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META-ANALYSIS

Associations between *CD24* gene polymorphisms and inflammatory bowel disease: A meta-analysis

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Abstract

AIM: To evaluate the relationships between *CD24* gene polymorphisms and the risk of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD).

METHODS: The PubMed, Web of Science and Cochrane Library databases were searched (up to May 30, 2014). The search terms "CD24", "inflammatory bowel disease", "Crohn's disease", "Ulcerative colitis", "IBD", "CD" or "UC"; and "polymorphism", "mutation" or "variant" were used. Association studies were limited to the English language, but no limitations in terms of race, ethnicity or geographic area were employed. Stata SE12 software was used to calculate the pooled odds ratios (ORs) with 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant. The information was independently extracted from each eligible study by two investigators. Two common polymorphisms, C170T (rs8734) and TG1527del (rs3838646), in the *CD24* gene were assessed.

RESULTS: A total of three case-control studies including 2342 IBD patients and 1965 healthy controls were involved in this meta-analysis. The patients and controls were from Caucasian cohorts. The three articles included in this meta-analysis all conformed to Hardy-Weinberg equilibrium. This meta-analysis revealed that there were no significant associations between the two *CD24* polymorphisms and the risk for IBD (all $P > 0.05$). However, in a disease subgroup analysis, we found that the *CD24* C170T polymorphism was associated with an increased risk of UC in a dominant model (OR = 1.79, 95%CI: 1.15-2.77, $P = 0.009$) and an additive model (OR = 1.87, 95%CI: 1.19-2.93, $P = 0.007$), but this relationship was not present for CD. The CD24 TG1570*del* polymorphism was significantly associated with CD in the additive model (OR = 1.24, 95%CI: 1.01-1.52, $P = 0.037$).

CONCLUSION: Our findings provide evidence that the *CD24* C170T polymorphism might contribute to the susceptibility to UC, and the CD24 TG1527del polymorphism might be associated with the risk of CD.

Key words: CD24; Polymorphism; Inflammatory bowel disease; rs8734; rs3838646; Meta-analysis

Core tip: CD24 is a significant immune regulatory mediator of inflammatory bowel disease (IBD). Some recent studies have demonstrated that *CD24* gene polymorphisms are associated with the susceptibility to IBD, but the findings of other studies are contradictory. The present study sought to provide a more precise estimate of this potential association. A meta-analysis of Caucasian cohorts found that the *CD24* C170T polymorphism was associated with the susceptibility to UC and that the CD24 TG1527*del* polymorphism was associated with CD.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a relapsing and chronic inflammatory disorder that is composed of two types of diseases, Crohn's disease (CD) and ulcerative colitis (UC). The incidence of IBD is increasing worldwide. IBD places a heavy burden on patients because it reduces life quality and the ability to work and increases disability[1]. The etiology of IBD is complicated and obscure but is primarily related to genetic, environmental, immune and infectious factors and interactions between these factors. Based on assessments of familial clustering and the high concordance in monozygotic twins, it is well established that a genetic component is implicated in the pathogenesis of IBD[2-4]. Recent studies have revealed that many gene variations are associated with the susceptibility to IBD, such as NOD2[5-7], ATG16L1[8,9], DLG5[10,11] and IL23R[12].

CD24 is a glycophosphatidylinositol (GPI)-anchored mucin-like cell surface glycoprotein that is expressed in a wide variety of cell types, including activated T cells[13], B cells[14], macrophages[15], and dendritic cells[16]. Human CD24 is encoded by a gene located on chromosome 6 and plays important roles in lymphocyte maturation[13,17-19], neuronal development[20], intercellular signal transmission and immune regulation. Some single nucleotide polymorphisms (SNPs) in the *CD24* gene have been shown to be associated with the susceptibilities to several chronic inflammatory and autoimmune diseases, such as multiple sclerosis (MS)[21,22], systemic lupus erythematous (SLE)[23,24], and others. There are some studies of the correlations between *CD24* SNPs and risk factors for IBD pathogenesis[25-27]. C170T (rs8734) and TG1527*del* (rs3838646) are two common CD24 genetic polymorphisms that are potentially related to IBD; however, the findings related to these polymorphisms are contradictory. To shed some light on the contradictory findings and provide a more precise estimate of the potential associations, we performed this meta-analysis to investigate whether the two *CD24* polymorphisms (C170T and TG1527del) contribute to the susceptibility to IBD.

