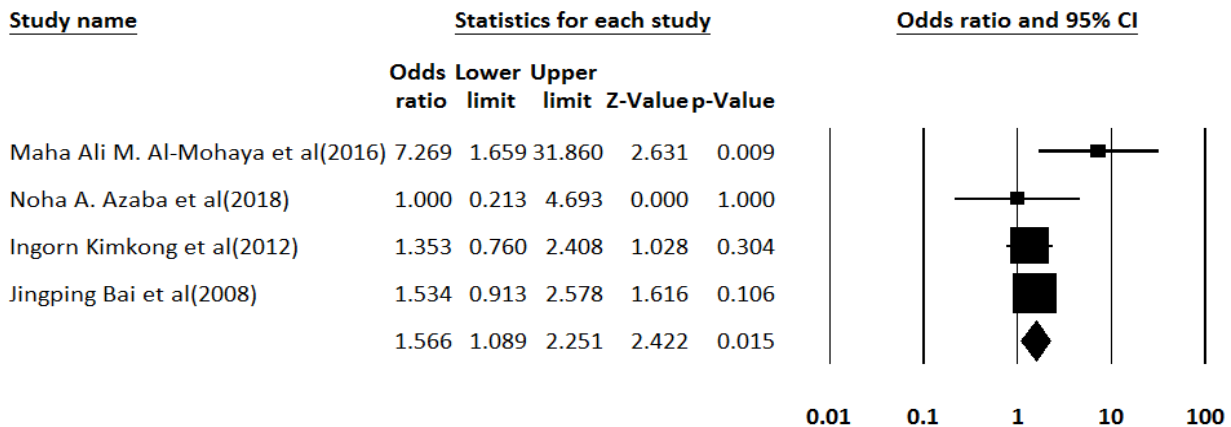


Figure 4. Forest plot of the IFN- γ +874A/T polymorphism and OLP susceptibility in heterozygote model (AT vs AA). CI=confidence interval, OR=odds ratio.

Recessive model (TT vs AA + AT):

A total of 4 articles were included in the meta-analysis. In patients with Lichen planus, 48 cases had TT genotype and 89 cases in control group. Heterogeneity was not significant between studies (Q-value = 2.65, df = 3, I² = 0.00, p-value = 0.44). Based on

the results of the meta-analysis using fixed effects model, it was observed that the chance of TT vs AA + AT genotype in patients with lichen planus was 1/1 times higher than control group. This value was statistically significant (OR = 1.73; 95% CI = 1.13-2.64, p-value = 0.011). Figure 5 shows the forest diagrams related to the meta-analysis.

TT vs AT+AA

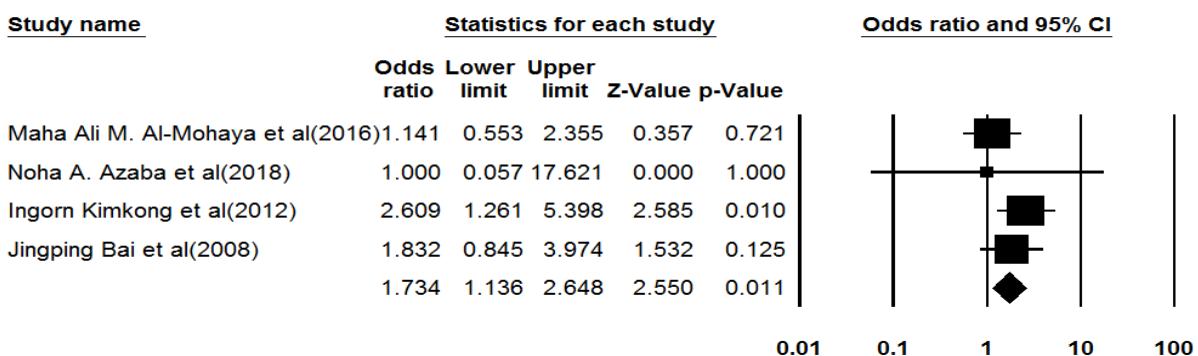


Figure 5. Forest plot of the IFN- γ +874A/T polymorphism and OLP susceptibility in recessive model (TT vs AA+AT). CI=confidence interval, OR=odds ratio.

Dominant model (AT + TT vs AA):

A total of 4 articles were included in the meta-analysis. There were 124 AA genotypes in patients with Lichen planus and 310 in the control group. The amount of heterogeneity between studies was not significant (Q-value = 3.86, df = 3, I² = 22.33, p-value = 0.27).

Based on the results of meta-analysis using fixed effects model, it was observed that the chances of AT + TT vs AA genotype were 0.57 times higher than that of control group. This value was statistically significant (OR = 1.75; 95% CI = 1.28-2.43, p-value = 0.001). Figure 6 shows the forest diagrams related to the meta-analysis.

