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Original Article

Association between the *MYO9B* polymorphisms and celiac disease risk: a meta-analysis

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Abstract: Background: There is no consensus regarding the association between polymorphisms in the myosin IXB (*MYO9B*) gene and celiac disease (CD) risk. In this study, we performed a meta-analysis to evaluate genetic variants in *MYO9B* with CD. Methods: Four *MYO9B* polymorphisms (rs1545620, rs1457092, rs2305767 and rs2305764) were assessed. A literature search was conducted using PubMed, Scopus, and Web of Science databases until June 2015. Odds ratio (OR) and 95% confidence interval (CI) were used to investigate the strength of the association under dominant, recessive, homozygote and allelic comparison models. Results: Seven case-control studies with a total of 1965 CD patients and 4894 controls were included in this meta-analysis. The results showed that rs1545620 was associated with CD risk in Europeans in dominant (OR=1.31, 95% CI: 1.10-1.58, P_z=0.003), recessive (OR=1.36, 95% CI: 1.08-1.72, P_z=0.009), homozygote (OR=1.55, 95% CI: 1.20-2.01, P_z=0.001), and allelic comparison models (OR=1.24, 95% CI: 1.10-1.40, P_z=0.001), whereas in a Latin American group there were significant associations of CD with rs1457092 in dominant (OR=15.30, 95% CI: 3.51-66.67, P_z<0.001), homozygote (OR=16.55, 95% CI: 3.62-75.65, P_z<0.001), and allelic comparison models (OR=1.95, 95% CI: 1.31-2.91, P_z=0.001), and rs2305767 in dominant (OR=5.35, 95% CI: 2.42-11.86, P_z<0.001) and allelic comparison models (OR=1.65, 95% CI: 1.11-2.45, P_z=0.013). There was no association between rs2305764 and CD risk in either Europeans or the Latin American group. Conclusion: rs1545620 is associated with CD risk in Europeans, whereas rs1457092 and rs2305767 are associated with CD risk in a Latin American group.

Keywords: Celiac disease, meta-analysis, myosin IXB, polymorphism

Introduction

Celiac disease (CD) is a chronic immune-mediated disorder characterized by a gluten-sensitive enteropathy resulting in damage to the mucosa in the small intestine [1]. It is the commonest immunological gastrointestinal disorder in the western world, affecting 0.6 to 1.0% of the population in the USA and most European countries [2]. CD can present at any age, but most adult cases occur in the 4th and 5th decades of life. The majority of patients present with 'classical' symptoms of malabsorption: weight loss, diarrhea or failure to thrive [1]. However, it has become increasingly clear that the clinical features of CD are varied and may include 'non-classical' presentations, including anaemia, abdominal pain, glossitis and irritable bowel syndrome type symptoms [2]. Lifelong adherence to a strict gluten-free diet is the only current effective treatment for the disease [3].

Genetic factors play a critical role in predisposition to CD. The strongest and best-characterized genetic susceptibility factor in CD is the human leukocyte antigen (*HLA*)-*DQ* locus [4, 5]. *HLA-DQ* is responsible for presentation of toxic cereal derived peptides to intestinal immune cells. The *HLA-DQ2* haplotype (*DQA1*0501/DQB1*0201*) is found in greater than 90% of Northern European CD patients; however, it is also found in one third of the general population, implicating that the *HLA* association is necessary but not sufficient to explain the hereditary nature of the disease [6]. The *HLA-DQ* locus is estimated to account for 35% of the heritable risk of CD [6]. Recent genome-wide association (GWA) and multilineage studies have identified a number of common non-HLA genes which also contribute to the development of CD, including cytotoxic T-lymphocyte antigen 4 (CTLA-4), interleukin-2 (IL-2), protein tyrosine phosphatase nonreceptor 22 (PTPN-

