REVIEW

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Associations of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with susceptibility to celiac disease: evidence from a meta-analysis and literature review

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ABSTRACT – **Background** – There has been little evidence to suggest that the IL-6 -174G>C and IL-10 -1082A>G polymorphisms are significantly associated with susceptibility to celiac disease. Thus, we performed the present meta-analysis to explore the potential association between these polymorphisms and celiac disease risk. **Methods** – Eligible studies were searched in PubMed, Medline, Embase, Web of Science and CNKI database up to April 20, 2019. Odds ratios with 95% confidence interval were calculated to assess the potential associations. Moreover, we performed the heterogeneity, sensitivity, and publication bias tests to clarify and validate the pooled results. **Results** – Overall, nine case-control studies involving five studies with 737 cases and 1,338 control on IL-6 -174G>C polymorphism and four studies with 923 cases and 864 controls on IL-10 -1082A>G polymorphism were selected. The pooled ORs showed that the IL-6 -174G>C and IL-10 -1082A>G polymorphisms were not significantly associated with increased risk of celiac disease under all five genetic models. There was no publication bias. **Conclusion** – To the best of our knowledge, this is the first meta-analysis summarizing all of the available studies on the association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with celiac disease. Our results suggest that the IL-6 -174G>C and IL-10 -1082A>G polymorphisms may not be associated with increased risk of celiac disease. Moreover, large and well-designed studies are needed to fully describe the association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with celiac disease.

HEADINGS – Celiac disease. Interleukin-6. Interleukin-10. Genetic polymorphism.

INTRODUCTION

Celiac disease (CD), also called gluten intolerance, is a chronic and immune-mediated enteropathy with intestinal and extraintestinal manifestations triggered by the ingestion of gluten-containing grains in genetically predisposed individuals[1-3]. A review of celiac disease studies showed a biopsy-proven prevalence ranging from 0.15% to 1.9% in unselected populations of North America and Western Europe[4]. The diagnosis of CD can take several years to confirm and often times the diagnosis can be delayed by patients with a normal or high body mass index (BMI)[5].

The actual etiology of CD is not fully understood, but some risk factors have been implicated in its development, including an association of genetic and environmental factors[6,7]. Nevertheless, few environmental factors such as Infant feeding practices that influence the risk of having CD have been identified[8]. The genetics of CD is closely related to HLA class II molecules HLA-DQ2 or HLA-DQ8, and has received attention for a decade with numerous studies published and several recent reviews. Moreover, genome-wide association studies (GWAS) have expanded our understanding of genetic predisposition and revealed contribution of genes encoding for the pro-inflammatory cytokines in susceptibility to CD[9].

The human IL-6 gene is mapped to chromosome 7p21-24, consists of seven exons and spanning 12.8 kb of genomic DNA[10]. Moreover, the IL-10 gene is mapped to the long arm of chromosome 1 (1q31-32), composed of five exons and spans about 4.7 kb[11,12]. The importance of IL-6 and IL-10 in many physiological and pathological processes, particularly in the autoimmune disease, has been reported[13,14]. In recent decade, a number of studies have reported the association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with CD susceptibility. However, those studies have drawn inconsistent conclusions, because individual study with small sample sizes may be underpowered to detect the association of L-6 -174G>C and IL-10 -1082A>G polymorphisms on susceptibility of CD. In order to get more precision results for the polymorphism and the risk of CD, we carried out a first meta-analysis including all eligible studies published to date to comprehensively examine the association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with susceptibility to CD.

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METHODS

Identification and eligibility of relevant studies

A comprehensive computer searches were carried out in PubMed, Google Scholar, EBSCO, EMBASE, Web of science, Scientific Information Database (SID), Islamic World Science Citation Center (ISC), Wanfang, Ovid, Weipu, China National Knowledge Infrastructure (CNKI) database to collect case-control studies related to the association of association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with CD up to April 20, 2019. The keywords were as follows: (''celiac disease'' OR '' coeliac disease'' OR ''gluten intolerance'' OR ''celiac sprue'' OR ''nontropical sprue'' OR ''endemic sprue'') AND (''*interleukin 6*'' OR ''IL-6'' OR ''-174G>C'' OR ''rs1800795'') AND ('' *interleukin 10'' OR* ''IL-10'' OR ''-1082A>G'' OR ''rs1800896'') AND (''SNPs'' OR ''polymorphism'' OR ''mutation'' OR ''variation'' OR ''allele''). Furthermore, bibliographies of main retrieved case-control and review articles were also checked by a manual search to identify additional eligible studies. Searches were limited to published studies in Persian, Chinese and English.