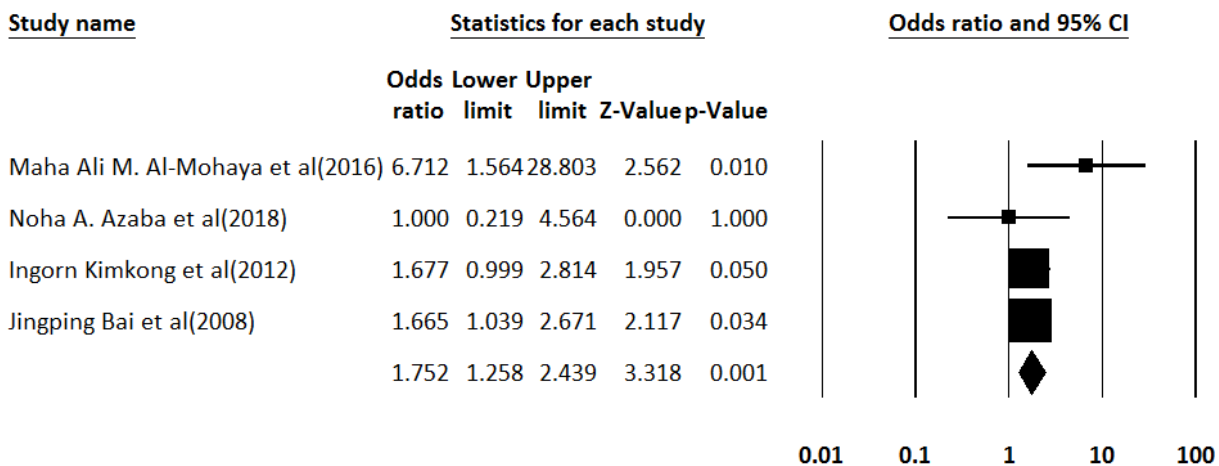


Figure 6. Forest plot of the IFN- γ +874A/T polymorphism and OLP susceptibility in dominant model (TT+AT vs AA). CI=confidence interval, OR=odds ratio.

Discussion

Many studies have identified IFN- γ as a key role in the pathogenesis of OLP (3-7). Recent studies have also shown links between IFN- γ gene polymorphism and OLP (12-14). The purpose of the present study was to identify and systematically analyze all relevant clinical studies to investigate the association of the IFN- γ (+874 A/T) gene polymorphism and susceptibility to OLP. The present study is the first quantitative evaluation of the association between IFN- γ (+874 A/T) gene polymorphism and OLP. Three case-control studies and 1 cohort study were selected to

evaluate IFN- γ (+874 A/T) gene polymorphism in OLP based on inclusion and exclusion criteria. SNP of some genes can alter protein expression, for example there are three possible genotypes for +874 T / A: AA, AT and TT. Each of these genotypes is thought to represent the expression of different levels of IFN- γ (10, 11, 19-23). Following the meta-analysis, there was a positive relationship between IFN- γ (+874 A/T) gene polymorphism and the risk of OLP. In fact, the T allele, and the T allele genotypes (AT and TT genotypes), were more frequently present in OLP than in healthy patients. This finding is similar to the results of studies by

Al-Mohaya et al (24), Kimkong et al (14) and Bai et al (12). However Azaba et al (15) found no significant association between IFN- γ (+874 A/T) gene polymorphism and the risk of OLP. In a closer look at studies, Al-Mohaya et al found that IFN- γ (+874 A/T) gene polymorphism has a significant association with the risk of OLP in the Saudi population (24). The results of the Kimkong et al studies showed that the frequency of the T allele was significantly higher in Thailand OLP patients than in healthy controls(14). Bai et al also found a higher T allele frequency in the Chinese population than in the healthy population(12). However, the results of Azab et al studies did not show a significant relationship between IFN- γ (+874 A/T) gene polymorphism and the risk of OLP disease (15).

This heterogeneity in studies in some comparative models and contradictory conclusions may be attributed to various factors. First, the studies included people from different populations who were conducted in different countries and could be the result of differences in the race of the subjects studied, such as in Saudi Arabia, Thailand, China, and Egypt. Second, it may be the result of different etiologies of OLP. Third, some studies did not use HWE (Hardy – Weinberg equilibrium). Another reason may be related to the low statistical population of some studies.

Similar to this meta-analysis, which shows the association of IFN- γ (+874 A/T) gene polymorphism and the chance of developing OLP, other studies have shown that this SNP is associated with other diseases as well (25-29). Another meta-analysis conducted in 2016 showed a significant relationship between IFN- γ (+874 A/T) gene polymorphism and the chance of autoimmune diseases(16).

These studies demonstrate the importance of this SNP in the development of diseases and the need for further studies to better investigate the role of this SNP. Also in a study reported by et al Marco Carrozzo (13), they identified the first intron of the IFN- γ gene promoter as an important risk factor in the development of OLP oral lesions, indicating that other sites of this gene also need to be further investigated.

This meta-analysis may provide further evidence for understanding the pathogenesis and progression of OLP, as well as a pathological basis for physicians to prognosis and better treatment of this disease.

Conflict of interest:

The authors declare that there is no conflict of interest.

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