MATERIALS AND METHODS

Literature search

We conducted a literature search for relevant studies on the relationships between polymorphisms of *CD24* and IBD risk in the PubMed, Web of Science, and Cochrane Library databases (up to May 30, 2014). The following search terms were used: "CD24"; and "inflammatory bowel disease", "Crohn's disease", "Ulcerative colitis", "IBD", "CD", or "UC"; and "polymorphism", "mutation", or "variant". The searched studies were limited to the English language.

Inclusion and exclusion criteria

Eligible studies were required to meet the following inclusion criteria: (1) case-control studies evaluating at least one polymorphism of the *CD24* gene; (2) studies containing original data; (3) studies with genotype or allelic distributions; (4) studies containing sufficient data to calculate odds ratios (ORs); and (5) studies in which the genotype distribution of the control population was in Hardy-Weinberg equilibrium (HWE). No limitations related to race, ethnicity or geographic area were utilized.

The exclusion criteria were as follows: (1) irrelevant and review articles; (2) studies containing overlapping data; (3) articles that did not provide detailed genotype data; (4) investigations of the associations of other genes with IBD or the relationships between *CD24* gene polymorphisms and other diseases; and (5) studies in which family members were studied because the analysis were based on linkage considerations.

Data extraction and synthesis

The following information was extracted from each eligible study independently by two investigators: first author's surname, year of publication, ethnicity of the study population, and the number of cases and controls for the *CD24* genotype. The allele and genotype frequencies of the *CD24* polymorphisms

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

First author	Year	Country	Ethnicity	Sample size			Polymorphisms	Genotype method
				UC	CD	Control		
Diaz-Gallo LM	2011	Spain	Caucasian	632	737	1257	P170 P1527	PCR
Van Limbergen	2013	Scottish	Caucasian	342	395	498	P1527	PCR
Lisiansky V	2014	Israel	Caucasian	174	62	210	P170 P1527	PCR-RFLP

UC: Ulcerative colitis; CD: Crohn's disease; RFLP: Restricted fragment length polymorphisms; PCR: Polymerase chain reaction.

Table 2 Distributions of two *CD24* genotypes and alleles among the inflammatory bowel disease patients and controls

Study	Arms	C170T						Arms	TG1570*del*					
		A	V	AA	AV	VV	HWE		TG	*del*	TGTG	TG*del*	*deldel*	HWE
Diaz-Gallo *et al*[26], 2011	CD (n = 366)	534	198	200	134	32		CD (n = 371)	662	80	301	60	10	
	UC (n = 322)	448	196	161	126	35		UC (n = 310)	580	40	270	40	0	
	Control (n = 628)	904	352	317	270	41	0.100	Control (n = 629)	1170	88	547	76	6	0.448
Lisiansky *et al*[25], 2014	CD (n = 31)	42	20	12	18	1		CD (n = 31)	57	5	26	5	0	
	UC (n = 87)	108	66	29	50	8		UC (n = 87)	165	9	78	9	0	
	Control (n = 105)	163	47	63	37	5	0.884	Control (n = 105)	198	12	93	12	0	0.534
Van Limbergen *et al*[27], 2013	CD (n = 395)	-	-	-	-	-			719	71	326	67	2	
	UC (n = 310)	-	-	-	-	-			623	61	283	57	2	
	Control (n = 498)	-	-	-	-	-			905	91	411	83	4	0.932

UC: Ulcerative colitis; CD: Crohn's disease; HWE: Hardy-Weinberg equilibrium.

were calculated from each article by the allele counting method. Disagreements were resolved by discussion.

Statistical analysis

Stata SE12 software was used to calculate the pooled ORs with 95% confidence intervals (CIs) based on the available data from each article. $P < 0.05$ was considered statistically significant. The allelic model (A *vs* V or TEL *vs* del), recessive model (AA *vs* AV + VV or TGTG *vs* TG*del* + *deldel*), dominant model (AA + AV *vs* VV or TGTG + TG*del vs deldel*), and additive model (AA *vs* VV or TGTG *vs deldel*) were estimated for genotype comparisons. Cochran's *Q*-statistic and the I^2 test were used to test the heterogeneity among the included studies, and $P < 0.1$ and $I^2 > 50\%$ suggested significant differences in study heterogeneity. When significant heterogeneity was observed across studies, the pooled results were based on random effects models. The χ^2 test was applied to assess whether the genotype distributions of the control populations conformed to HWE, and $P < 0.05$ was considered statistically significant. Begg's funnel plot and Egger's test were used to detect publication bias[28].

