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Review Article

Association between interleukin-10 (IL-10) polymorphism (-1,082, A/G) and Sjogren's syndrome: an updated meta-analysis

Sang Wook Kang[1], Su Kang Kim[2], Kyong Jin Cho[3], Chung-Hun Oh[4,5], Ju Yeon Ban[1,5]

[1]Department of Dental Pharmacology, College of Dentistry, Dankook University, Cheonan, Republic of Korea; [2]Kohwang Medical Institute, School of Medicine, Kyung Hee University, Seoul, Republic of Korea; [3]Department of Ophthalmology, Dankook University Hospital, Republic of Korea; [4]Department of Oral Physiology, College of Dentistry, Republic of Korea; [5]Department of Medical Laser, Graduate School, Dankook University, Cheonan, Republic of Korea

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Abstract: To evaluate the association between the polymorphism (-1082, A/G) of the *IL-10* gene and a susceptibility for Sjogren's syndrome (SS). We searched electronic databases including PubMed, Scopus, and Embase databases, and a total of 5 studies including 903 healthy controls and 382 SS cases were analyzed. The meta-analysis of the -1082 polymorphism of the *IL-10* gene was carried out with pooled ORs, 95% CI, and *p* value calculated using the allele, dominant and recessive model. Statistical significance was found in primary SS (pSS) cases in the allele model (G vs. A, OR=0.763, 95% CI=0.610-0.955, P=0.018) and the dominant model (G/G+G/A vs. A/A, OR=0.664, 95% CI=0.479-0.920, P=0.014). Our meta-analysis revealed that the polymorphism (-1,082, A/G) of the *IL-10* gene might be related to a susceptibility for pSS.

Keywords: *IL-10*, polymorphism, case and control study, meta-analysis, Sjogren's syndrome

Introduction

Interleukin-10 (IL-10) is well known to play a major role in innate and adaptive immune responses [1]. First, it is known to be a cytokine synthesis inhibitory factor due to its role in regulating Th1 activation and cytokine production [2, 3]. IL-10 regulates the growth or differentiation of various immune cells including B cells, NK cells, T cells, etc., and it also controls the human immune response and tolerance [4]. An inhibitory effect on the T lymphocytes of IL-10 mainly occurs through the inhibition of antigen-presenting cells (APC) and MHC class II expression [1]. The dysregulation of IL-10 could affect the immune and inflammatory response, resulting in immuno-deficiency or autoimmunity [5]. A previous study suggested that the polymorphisms in the promoter region of the *IL-10* gene could affect IL-10 production and increase the risk of systemic lupus erythematosus [6]. Patients with rheumatoid arthritis also exhibited an association between the promoter polymorphism of the *IL-10* gene and autoantibody production [7]. Likewise, several studies have tried to clarify the link between the *IL-10* polymorphism and autoimmune disease. Polymophism (-1, 082) of the *IL-10* gene might be useful to predict disease behavior in Crohn's disease [8], and promoter haplotypes of the gene could be associated with rheumatoid arthritis (RA) [9, 10].

Sjogren's syndrome (SS) is an autoimmune disease that is characterized by lymphocytic infiltration of exocrine glands, resulting in sicca symptoms of dry eyes and dry mouth [11]. Its annual incidence was reported to vary between 3.9 and 5.3 individuals per 100,000 [12]. SS has also been studied for its inflammatory and autoimmune nature. An increase in the Th1 cytokine expression frequency was reported in minor salivary glands of patients with primary SS [13]. The IL-10 levels in the saliva of SS patients are reported to be correlated with the degree of xerophthalmia and xerostomia [14]. IL-10 protein production has a close association with the *IL-10* gene promoter