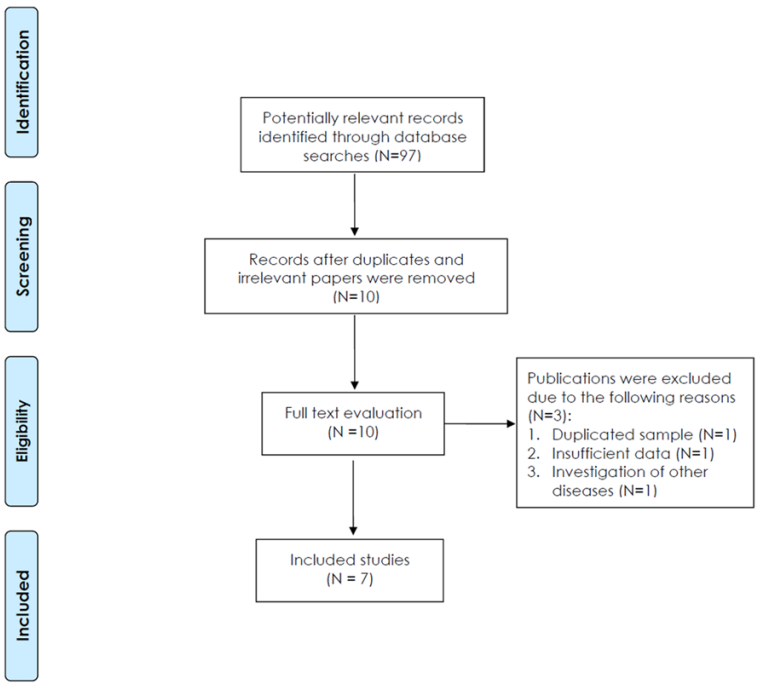

Figure 1. Prisma flow diagram.

22), and SH2B adaptor protein 3 (SH2B3) [7-10]. Identifying non-*HLA* genetic factors for CD will not only lead to a greater understanding of CD pathogenesis, but also allow the generation of newer therapeutic modalities.

The Myosin IXB (*MYO9B*) gene is located at 19p13.1 and was recently considered as a susceptibility gene to CD [11]. *MYO9B* encodes a Ras homologous (Rho) family guanosine-triphosphatase (GTPase) activating protein, which is involved in epithelial cell cytoskeletal organization and influences tight junction assembly [12, 13]. Human MYO9B is expressed in intestinal epithelial cells, and increased *MYO9B* gene expression is correlated with increased intestinal permeability *in vivo* [14]. MYO9B is also highly expressed in immune cells, suggesting a direct role in immune function [15]. Many single nucleotide polymorphisms (SNPs) have been identified in the *MYO9B* gene. Among them, four polymorphisms are most frequently analyzed: rs1545620 A>C (exon 20), rs1457092 C>A (intron 20), rs2305767 A>G (intron 14), and rs2305764 A>G (intron 28). Several association studies have evaluated the relationship of these polymorphisms with CD, but the results of these studies remain contradictory rather than convincing, possibly because single studies may have been underpowered. Given the amount of accumulated data and the still equivocal role of *MYO9B* in the etiology of CD, we aim to perform a meta-analysis of published case-control studies to investigate potential associations between the *MYO9B* polymorphisms and CD risk.

Materials and methods

Literature search

The literature searches were conducted using PubMed, Scopus, and Web of Science until June 2015 for eligible studies. The search strategy included using the keywords "celiac disease, CD, case-control studies, polymorphism, risk, genetics, myosin IXB, and MYO9B". All relevant publications identified through the search were scanned on the basis of title and abstract by one of us and were rejected in the initial screening if the study clearly did not meet the inclusion criteria. The remaining studies were then evaluated in their entirety. Only papers published in the English language were considered for inclusion. The reference lists of identified studies were also searched by hand for relevant papers.

Inclusion and exclusion criteria

Qualified studies had to meet the following criteria: (1) case-control study, regardless of sample size; (2) sufficient data for calculating an odds ratio (OR) with 95% confidence interval (CI); (3) studies published as full-length articles or letters in English. The major exclusion criteria were as follows: (1) no control subjects; (2) evaluation of other variants; (3) family-based study; (4) insufficient data for genotype distribution; (5) duplicate data.

Data extraction

For each study, the following information was extracted using standard forms: first author, publication year, country, ethnicity, sample size, age of subjects, genotyping method, and geno-

Table 1. Characteristics of eligible studies in meta-analysis

First author	Year	Country	Ethnicity	Number		Age of subjects	Genotyping method
				Patients	Controls		
Loeff	2012	Chile	Latin Americans	104	104	Children	Taqman assays
Wolters	2007	Netherlands	Europeans	421	1624	Children and adults	Taqman assays
Latiano	2007	Italy	Europeans	337	452	Children and adults	Taqman assays
Sánchez	2007	Spain	Europeans	90	345	NR	Taqman assays
Cirillo	2007	Italy	Europeans	223	600	Children	PCR-RFLP
Núñez	2006	Spain	Europeans	415	433	NR	Taqman assays
Hunt	2006	UK	Europeans	375	1336	Children and adults	Taqman and Sequenom methods

NR, not reported; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; UK, united kingdom.

type distribution. Two reviewers extracted data from the published studies. Disagreements were resolved by discussion and consensus.