RESULTS

Literature search for eligible studies

Based on the research criteria, a total of 49 articles were identified, and 29 of these articles were excluded because they were not relevant to *CD24* SNPs and the risk for IBD. Eight repetitive studies and 9 reviews were also excluded. Ultimately 3 case-control studies consisting of 2342 IBD patients (UC = 1148, CD = 1194) and 1965 controls were included in our paper. These articles were conducted with Spanish, Scottish and Israeli Caucasians. The characteristics of the 3 studies are summarized in Table 1. The distributions of the *CD24* genotypes and alleles among the IBD patients and controls are listed in Table 2.

Association of the CD24 C170T polymorphism with IBD susceptibility

Two studies including 806 IBD patients (CD = 397, UC = 409) and 733 controls were selected in this meta-analysis. A statistical test suggested that heterogeneity was present (for the allele: I^2 = 87.7%, P = 0.004; for the recessive model: I^2 = 92.8%, $P < 0.001$; for the additive model: I^2 = 73.9%, P = 0.051); therefore, the random effects model was used in these model analysis. No significant associations between the CD24 C170T polymorphism and the IBD risk were revealed (V *vs* A: OR = 1.39, 95%CI: 0.73-2.64, P = 0.314; VV *vs* AA: OR=1.32, 95%CI: 0.40-4.39, P = 0.654; VV + VA *vs* AA: OR = 0.64, 95%CI: 0.21-1.90, P = 0.420; VV *vs* AA + VA: OR=0.94, 95%CI: 0.62-1.43, P = 0.777). Subgroup analysis indicated no modifying effects of the *CD24* C170T polymorphism on the risk of CD (V *vs* A: OR = 1.16, 95%CI: 0.69-1.93, P = 0.583; VV *vs* AA: OR = 1.23, 95%CI: 0.76-1.99, P = 0.405; VV + VA *vs* AA: OR = 0.76, 95%CI: 0.28-2.07, P = 0.594; VV *vs* AA +VA: OR = 1.32, 95%CI: 0.83-2.11, P = 0.245). However, we observed a significant association between the *CD24* C170T polymorphism and UC risk for the dominant model (OR = 1.79, 95%CI: 1.15-2.77, P = 0.009) and the additive model (OR = 1.87, 95%CI: 1.19-2.93, P = 0.007) (Figure 1, Table 3).