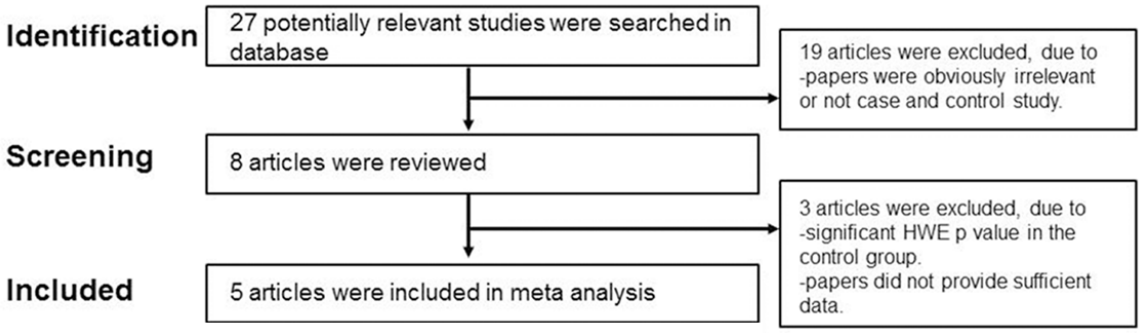

Figure 1. Flow chart illustrating the search strategy used in this meta-analysis to identify studies that examined the association between the *IL-10* polymorphism (-1,082, A/G) and a susceptibility for Sjogren's syndrome.

polymorphism [15]. *IL-10* -592, -819, and -1082 are well-known single nucleotide polymorphism in the promoter region of *IL-10* gene, and their haplotypes were investigated to show an association with SS [16-20].

These previous studies investigated the association between the *IL-10* polymorphism and SS, but the results are not obvious. In 2013, a meta-analysis studied the association between the *IL-10* polymorphisms and the development of SS to clarify this association in bigger samples [21]. Since then, two more studies have reported on the relation between the *IL-10* polymorphism and the development of SS [16, 22]. Therefore, the aim of this meta-analysis is to update previous meta-analyses and to evaluate the association of the *IL-10* polymorphism with a susceptibility for SS.

Method

Search strategy

To identify all of the eligible studies investigating the association between the *IL10* polymorphism (-1,082, A/G) and a susceptibility for SS, we conducted a systematic literature search in PubMed, Scopus, and Embase databases up to June 1, 2016. The following search terms were used to find these articles: "Sjogren's Syndrome", or "SS", and "IL-10", "polymorphism", "polymorphisms", or "-1,082" and/or "meta analysis". These keywords were used in combination or in isolation. Previous meta-analyses on the *IL-10* (-1,082, A/G) polymorphism and SS were checked as reference, and additional studies were obtained through a manual search of the references of the original studies.

Inclusion criteria and exclusion criteria

The studies were included if they met the following criteria: (1) evaluation of the association between the *IL-10* polymorphism (-1,082, G/A) and SS; (2) designed using the methodology of a case-control study; (3) contained sufficient distribution of *IL-10* polymorphisms (-1,082, A/G) in the SS group and the control group to estimate an odds ratio (OR), 95% confidence interval (CI), and *p* value. Studies were excluded from the meta-analysis if they consisted of articles with insufficient genetic data or deviated from HWE in the control group.

Data extraction

The data were extracted and consensus was reached for all items by the researchers. If the results were different, they would check the data again and have a discussion to come to an agreement. The data extracted from the selected articles included the first author's name, year of publication, subject population, number of cases and controls, and genotype frequency of the *IL-10* polymorphism (-1,082, G/A).

Statistical analysis

The meta-analysis was anducted using the comprehensive meta-analysis software (Corporation, NJ, USA). The pooled *p* value, OR and 95% CI were used to measure the association between the risk for SS and *IL-10* polymorphism (-1,082, G/A). The random effects model or the fixed effects model was used and sensitivity analysis was performed to determine the influence of each study on the final results. We first calculated the hetero-

Table 1. Information of eligible studies included in the meta-analysis

Diseases	Authors (year)	Country	Study design	Ethnicity	Genotyping method	Gender*	Age	Control		Case		Control			Case			HWE
								G	A	G	A	G/G	G/A	A/A	G/G	G/A	A/A	
pSS	Vázquez-Villamar et al. 2015	Mexico	Case-control study	Mexican Mestizos	PCR-RFLP	0/111	57±10	72	150	65	157	11	50	50	6	53	52	0.77
pSS	Font et al. 2002	Spain	Case-control study	Caucasian	Direct sequencing	4/59	57 (20-83)	103	197	61	65	21	61	68	13	35	15	0.229
pSS	Hulkkonen et al. 2001	Finland	Case-control study	Caucasian	Direct sequencing	2/60	60±11	343	457	65	59	77	189	134	16	33	13	0.479
pSS	Origuchi et al. 2003**	Japan	Case-control study	Asian				14	200	8	86	0	14	93	0	8	39	0.469
sSS	Souza et al. 2014	Brazil	Case-control study	Brazilian	PCR-RFLP	0/19	56.65 (39-77)	37	59	8	30	10	17	21	1	6	12	0.08