Inclusion criteria and exclusion criteria

We selected eligible studies according to the following criteria: (1) studies with case-control and cohort design; (2) evaluated the association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with CD; (3) adequate data to that odds ratios (ORs) with 95% confidence intervals (CIs); (4) the study had to be published using human subjects. Exclusion criteria were: (1) insufficient data on the distribution of IL-6 -174G>C and IL-10 -1082A>G loci genotypes; (2) case-only, linkage and family based studies; (3) case reports, posters, reviews, abstracts, letter to editors, previous meta-analyses; and (4) duplicates of previous studies or data. If a study was subsequently updated, we selected the study with the largest sample size. The authors independently checked all studies to examine whether the eligible studies fulfilled the inclusion criteria.

Data extraction

Two independent investigators reviewed and extracted data from all eligible publications based on the inclusion and exclusion criteria listed above. Discrepancies were adjudicated by a third author until consensus was reached on all items. The data extracted from each eligible study included the first author's name, year of publication, number of cases and controls, ethnicity, country of study population, source or design of experiment (population- or hospital-based controls), genotyping methods, number of genotyped cases and controls for IL-6 -174G>C and IL-10 -1082A>G loci, Hardy-Weinberg equilibrium (HWE) in controls, and minor allele frequency (MAF). Disputes were settled by consulting the third person. The cases and controls ethnicities were categorized as Caucasian, Asian, African or Mixed.

Statistical analysis

In this meta-analysis, the crude odds ratio (OR) with the corresponding 95% confidence intervals (95% CI) were used to assess the strength of association of the IL-6 -174G>C and IL-10 -1082A>G polymorphisms with risk of CD. The Z-test was used to measure the significance of the pooled OR, and statistical significance was defined as P<0.05 (two-tailed). Five genetic models were used for pooling the ORs, i.e., allele (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. AA), dominant (BB+BA vs. AA) and recessive (BB vs. BA+AA), respectively. The presence of heterogeneity between studies was evaluated with the Cochran's Q statistic; in which $P<0.10$ indicated significant heterogeneity. Moreover, a Chi-square-based I^2 test was used to quantify the degree of heterogeneity ($I^2<25\%$, no heterogeneity; $25\%<I^2<50\%$, moderate heterogeneity; $50\%<I^2<75\%$, large heterogeneity; $I^2>75\%$, extreme heterogeneity). Accordingly, the pooled ORs were examined using a fixed-effects (Mantel-Haenszel method) (if $P>0.05$ or $I^2<50\%$); otherwise, random-effects model (DerSimonian- Laird method) was utilized (if $P<0.05$ or $I2>50\%$) based on the level of heterogeneity. For each case-control study, departure of the IL-6 -174G>C and IL-10 -1082A>G polymorphisms frequencies in control groups from the Hardy-Weinberg equilibrium (HWE) was examined using the chi-square test, and deviation was considered when $P<0.05$. We have tested our results stability and reliability using sensitivity analysis, in which one study was deleted each time and the analyses were repeated. Publication bias was tested with the funnel plot and Egger's linear regression asymmetry test; $P<0.05$ suggested statistically significant publication bias. All analyses were performed with the Comprehensive Meta-Analysis (CMA) 2.0 software (Biostat, USA). Two-sided P-values <0.05 were considered statistically significant. If P value >0.05, the genotype distribution of the control group conformed to HWE.

RESULTS

Study characteristics

The selection process of eligible studies is shown in FIGURE 1. According to our search strategy, 93 articles were initially screened. After duplicates had been removed, then, 48 articles were deter-