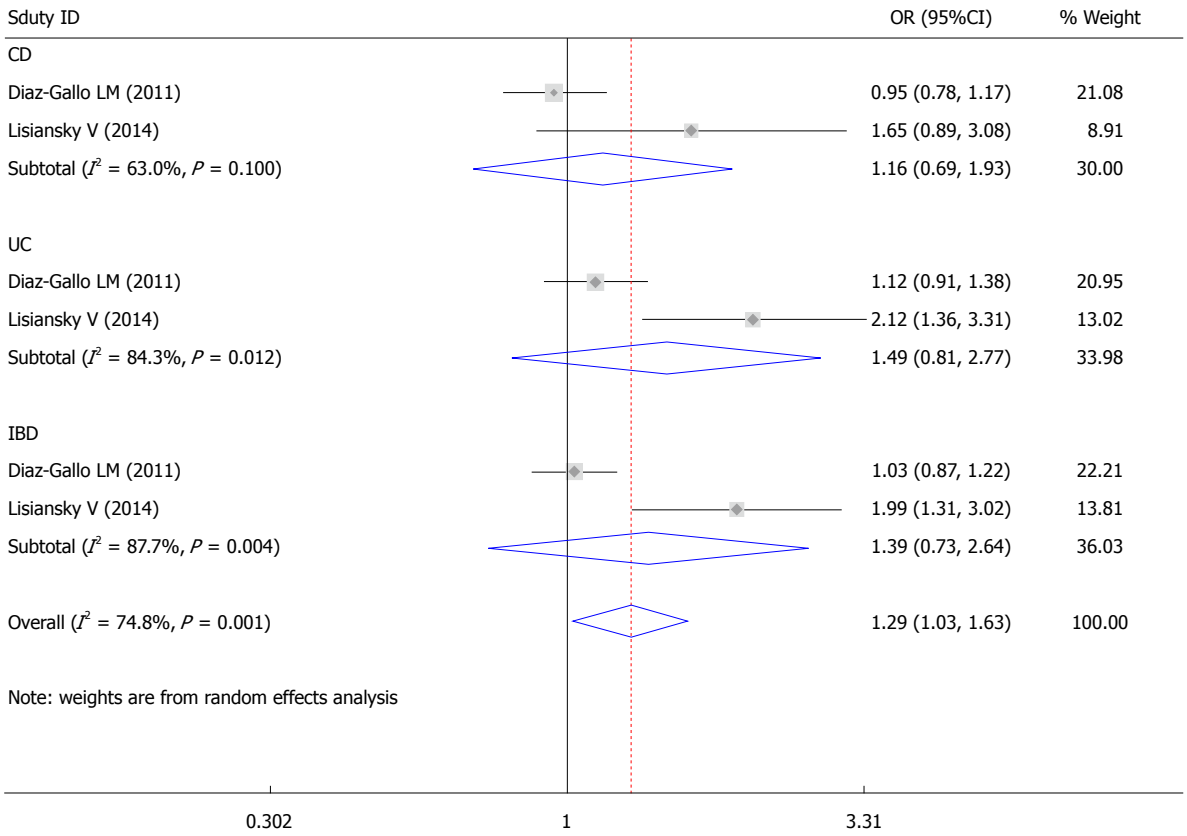

Figure 1 Pooled analysis of the variant allele *CD24*-C170T in the IBD, UC, and Crohn's disease subgroups. ORs and 95%CIs of the individual studies and pooled analysis of the associations between the *CD24* C170T C allele and the disease risks for Crohn's disease (CD) (OR = 1.16, 95%CI: 0.69-1.93), ulcerative colitis (UC) (OR = 1.49, 95%CI: 0.81-2.77), and inflammatory bowel disease (IBD) (OR = 1.39, 95%CI = 0.73-2.64). OR: Odds ratio.

Table 3 Meta-analysis of the associations between two promoter polymorphisms of *CD24* and inflammatory bowel disease

Polymorphism	Disease	Test of association			Test of heterogeneity		
		OR	95%CI	*P* value	Model	*P* value	I^2 (%)
P170V *vs* A	CD	1.16	0.69-1.93	0.583	R	0.100	63.0
	UC	1.49	0.81-2.77	0.203	R	0.012	84.3
	IBD	1.39	0.73-2.64	0.314	R	0.004	87.7
VV + AV *vs* AA	CD	0.76	0.28-2.07	0.594	R	0.019	81.9
(recessive)	UC	0.59	0.21-1.70	0.330	R	0.001	90.5
	IBD	0.64	0.21-1.90	0.420	R	< 0.001	92.8
VV *vs* AA + AV	CD	1.32	0.83-2.11	0.245	F	0.527	0.0
(dominant)	UC	1.79	1.15-2.77	0.009	F	0.816	0.0
	IBD	0.94	0.62-1.43	0.777	F	0.287	11.8
VV *vs* AA	CD	1.23	0.76-1.99	0.405	F	0.888	0.0
(additive)	UC	1.87	1.19-2.93	0.007	F	0.272	17.1
	IBD	1.32	0.40-4.39	0.654	R	0.051	73.9
P1527*del* *vs* TG	CD	1.24	1.01-1.52	0.037	F	0.101	56.5
	UC	0.95	0.76-1.19	0.649	F	0.967	0.0
	IBD	1.18	0.99-1.41	0.063	F	0.803	0.0
deldel + TG*del* *vs* TGTG	CD	0.80	0.63-1.02	0.068	F	0.207	36.5
(recessive)	UC	1.02	0.79-1.33	0.870	F	0.980	0.0
	IBD	0.82	0.67-1.01	0.061	F	0.870	0.0
deldel *vs* TGTG + TG*del*	CD	1.87	0.81-4.32	0.143	F	0.133	55.7
(dominant)	UC	0.40	0.10-1.63	0.201	F	0.345	0.0
	IBD	1.23	0.54-2.76	0.625	F	0.436	0.0
deldel *vs* TGTG	CD	1.93	0.84-4.47	0.123	F	0.121	58.4
(additive)	UC	0.40	0.10-1.64	0.203	F	0.348	0.0
	IBD	1.27	0.56-2.86	0.572	F	0.439	0.0

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease.