Statistical analysis

All statistical analyses were performed using Stata version 11.0. Raw data without adjustment were used for calculation of the study-specific estimates of ORs and 95% CIs. The presence of heterogeneity between studies was explored with the Cochran's Q statistic; $P<0.10$ indicated significant heterogeneity. The pooled estimation of the OR of each study was calculated by the Mantel-Haenszel fixed effects model or the Dersimonian-Laird random effects model [16]. The random effects model uses weights that incorporate both the within-study and between-study variance. The overall pooled ORs were calculated assuming dominant, recessive, homozygote and allelic comparison models. The significance of the pooled OR was determined by the Z test and $P<0.05$ was considered as statistically significant. Subgroup analysis was performed according to ethnicity. Considering that the number of included studies was small, sensitivity analysis was not conducted. Publication bias was evaluated through the Begg's test, with $P<0.05$ being considered statistically significant. Funnel plot displaying the log odds ratios of individual studies on the vertical axis and the standard errors of the log odds ratios on the horizontal axis was also constructed to assess publication bias.

Results

Study characteristics

We retrieved 97 published studies using our search criteria (**Figure 1**). Seven studies published between 2006 and 2012 met our inclusion criteria with a total of 1965 CD patients and 4894 controls (**Figure 1**) [17-23]. In terms of ethnicity, six studies were performed in Europeans [17-22], whereas one study was undertaken in a Latin American mixed group [23]. In terms of age, two studies were performed in children [19, 23], three studies were undertaken in both children and adults [17, 21, 22], and two studies did not report any information on age [18, 20]. **Table 1** summarizes the characteristics of the seven studies included in our meta-analysis.

Quantitative data synthesis

Two studies evaluated the rs1545620 polymorphism [21, 22]. All subjects were Europeans. Pooling data from these showed a significant association between CD risk and rs1545620 in dominant (OR=1.31, 95% CI: 1.10-1.58, P_z=0.003) (**Table 2**), recessive (OR=1.36, 95% CI: 1.08-1.72, P_z=0.009) (**Table 2**), homozygote (OR=1.55, 95% CI: 1.20-2.01, P_z=0.001) (**Table 2**), and allelic comparison models (OR=1.24, 95% CI: 1.10-1.40, P_z=0.001) (**Table 2**; **Figure 2**).

Four studies assessed the association between the rs1457092 SNP and CD risk [17, 20, 22, 23]. Among them, three studies were conducted in Europeans [17, 20, 22], whereas one study was performed in Latin Americans [23]. Pooling the data from these studies showed no association between the polymorphism and CD in all study subjects in dominant (OR=1.35, 95% CI: 0.86-2.13, P_z=0.196) (**Table 2**), recessive (OR=1.29, 95% CI: 0.86-1.95, P_z=0.222) (**Table 2**), homozygote (OR=1.81, 95% CI: 0.87-3.78, P_z=0.112) (**Table 2**), and allelic comparison models (OR=1.25, 95% CI: 0.94-1.65, P_z=0.126) (**Table 2**; **Figure 3**). In subgroup analysis according to ethnicity, we did not find an

Table 2. Meta-analysis of polymorphisms in the *MYO9B* gene and CD risk

Polymorphism	No. of studies	Dominant			Recessive			Homozygote			Allelic comparison		
		OR (95% CI)	P_{het}	P_z	OR (95% CI)	P_{het}	P_z	OR (95% CI)	P_{het}	P_z	OR (95% CI)	P_{het}	P_z
rs1545620													
Total	2	1.31 (1.10-1.58)	0.534	0.003	1.36 (1.08-1.72)	0.559	0.009	1.55 (1.20-2.01)	0.494	0.001	1.24 (1.10-1.40)	0.415	0.001
Europeans	2	1.31 (1.10-1.58)	0.534	0.003	1.36 (1.08-1.72)	0.559	0.009	1.55 (1.20-2.01)	0.494	0.001	1.24 (1.10-1.40)	0.415	0.001
rs1457092													
Total	4	1.35 (0.86-2.13)	<0.001	0.196	1.29 (0.86-1.95)	0.016	0.222	1.81 (0.87-3.78)	<0.001	0.112	1.25 (0.94-1.65)	0.001	0.126
Europeans	3	1.12 (0.84-1.48)	0.057	0.441	1.22 (0.73-2.05)	0.009	0.440	1.27 (0.71-2.27)	0.006	0.422	1.11 (0.86-1.45)	0.008	0.423
Latin Americans	1	15.3 (3.51-66.67)	NA	<0.001	1.62 (0.90-2.90)	NA	0.106	16.55 (3.62-75.65)	NA	<0.001	1.95 (1.31-2.91)	NA	0.001
rs2305767													
Total	4	1.10 (0.65-1.87)	<0.001	0.717	0.82 (0.61-1.11)	0.183	0.195	0.77 (0.48-1.24)	0.028	0.284	0.96 (0.72-1.27)	0.001	0.765
Europeans	3	0.80 (0.60-1.08)	0.053	0.142	0.82 (0.58-1.16)	0.092	0.254	0.72 (0.44-1.17)	0.022	0.181	0.85 (0.67-1.07)	0.021	0.161
Latin Americans	1	5.35 (2.42-11.86)	NA	<0.001	0.66 (0.11-4.04)	NA	0.653	2.59 (0.38-17.92)	NA	0.334	1.65 (1.11-2.45)	NA	0.013
rs2305764													
Total	7	1.09 (0.91-1.30)	0.048	0.352	1.12 (0.84-1.49)	0.002	0.447	1.16 (0.83-1.62)	0.001	0.375	1.07 (0.92-1.25)	0.002	0.383
Europeans	6	1.08 (0.89-1.31)	0.026	0.413	1.15 (0.84-1.57)	0.001	0.389	1.18 (0.82-1.69)	0.001	0.375	1.08 (0.91-1.27)	0.001	0.380
Latin Americans	1	1.15 (0.55-2.40)	NA	0.708	0.88 (0.44-1.78)	NA	0.720	1.01 (0.40-2.56)	NA	0.979	1.00 (0.68-1.47)	NA	1.000