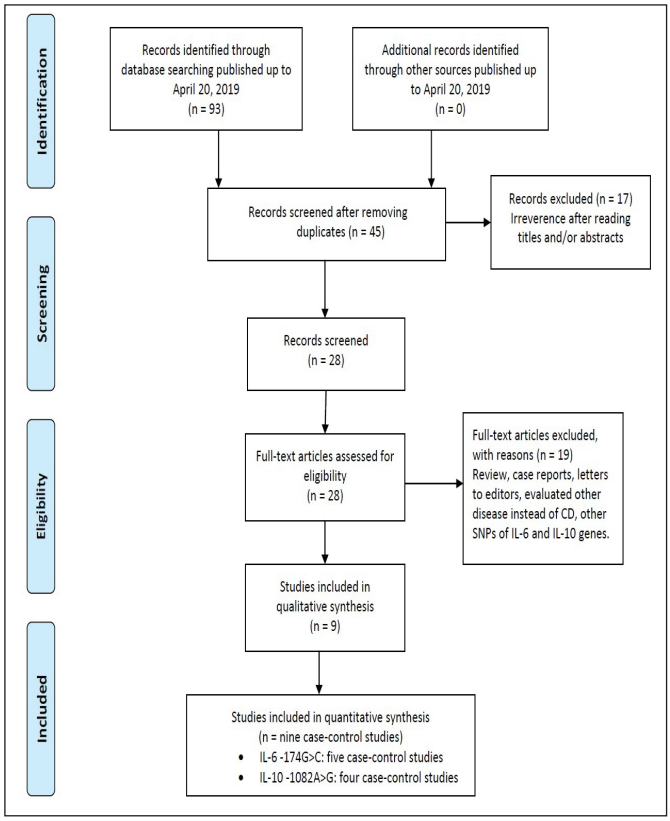

FIGURE 1. Flow chart of study selection process in a systematic review.

mined to be irrelevant papers and not related to the association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with CD and were initially excluded. Afterward, 19 studies that focused on other SNPs rather than IL-6 -174G>C and IL-10 -1082A>G polymorphisms, review articles, case only studies and studies with insufficient data polymorphism were excluded. Finally, a total of nine case-control studies involving five studies with 737 cases and 1,338 control on IL-6 -174G>C polymorphism[15-19], and four studies with 923 cases and 864 controls on IL-10 -1082A>G polymorphism[16,20-22] were selected. The Characteristics of included studies are shown in TABLE 1. All of the selected papers were written in English and published between 2006 and 2018. Among them, eight studies were based on Caucasian (Spain, Italy, and Sweden), and one was based Middle-East Asian (Iran). The IL-6 -174G>C and IL-10 -1082A>G polymorphisms frequencies in each study, results of HWE test in control groups and MAFs are shown in TABLE 1. The distribution of genotypes in all studies was consistent with HWE except for two studies on c IL-6 -174G>C (TABLE 1).

Quantitative synthesis

IL-6 -174G>C polymorphism

TABLE 2 listed the main results of the meta-analysis of IL-6 -174G>C polymorphism with CD risk. When all the eligible studies were pooled into meta-analysis, the results showed that IL-6 -174G>C polymorphism was not significantly associated with increased risk of CD under all genetic models i.e., allele (A vs G:

TABLE 1. Characteristics of literatures included in the meta-analysis.

First author	Country (ethnicity)	Genotyping technique	SOC	Case/ Control	Cases					Controls					MAFs	HWE
					Genotype			Allele		Genotype			Allele			
					GG	GC	CC	G	C	GG	GC	CC	G	C		
IL-6 -174G>C																
Garrote 2005	Spain (Caucasian)	SSP-PCR	HB	44/95	24	14	6	62	26	42	41	12	125	65	0.342	0.687
Barisani 2006	Italy (Caucasian)	PCR-SSP	HB	155/202	62	73	20	197	113	75	96	31	246	158	0.391	0.975
Dema 2009	Spain (Caucasian)	TaqMan	PB	332/835	136	154	42	426	238	386	358	91	1130	540	0.323	0.558
de Albuquerque 2015	Italy (Caucasian)	PCR-RFLP	HB	101/100	52	40	9	71	29	43	53	4	69	31	0.305	0.012
Barartabar 2018	Iran (Asian)	PCR-RFLP	NS	105/106	38	60	7	136	74	12	90	4	114	98	0.462	≤0.001
IL-10 -1082A>G					**AA**	**GA**	**GG**	**A**	**G**	**AA**	**GA**	**GG**	**A**	**G**		
Hahn-Zoric 2003	Sweden (Caucasian)	PCR-RFLP	HB	93/103	31	41	21	103	83	18	59	26	95	111	0.539	0.121
Lio 2005	Italy (Caucasian)	ARMS-PCR	HB	110/220	34	52	24	120	100	66	102	52	224	206	0.468	0.306
Barisani 2006	Italy (Caucasian)	PCR-RFLP	HB	155/202	46	83	26	175	135	76	97	29	249	155	0.384	0.827
Zupin 2014	Italy (Caucasian)	TaqMan	PB	565/338	202	278	85	682	448	118	166	54	402	274	0.405	0.729

SOC: source of controls; HB: hospital based; PB: population based; RFLP: restriction fragment length polymorphism; ARMS: amplification-refractory mutation system; MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium.