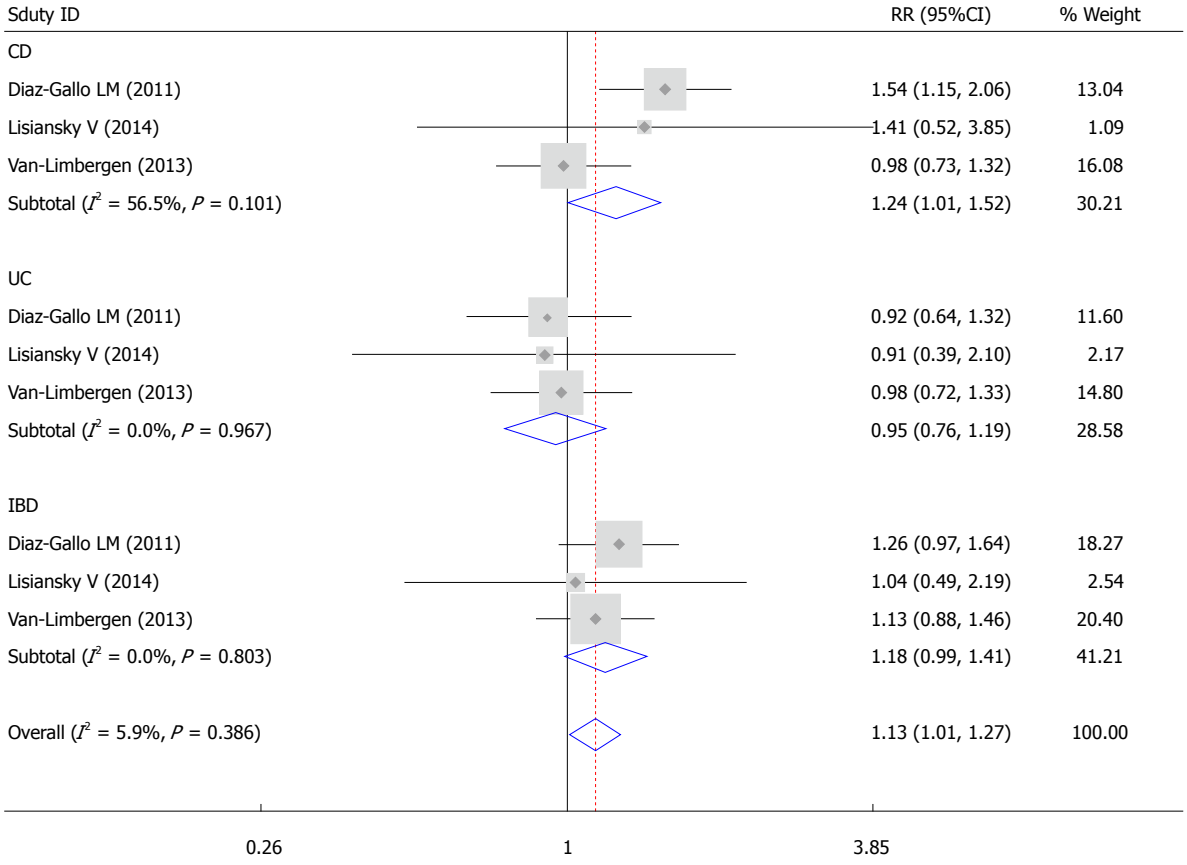

Figure 2 Pooled analysis of the variant allele *CD24* TG1527*del* in the IBD, UC and Crohn's disease subgroups. ORs and 95%CIs of the individual studies and the pooled analysis of the associations between the *CD24* TG1527*del* allele and the disease risks for Crohn's disease (CD) (OR = 1.24, 95%CI: 1.01-1.52), ulcerative colitis (UC) (OR = 0.95, 95%CI: 0.76-1.19) and inflammatory bowel disease (IBD) (OR = 1.18, 95%CI: 0.99-1.41). OR: Odds ratio.

Table 4 Egger's tests for C170 T and TG1527*del* of *CD24* and the inflammatory bowel disease risk in all of the included studies

Contrast models	Coefficient	95%CI	SE	*t*	*P* value
C170T					
V *vs* A	3.902	0.912 to 6.891	1.077	3.62	0.022
VV +AV *vs* AA	-4.527	-5.832 to 3.075	1.969	-0.70	0.501
VV *vs* AA + AV	0.200	-7.276 to -1.779	0.990	-4.57	0.010
VV *vs* AA	1.399	-2.040 to 4.838	1.239	1.13	0.322
TG1527*del*					
del vs TG	-0.435	-2.669 to 1.799	0.945	-0.46	0.659
deldel + TG*del vs* TGTG	0.444	-1.833 to 2.721	0.963	0.64	0.659
deldel vs TGTG + TG*del*	-2.977	-4.820 to -1.134	0.664	-4.48	0.011
deldel vs TGTG	-2.598	-4.249 to -0.947	0.595	-4.37	0.012

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease.