CD, celiac disease; CI, confidence interval; NA, not available; OR, odds ratio; P_{het}, *P* value for heterogeneity, P_z, *P* value for the overall effect.

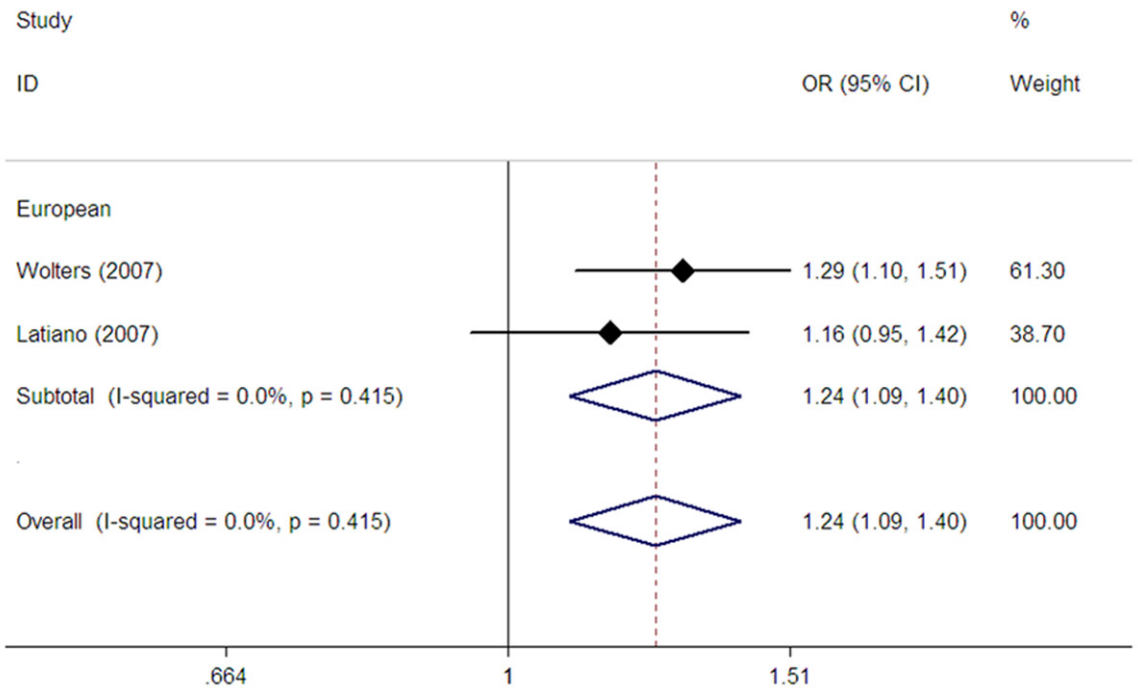

Figure 2. Forest plot of fixed effects meta-analysis investigating the rs1545620 polymorphism and CD risk in allele contrast.