TABLE 2. Meta-analysis results of association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with CD risk.

Polymorphism	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
IL-6 -174G>C	A vs G	Fixed	55.80	0.060	0.984	0.857-1.131	-0.227	0.820	0.806	0.142
	AA vs GG	Fixed	0.00	0.473	1.101	0.804-1.507	0.601	0.548	0.806	0.495
	AG vs GG	Random	82.44	≤0.001	0.654	0.378-1.311	-1.520	0.128	0.220	0.052
	AA+AG vs GG	Random	81.36	≤0.001	0.693	0.418-1.151	-1.417	0.157	0.086	0.046
	AA vs AG+GG	Fixed	0.00	0.542	1.149	0.856-1.543	0.924	0.356	0.462	0.425
IL-10 -1082A>G	A vs G	Fixed	44.29	0.146	0.973	0.848-1.116	-0.395	0.693	0.308	0.708
	AA vs GG	Fixed	36.43	0.194	0.925	0.696-1.230	-0.534	0.594	0.734	0.706
	AG vs GG	Random	64.46	0.038	0.921	0.618-1.373	-0.404	0.687	0.734	0.541
	AA+AG vs GG	Fixed	52.08	0.100	0.882	0.637-1.221	-0.757	0.449	0.308	0.418
	AA vs AG+GG	Fixed	0.00	0.859	0.960	0.747-1.234	-0.316	0.752	0.734	0.843

CD: celiac disease; OR: odds ratio; CI: confidence interval.

OR=0.984, 95% CI 0.857–1.131, *P*=0.820, FIGURE 2A), homozygote (AA vs GG: OR=1.101, 95% CI 0.804–1.507, *P*=0.548), heterozygote (AG vs GG: OR=0.654, 95% CI 0.378–1.311, *P*=0.128), dominant (AA+AG vs GG: OR=0.693, 95% CI 0.418–1.151, *P*=0.157), and recessive (AA vs AG+GG: OR=1.149, 95% CI 0.856–1.543, *P*=0.356).

IL-10 -1082A>G polymorphism

TABLE 2 listed the main results of the meta-analysis of IL-10 -1082A>G polymorphism with CD risk. When all the eligible studies were pooled into meta-analysis, the results showed that IL-10 -1082A>G polymorphism was not significantly associated with increased risk of CD under all genetic models genetic models i.e., allele (A vs. G: OR=0.973, 95% CI 0.848–1.116, *P*=0.693), homozygote (AA vs GG: OR=0.925, 95% CI 0.696–1.230, *P*=0.594), heterozygote (AG vs GG: OR=0.921, 95% CI 0.618–1.373, *P*=0.687), dominant (AA+AG vs GG: OR=0.882, 95% CI 0.637–1.221, *P*=0.449), and recessive (AA vs AG+GG: OR=0.960, 95% CI 0.747–1.234, *P*=0.752, FIGURE 2B).

Sensitivity analysis

Sensitivity analyses were performed after sequential removal of each of the included studies and HWE-violating studies to examine the influence of each individual data-set on the pooled ORs. However, the pooled ORs and 95% CIs were not significantly altered when any part of the study was omitted, which indicated that any single study had little impact on the overall ORs. Moreover, we included also those HWE-violating studies for IL-6 -174G>C polymorphism in the current meta-analysis. However, after those studies were excluded, the IL-6 -174G>C polymorphism association with CD risk was not adjusted (data not shown).