*, Ratio of gender, male/female; **, no data on genotype method, gender, and age; HWE, Hardy-Weinberg equilibrium.

Table 2. Overall analysis between IL-10 polymorphism (-1,082, A/G) and susceptibility of Sjogren's syndrome

Genotype comparison	Type	Population	Heterogeneity		Model	OR	Association test		Publication bias bias p
			P	I^2			95% CI	P	Egger's P
G *vs*. A	All	All	0.014	67.953	Random	0.882	0.581-1.340	0.558	0.456
		Caucasian	0.006	75.899	Random	0.913	0.563-1.480	0.712	0.339
	pSS	All	0.086	54.579	Fixed	0.763	0.610-0.955	0.018	0.965
		Caucasian	0.037	69.714	Random	0.762	0.500-1.161	0.206	0.900
GG *vs*. GA+AA	All	All	0.113	49.842	Fixed	0.86	0.561-1.319	0.49	0.116
		Caucasian	0.113	49.842	Fixed	0.86	0.561-1.319	0.49	0.116
	pSS	All	0.181	41.438	Fixed	0.801	0.517-1.239	0.319	0.342
		Caucasian	0.181	41.438	Fixed	0.801	0.517-1.239	0.319	0.342
GG+GA *vs*. AA	All	All	0.029	62.957	Random	0.755	0.440-1.296	0.309	0.695
		Caucasian	0.013	72.218	Random	0.769	0.397-1.486	0.434	0.713
	pSS	All	0.088	54.158	Fixed	0.664	0.479-0.920	0.014	0.621
		Caucasian	0.039	69.207	Random	0.613	0.325-1.157	0.131	0.114

OR, odds ratio; CI, confidence interval.

geneity of the studies. The heterogeneity assumption was calculated using the chi-square-based Q test and I^2 test. The random-effects Mantel–Haenszel method was adopted when the result of the Q test was P<0.05 or the I^2 statistic was >50%. This indicated that a statistically significant heterogeneity was present between the studies. Otherwise, the fixed-effects Mantel-Haenszel method was adopted.

For a meta-analysis of the *IL-10* polymorphism (-1,082, G/A), the pooled ORs, 95% CI, and *p* value were calculated using a combination of the genotype. We evaluated the risks of the "G allele vs. A allele", "G/G genotype vs. G/A+A/A genotype", and "G/G+G/A genotype vs. A/A genotype" on the risk of SS, assuming dominant and recessive effects of the variant A allele, respectively [23]. Egger's linear regression test was performed to observe the publication bias, and P<0.05 was regarded to be a statistically significant evidence of asymmetry.

Result

Study characteristics

Figure 1 shows a flow chart illustrating the search strategy used in this meta-analysis to identify studies that examined the association between the *IL-10* polymorphism (-1,082, A/G) and the susceptibility for Sjogren's syndrome. First, 27 articles were searched through databases including PubMed, Scopus, and Embase. Of the 27 articles, 19 articles were excluded because the papers were obviously irrelevant or were not case and control studies. Three articles that deviated from HWE in the control group were also excluded in meta-analysis. Finally, five articles were included in the meta-analysis, and the characteristics of these eligible articles are summarized in **Table 1**. There were four articles with primary SS (pSS) and one article with secondary SS (sSS).

IL-10 polymorphism (-1,082, A/G) and susceptibility of Sjogren's syndrome

We first evaluated the relationship between a susceptibility for SS and the *IL-10* polymorphism (-1,082, A/G) (**Table 2**). No association was observed between the *IL-10* polymorphism (-1,082, A/G) and SS in the allele, dominant, and recessive model (P>0.05, respectively). Also, no significant association was observed in the Caucasian population.