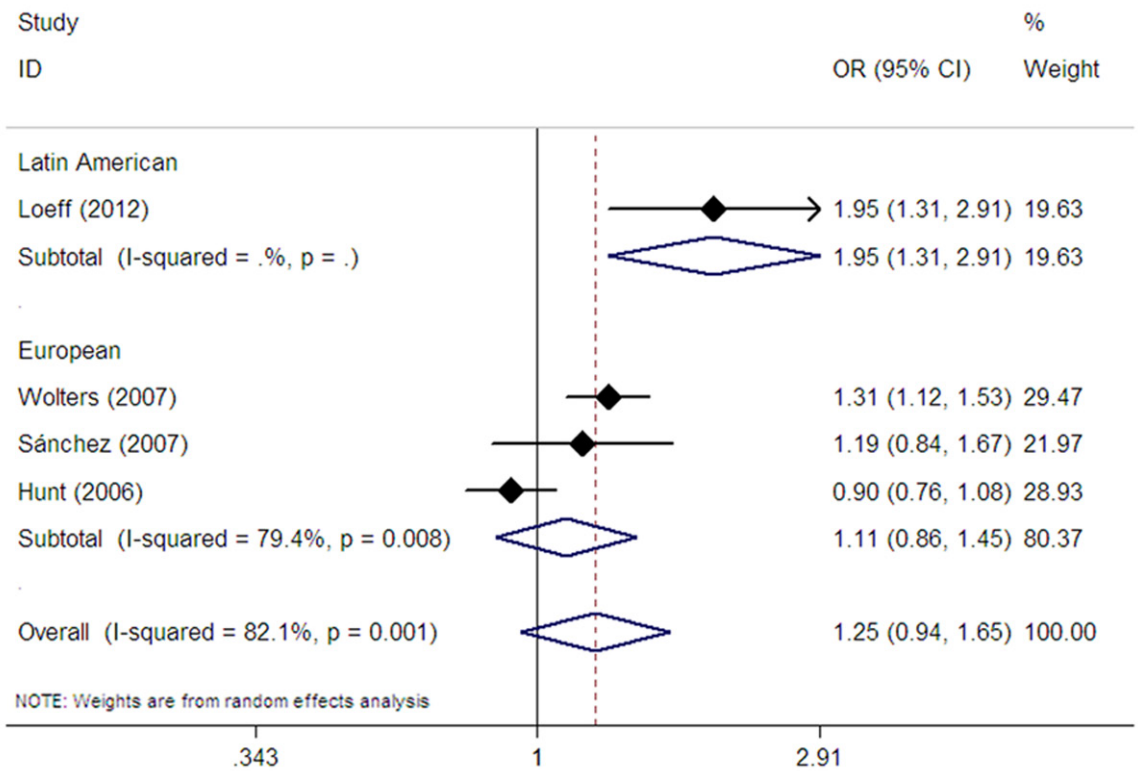

Figure 3. Forest plot of random effects meta-analysis investigating the rs1457092 polymorphism and CD risk in allele contrast.

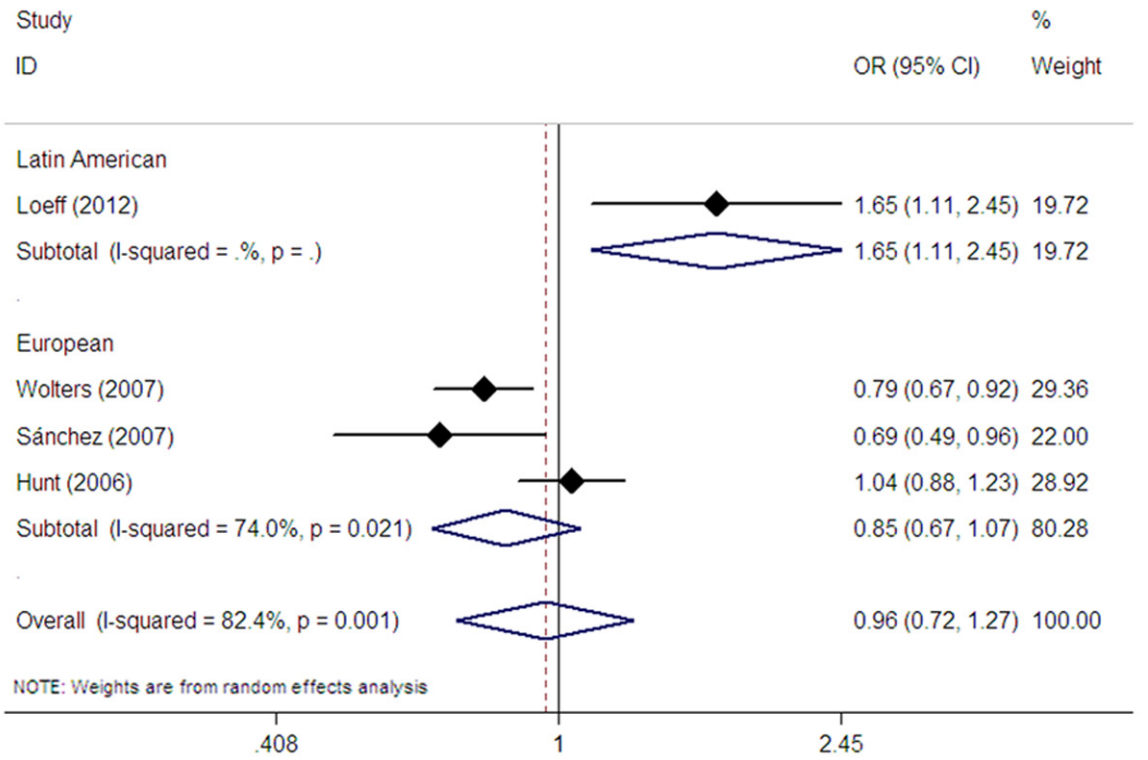

Figure 4. Forest plot of random effects meta-analysis investigating the rs2305767 polymorphism and CD risk in allele contrast.