Publication bias

We used visual inspection of funnel plots and Egger's test to evaluate the publication bias in the current meta-analysis. The shape of funnel plots showed no obvious asymmetry and the result of Egger's test did not show statistical evidence for bias. The Egger's test also showed that All the *P* values were more than 0.05 for IL-10 -1082A>G (TABLE 2). Thus, no evident publication bias was found in present study, and the result of the study is reliable and credible. However, publication bias in the included studies for IL-6 -174G>C polymorphism showed evidence of an asymmetry under dominant model and supported by Egger's test (P_{Beggs}=0.086 and P_{Eggers}=0.046, TABLE 2). Thus, we utilized the Duval and Tweedie non-parametric "trim and fill" method to testing and adjusting the publication bias for IL-6 -174G>C polymorphism. However, the results did not adjust, indicating that our results were statistically robust and reliable (FIGURE 3).

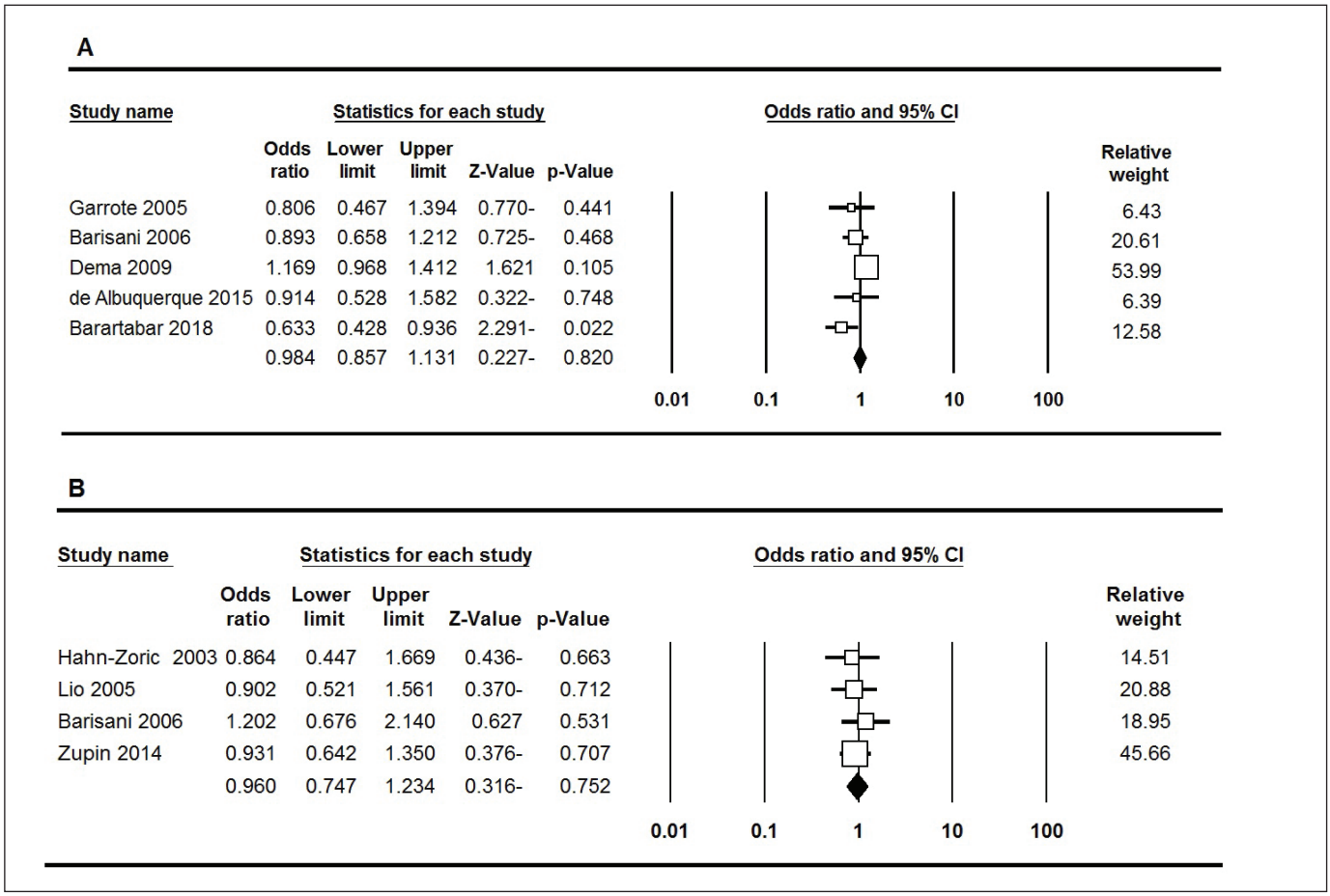

FIGURE 2. Forest plot of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with CD. **A)** IL-6 -174G>C (allele model: A vs G); **B)** IL-10 -1082A>G (recessive model: AA vs AG+GG).