Second, we analyzed the relationship between primary SS and the IL-10 polymorphism (-1,082, A/G). In the subgroup analysis according to SS type, the pooled OR, 95% CI, and *p* value were obtained in the allele model (G vs. A, OR=0.763, 95% CI=0.610-0.955, P=0.018)

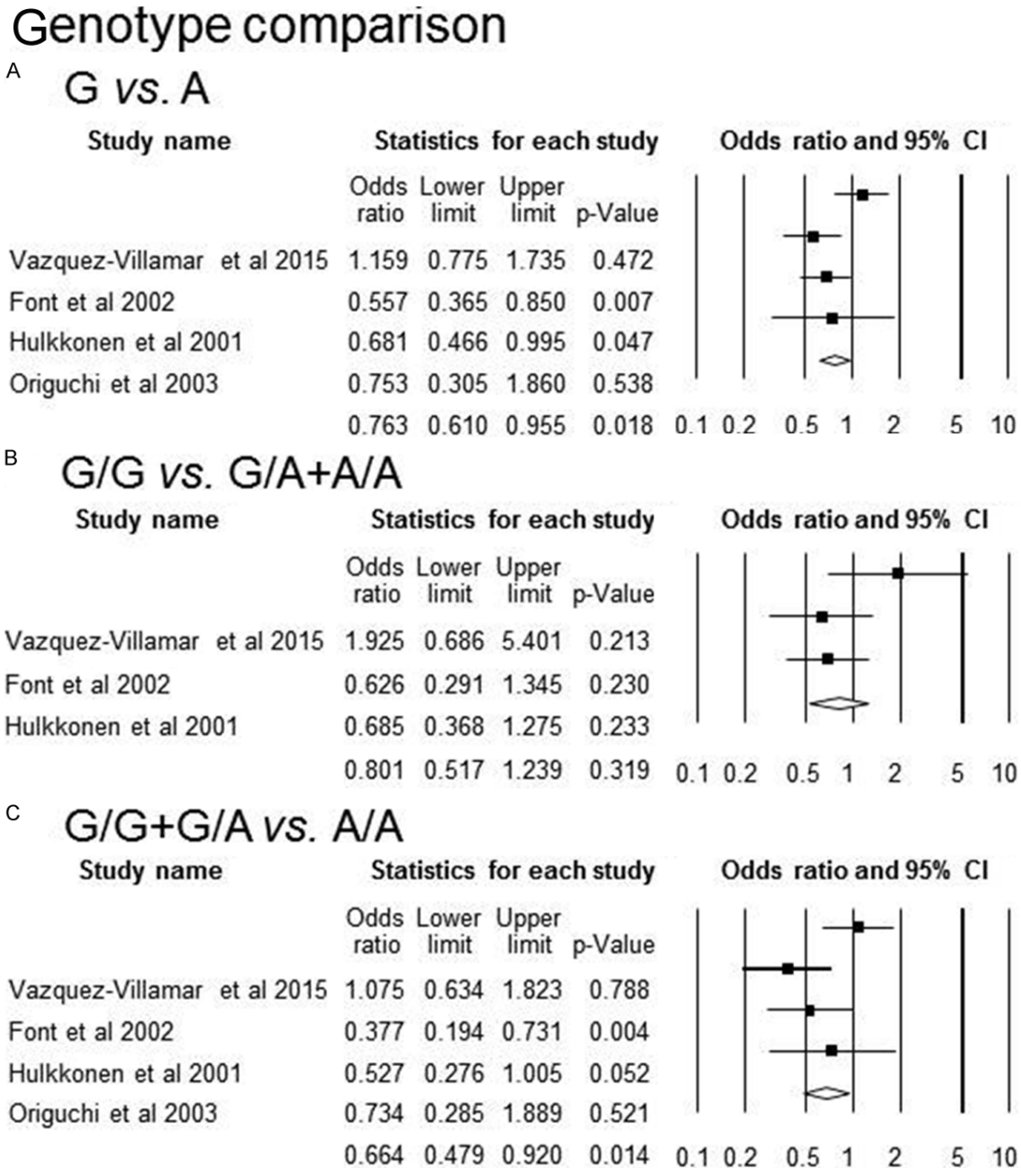

Figure 2. Odds ratio and 95% CI of individual and pooled data for the *IL-10* polymorphism (-1,082, A/G) and a susceptibility for primary Sjogren's syndrome. A: G allele vs. A allele; B: G/G genotype vs. G/A genotype+A/A genotype; C: G/G genotype+G/A genotype vs. A/A genotype.