association between rs1457092 and CD risk in Europeans in dominant (OR=1.12, 95% CI: 0.84-1.48, P_z=0.441) (**Table 2**), recessive (OR=1.22, 95% CI: 0.73-2.05, P_z=0.440) (**Table 2**), homozygote (OR=1.27, 95% CI: 0.71-2.27, P_z=0.422) (**Table 2**), and allelic comparison models (OR=1.11, 95% CI: 0.86-1.45, P_z=0.423) (**Table 2**; **Figure 3**). However, a single Latin American study showed an association between rs1457092 and CD risk in dominant (OR=15.30, 95% CI: 3.51-66.67, P_z<0.001) (**Table 2**), homozygote (OR=16.55, 95% CI: 3.62-75.65, P_z<0.001) (**Table 2**), and allelic comparison models (OR=1.95, 95% CI: 1.31-2.91, P_z=0.001) (**Table 2**; **Figure 3**).

The *MYO9B* rs2305767 polymorphism was evaluated in four studies [17, 20, 22, 23]. Among them, three studies were undertaken in Europeans [17, 20, 22], whereas one study was conducted in Latin Americans [23]. The pooled analysis showed no association between rs2305767 and CD risk in all study subjects in dominant (OR=1.10, 95% CI: 0.65-1.87, P_z=0.717) (**Table 2**), recessive (OR=0.82, 95% CI: 0.61-1.11, P_z=0.195) (**Table 2**), homozygote (OR=0.77, 95% CI: 0.48-1.24, P_z=0.284) (**Table 2**), and allelic comparison models (OR=0.96, 95% CI: 0.72-1.27, P_z=0.765) (**Table 2**; **Figure 4**). In subgroup analysis based on ethnicity, no association between rs2305767 and CD risk was found in Europeans in dominant (OR=0.80, 95% CI: 0.60-1.08, P_z=0.142) (**Table 2**), recessive (OR=0.82, 95% CI: 0.58-1.16, P_z=0.254) (**Table 2**), homozygote (OR=0.72, 95% CI: 0.44-1.17, P_z=0.181) (**Table 2**), and allelic comparison models (OR=0.85, 95% CI: 0.67-1.07, P_z=0.161) (**Table 2**; **Figure 4**). However, the single Latin American study revealed an association between rs2305767 and CD risk in dominant model (OR=5.35, 95% CI: 2.42-11.86, P_z<0.001) (**Table 2**) and allelic comparison model (OR=1.65, 95% CI: 1.11-2.45, P_z=0.013) (**Table 2**; **Figure 4**).

Seven studies evaluated the rs2305764 polymorphism [17-23]. Among them, six studies were conducted in Europeans [17-22], whereas one study was performed in Latin Americans [23]. Pooling these seven studies did not show an association between rs2305764 and CD risk in all study subjects in dominant (OR=1.09, 95% CI: 0.91-1.30, P_z=0.352) (**Table 2**) , recessive (OR=1.12, 95% CI: 0.84-1.49, P_z=0.447)