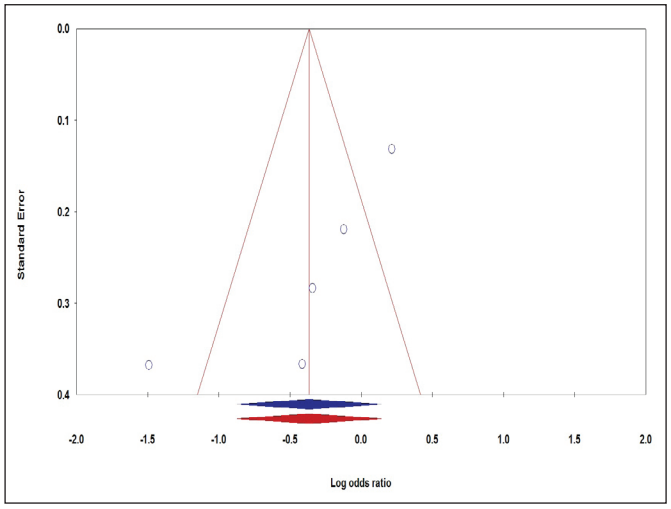

FIGURE 3. Funnel plot for publication bias in the meta-analysis of IL-6 -174G>C polymorphism and CD risk under the dominant model (AA+AG vs GG). "Blue" without and "red" with trim and fill method.

DISCUSSION

CD is a long term and complex immune-mediated enteropathy with a very strong genetic component. Multiple genetic findings over the last decade have added to the already known HLA-DQ2 and HLA-DQ8 haplotypes influence numerous loci associated to risk of CD[23]. In the present study, we performed a comprehensive meta-analysis to evaluate the association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms to susceptibility CD based on all available studies. The results demonstrated that the IL-6 -174G>C and IL-10 -1082A>G polymorphisms not significantly associated with risk of CD in overall population. Most of the studies included in this meta-analysis were recruited from Caucasian populations. So, we did not analyze the association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with CD risk by ethnicity, and future studies should address this point.

As a pleiotropic cytokine, IL-6 can regulate many cell functions, including immune defensive mechanism, cell proliferation, and differentiation, and also the production of haemocytes. Previous epidemiological studies have shown an association between IL-6 -174G>C polymorphism and CD risk, but the results are controversial and inconclusive. For example, de Albuquerque et al., in a case-control of 192 CD cases and 96 controls from northeast Italy evaluated the association IL-6 -174G>C polymorphism with CD. Their results showed a statistically significant association between IL-6 -174 G>C polymorphism and CD[18]. Dema et al., have reported that the IL-6 -174G>C polymorphism was significantly associated with increased risk of CD susceptibility in Spanish girls[17]. However, Barartabar et al., not found a significant association between IL-6 -174G>C polymorphism and increased risk of CD in an Iranian population[19]. This inconsistency could result from relatively small sample size, from genetic ethnical heterogeneity or from unknown local environmental factors. In current meta-analysis, we pooled all five eligible case-control studies addressing the association of the IL-6 -174 G>C polymorphism with CD, and the results revealed a negative association between this polymorphism and risk of CD.

There has been little evidence to suggest association between the IL-10 -1082A>G polymorphism and CD risk, and their results are inconclusive. Hahn-Zoric et al., have evaluated the association of the IL-10 -1082A>G and TNF- -308 G>A polymorphisms with CD risk in a Swedish population. Their results showed a possible involvement of IL-10 -1082A>G polymorphism in the development of CD[20]. Zupin et al., in a study evaluated the association of IL-10 -1082A>G, -819T>C and -592A>C polymorphisms with CD risk in 565 cases and 576 controls from north-eastern Italy[22]. Their results showed that the IL-10 polymorphisms were not significantly associated with increased risk CD in the population. Lio et al., not found differences in genotype frequencies of IL-10 -1082A>G polymorphism between cases with CD and controls in an Italian population[21]. To statistically discuss this association, we designed the present meta-analysis based on all previously published studies. After data syntheses, we found no significant association between IL-10 -1082A>G polymorphism and the susceptibility to CD in overall population. For the low penetrance CD susceptibility gene effects from SNP, these important genetic and environmental factors should be adequately considered.