and the dominant model (G/G+G/A vs. A/A, OR=0.664, 95% CI=0.479-0.920, P=0.014) (**Table 2** and **Figure 2**). The *p* value was identified through a sensitivity analysis.

The funnel plots were created by plotting the standard error against the OR for each study. No evidence of asymmetry was indicated in the funnel plots (P>0.05) and Egger's linear regression test showed that there was no publication bias (P>0.05).

Discussion

Sjogren's syndrome is one of the more prevalent forms of autoimmune disease with a

complex pathogenesis, and its etiopathogenesis and immunopathology have not yet been completely elucidated. SS is best characterized by the lymphocytic infiltration of the exocrine glands and epithelia, and this causes xerophthalmia and xerostomia [12]. An altered cytokine balance has already been reported to in SS patients [24]. IL-10 is a famous cytokine that plays an important role in the inflammatory and immune responses, and its expression patterns could be influenced by genetic factors that cause alterations in the IL-10 expression and disease [1]. Several reports indicated that a reduced expression of IL-10 is associated with the development of some autoimmune disorders [25, 26]. Thus, we have performed this meta-analysis to evaluate the association between the polymorphism (-1082, A/G) of the IL-10 gene and the development of SS.

As mentioned above, a meta-analysis had already examined the association between the *IL-10* polymorphism and the development of SS and reported the association of IL-10 and pSS [21]. The study had included a total of 7 articles [17-20, 27-29]. Among these, however, no genotype data had been presented in those written by Limaye et al. and Willeke et al., so these were excluded from the current meta-analysis. The articles by Marka et al. and Gottenberg et al. were also excluded because they were not in Hardy-Weinberg equilibrium, and two recent studies testing for an association between the *IL-10* polymorphism and SS were added in this meta-analysis [16, 22]. Finally, a total of 5 studies including 903 healthy controls and 382 SS cases were examined.

Our results showed a statistical significance in pSS, but this result needs to be interpreted carefully. When all SS cases are included (pSS+sSS), there was no significance. However, when we excluded the sSS cases, we found a statistical association. The study by Origuchi et al. was performed in the Japanese population. According to the NCBI HapMap database (http://www.ncbi.nlm.nih.gov), the genotype frequency of polymorphism (-1082, A/G) of the *IL-10* gene differs according to ethnicity. The genotype frequency of polymorphism (-1082, A/G) of the *IL-10* gene is almost monomorphic in the Japanese populashion (AA:GA:GG=0.907:0.081:0.011). Since that could have affected our result, the data should be ruled out in the analysis process by using a sensitivity analysis.

Our results showed no association between polymorphism (-1082, A/G) of the *IL-10* gene and SS. However, we could not examine the ethnic distribution because most studies included Caucasian populations while only one was carried out with an Asian population. There were too few studies on Asians and no studies on African populations to examine the ethnic distribution of the polymorphism (-1082, A/G) of the *IL-10* gene and the development of SS. Some previous studies found a statistically significant association with the GCC haplotype [17, 19, 20]. Souza et al. and Marka et al. reported no association in the genotype of the polymorphism (-1082, A/G) of the *IL-10* gene and the development of SS [22, 28].

Although our result failed to show a statistical association between the *IL-10* gene and a susceptibility for SS, our results could show a statistical significance in the allele and genotype distribution in pSS. And no evidence of publication bias or influence of each individual study was observed. Our results showed a possible association between the polymorphism (-1082, A/G) of the *IL-10* gene and pSS. If more results are accumulated in further studies, this association would become clearer.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ju Yeon Ban, Department of Dental Pharmacology, School of Dentistry, Dankook University, Cheonan 31116, Republic of Korea. E-mail: jyban@dankook.ac.kr

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