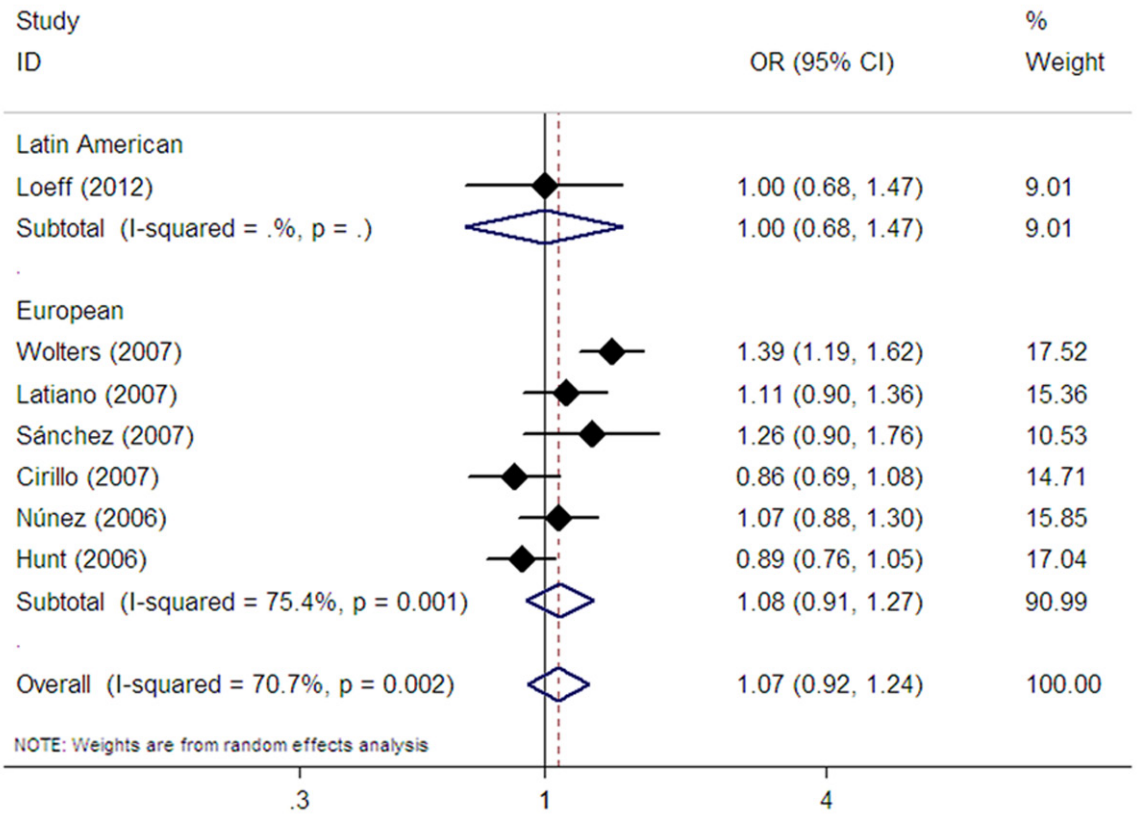

Figure 5. Forest plot of random effects meta-analysis investigating the rs2305764 polymorphism and CD risk in allele contrast.

Table 3. Begg's test for evaluating publication bias

Polymorphism	*P* for dominant model	*P* for recessive model	*P* for homozygote model	*P* for allelic comparison model
rs1545620	1.000	1.000	1.000	1.000
rs1457092	0.734	1.000	0.734	0.734
rs2305767	0.308	0.734	0.734	0.308
rs2305764	0.548	1.000	1.000	1.000

(**Table 2**), homozygote (OR=1.16, 95% CI: 0.83-1.62, P_z=0.375) (**Table 2**), and allelic comparison models (OR=1.07, 95% CI: 0.92-1.25, P_z=0.383) (**Table 2** and **Figure 5**). In subgroup analysis stratified by ethnicity, pooling the data from six studies provided no evidence for an association between the polymorphism and CD risk in Europeans in dominant (OR=1.08, 95% CI: 0.89-1.31, P_z=0.413) (**Table 2**), recessive (OR=1.15, 95% CI: 0.84-1.57, P_z=0.389) (**Table 2**), homozygote (OR=1.18, 95% CI: 0.82-1.69, P_z=0.375) (**Table 2**), and allelic comparison models (OR=1.08, 95% CI: 0.91-1.27, P_z=0.380) (**Table 2**; **Figure 5**). The single Latin American study also revealed no association between rs2305764 and CD risk (**Table 2**; **Figure 5**).

Heterogeneity and publication bias

Between-study heterogeneity was found in the pooled analyses of the rs1457092, rs2305767 and rs2305764 polymorphisms (**Table 2**). Publication bias were evaluated through the Begg' test in all models. There was no significant evidence of publication bias for the rs1545620, rs1457092, rs2305767 and rs2305764 polymorphisms. **Table 3** showed the results of the Begg's test in detail. Funnel plot was generated for the rs2305764 polymorphism, and the shape seemed symmetrical (**Figure 6**).

Discussion

The present meta-analysis of seven studies, involving a total of 1965 CD patients and 4894 controls provides the most comprehensive

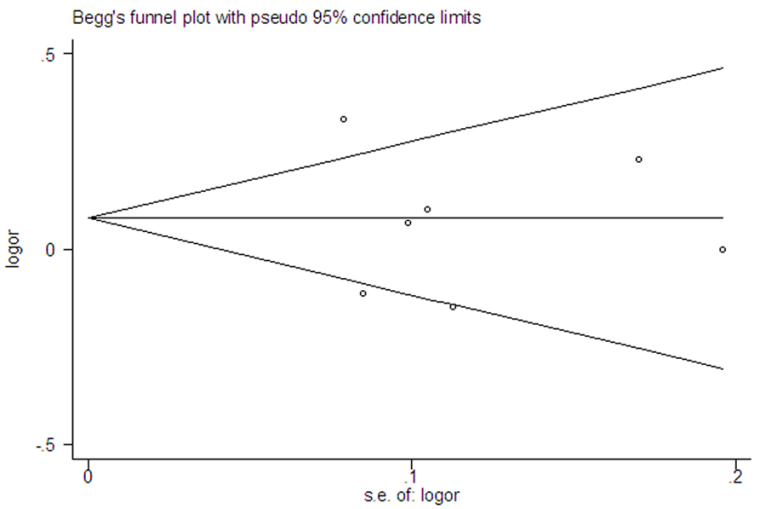

Figure 6. Begg's funnel plot for the rs2305764 polymorphism and CD risk.