To the best of our knowledge, our study is the first meta-analysis focused on the association of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with CD risk. In addition, the methodological issues for meta-analysis, such as, heterogeneity, publication bias, and sensitivity analysis for stability of results were all carefully investigated. Despite these advantages, some limitations in current study should be acknowledged when interpreting our results. First, this meta-analysis was limited by the small sample size, which needs further investigations. Second, in this meta-analysis study, all case-control studies were recruited from Caucasians and thus, the results may be applicable to the Caucasian populations only. Further studies in others ethnic groups are required to give more comprehensive understanding the exact role of these polymorphisms on CD risk. Third, only published studies were recruited in this meta-analysis, publication bias might have inevitably occurred. Fourth, only articles that were published in English, Persian and Chinese, and studies with available full-text articles were included in this meta-analysis; therefor, some eligible studies that have not been unpublished or were reported in other languages were missed, which may influence the pooled results. Finally, CD is a multifactorial disease that results from complex interactions between genetic and environmental factors. Due to the lack of uniform background data for recruited studies, our results were based on unadjusted estimates, data were not stratified by other factors such as age, gender, lifestyle factors, environment factors, and other risk factors of CD risk. With more data becoming available, it might be evaluate the association with more reliable results.

In summary, our pooled data indicated that the IL-6 -174G>C and IL-10 -1082A>G polymorphisms are not an important susceptibility genetic factor for CD development. However, to reach a definitive conclusion, further well-designed studies with larger sample size, detailed data and in others ethnic groups are required to further clarify the exact role of IL-6 -174G>C and IL-10 -1082A>G polymorphisms with CD risk. Moreover, gene-gene and gene-environment interactions studies should also be considered in future studies.

Authors' contribution

Conceived and designed the experiments: Aflatoonian M, Sivandzadeh G, Neamatzadeh H. Performed the experiments: Akbarian-Bafghi MJ, Morovati-Sharifabad M. Analyzed the data: Mirjalili SR, Neamatzadeh H. Contributed reagents/materials/analysis tools: Mirjalili SR, Neamatzadeh H, Aflatoonian M. Wrote the manuscript: Neamatzadeh H, Akbarian-Bafghi MJ, Aflatoonian M. Revised manuscript: Sivandzadeh G, Aflatoonian M.

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RESUMO – **Contexto** – Há poucas evidências para sugerir que os IL-6 -174G>C e IL-10 -1082A>G polimorfismos são significativamente associados com susceptibilidade para doença celíaca. Assim, foi realizada a presente meta-análise para explorar a potencial associação entre estes polimorfismos com o risco de doença celíaca. **Métodos** – Foram pesquisados estudos elegíveis no Pubmed, Medline, Embase, Web of Science e CNKI Database até abril de 2019. Razões de probabilidades com 95% de intervalo de confiança foram calculados para avaliar as potenciais associações. Além disso, observou-se a heterogeneidade, a sensibilidade e o viés de publicação para esclarecer e validar os resultados agrupados. **Resultados** – No total, nove estudos caso-controle envolvendo cinco estudos com 737 casos e 1.338 controle em IL-6 -174G>C polimorfismo e quatro estudos com 923 casos e 864 controles em IL-10 -1082A>G polimorfismo foram selecionados. As razões de probabilidade mostraram que o IL-6 -174G>C e IL-10 -1082A>G polimorfismos não estavam significativamente associados com aumento risco de doença celíaca nos cinco modelos genéticos. Não foi detectado viés de publicação. **Conclusão** – Pelo nosso conhecimento esta é a primeira meta-análise resumindo todos estudos disponíveis para associação de IL-6 -174G>C e IL-10 -1082A>G polimorfismos com doença celíaca. Estes resultados sugerem que os IL-6 -174G>C e IL-10 -1082A>G polimorfismos podem não ser associados com aumento risco de doença celíaca. Além disso, maiores estudos e mais bem desenhados são necessários para descrever totalmente a associação de IL-6 -174G>C e IL-10 -1082A>G polimorfismos com doença celíaca.

DESCRITORES – Doença celíaca. Interleucina-6. Interleucina-10. Polimorfismo genético.

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