assessment so far of the relevance to CD of four common *MYO9B* polymorphisms. The main findings are as follows: (1) the rs1545620 polymorphism is associated with CD risk in Europeans; (2) there is no association between CD risk and the rs1457092, rs2305767 and rs2305764 polymorphisms in all study subjects (Europeans and a Latin American group) and Europeans; and (3) rs1457092 and rs2305767 are associated with CD risk in a Latin American group.

MYO9B encodes a single-headed molecular motor containing a Rho-family GTPase-activating protein (GAP) domain in the tail region, which is a member of the class IX myosin family [12]. It is expressed in intestinal epithelial cells and is an integral structural component of the intestinal mucosa. MYO9B acts as a negative regulator facilitating inactivation of Rho GTPases and downregulates Rho-dependent signaling pathways [15]. Rho GTPases are key regulators of actin filament remodeling and tight junction assembly, both of which lead to an increase of epithelial paracellular permeability [13, 24]. The latter fact therefore leads to the hypothesis that *MYO9B* variants may modify the epithelial barrier function of the gut, thereby allowing gluten peptides to gain easy access to the deeper mucosal layer and be presented to the immune system. In this meta-analysis, we found that the rs1545620 polymorphism was associated with CD risk in Europeans, where as the rs1457092 and rs2305767 polymorphisms were associated with CD in a Latin American group. The rs1545620 SNP is a non-synonymous polymorphism resulting in an amino acid change (Alanine1011-Serine) in the neck region of the MYO9B protein, which is involved in the binding of calmodulin [25]. Calmodulin is a protein that modulates the motor activity of MYO9B on actin filaments [26]. The conformational change of the MYO9B protein induced by the rs1545620 SNP can result in lower MYO9B activity, and may therefore lead to a defect in the intestinal barrier and contribute to the pathogenesis of CD. Moreover, MYO9B is not specifically expressed in intestinal epithelial cells. It is also abundantly expressed in immune cells including leukocytes and macrophages [15, 27]. Given the pivotal role of MYO9B in immune cell shape and motility [27], it would be reasonable to hypothesize that the rs1545620 polymorphism may increase risk of CD by alternative mechanisms regulating the movement of immune cells to the site of inflammation. The rs1457092 and rs2305767 polymorphisms are intronic noncoding variations. Although part of the function of MYO9B is understood, it remains largely unknown how these two polymorphisms might influence MYO9B activity. To understand the precise mechanisms by which genetic variation of *MYO9B* predisposes to CD, more functional assays are needed in the future.

Ethnic differences between Europeans and Latin Americans in *MYO9B* association with CD were observed in this meta-analysis. It can be explained by several possible reasons. First, the two ethnic groups have distinct genetic background. Second, CD is a multifactorial disease determined by interactions between environmental and genetic factors. Individual genetic predisposition to CD may be modified by different environmental factors in different ethnic groups. Third, the discrepancy may partly be explained by clinical heterogeneity between different ethnic groups. Since the small number of included studies limited the statistical power to achieve a definitive conclu-

sion for each ethnic group, future studies using large sample numbers are needed to confirm the associations found in this meta-analysis.

There are several limitations to our study. First, we only included studies written in the English language, which may be a source of bias. Because significant results are more likely to be published in English. Second, because of the limitation of the published data, we were unable to conduct subgroup analysis based on age in children and adults, respectively. Third, between-study heterogeneity was found in some pooled analyses. Several potential factors, including ethnic heterogeneity, genotyping method, and age may contribute to it. Because there were insufficient data from the included studies, we did not perform meta-regression analysis to assess the sources of heterogeneity. Fourth, linkage disequilibrium among several *MYO9B* polymorphisms was reported in some studies [20, 21]. Therefore, it may be of interest to evaluate haplotype association with the disease. However, due to discrepancy in alleles and haplotype estimation methods, we did not perform haplotype estimation in our meta-analysis.

In summary, the results of our meta-analysis demonstrate that the rs1545620 polymorphism is associated with CD risk in Europeans, whereas the rs1457092 and rs2305767 polymorphisms are associated with CD in a Latin American group.

Disclosure of conflict of interest

None.

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