Association of the TG1527del polymorphism with IBD susceptibility

Three studies consisting of 1625 IBD patients (UC = 759, CD = 866) and 1232 controls were included in this meta-analysis. A statistical test revealed that there was no heterogeneity between the studies (for the allele: I^2 = 0%, P = 0.803; for the recessive model: I^2 = 0%, P = 0.870; for the dominant model: I^2 = 0%, P = 0.436; for the additive model: I^2 = 0%, P = 0.439); hence, the fixed effect model was used. The results did not indicate any significant association of the allele in the overall sample or the subgroup analysis with the exception that the del allele was related to CD susceptibility (OR=1.24, 95%CI: 1.01-1.52, P = 0.037) (Figure 2, Table 3).

Sensitivity analysis and publication bias

A sensitivity analysis conducted *via* the omission of individual studies did not materially alter the pooled results (data not shown). Begg's funnel plots did not reveal obvious asymmetries for any of the comparison models. However, Egger's tests revealed that there were some publication biases for both of the genetic allele analysis (V *vs* A, P_{Egger} = 0.022; VV *vs* AA + AV, P_{Egger} = 0.010; *deldel vs* TGTG + TG*del*, P_{Egger} = 0.011; *deldel vs* TGTG, P_{Egger} = 0.012) (Table 4).

DISCUSSION

The etiology of IBD has not been completely elucidated, but the contributions of immunological and genetic factors have been demonstrated. IBD is believed to arise partly due to multiple genetic factors. Many reports have used the genome-wide association study (GWAS) approach to identify novel candidate

single nucleotide polymorphisms (SNPs) for IBD[12,29,30]. To date, 99 variants have been identified as associated with CD and/or UC. Among these, only 28 variants have been shown to overlap in their contributions to the susceptibilities to both diseases[31]. Some risk loci for CD have no reported effect on UC. Similarly, some risk loci for UC have been shown to have little effect on UC. Different mutations of the same gene might be associated with different IBD diseases. IBD is an autoimmune disease that is related to the innate and adaptive immune systems[32,33]. Evidence from animal models indicates that the failure to suppress immunity to the abundant intestinal foreign antigen load can cause inflammation[34]. Certain genetic variations and changes in the immune system might contribute to the development of IBD, such as those related to macrophage migration inhibitory factor (MIF)[35,36] and interleukin-10 (IL-10)[37].

CD24 has been reported to play an important role in the immune system and to be associated with autoimmune diseases, including IBD. CD24 has been shown to be a ligand for P-selectin and to play an important role in recruiting leukocytes to inflamed tissue. CD24 has also been implicated in the activation and differentiation of B lymphocytes[38], and it has been identified as an important mediator in a CD28-independent co-stimulatory pathway related to the activation of both CD4 and CD8 T cells[39]. Ahmed *et al*[40] found that *CD24* is upregulated by Wnt signaling in regenerating tissue in IBD and can confer enhanced colony forming abilities and enhanced cell motilities, which play an important roles in tissue healing. The association between *CD24* polymorphisms and the risk of IBD has been reported in recent studies[25,26]. The *CD24* gene contains multiple SNPs, such as the C170T (rs8734), TG1527del (rs3838646), A1626G (rs1058881) and A1056G (rs1058818) polymorphisms. Among these SNPs, C170T and TG1527del have received much attention. However, the existing data are contradictory. Van Limbergen *et al*[27] reported that the *CD24* TG1527*del* gene polymorphism is not an important determinant of genetic susceptibility to IBD. However, Diaz-Gallo *et al*[26] demonstrated that a TG1527del SNP is associated with an increased risk of CD but not UC. To better understand of the associations between these two polymorphisms and IBD, a meta-analysis with a larger sample and subgroup analysis is necessary.

The present study is the first meta-analysis that has attempted to determine the potential roles of *CD24* polymorphisms in IBD. Our results revealed a significant association between the *CD24* C170T polymorphism and UC risk in the dominant (OR = 1.79, 95%CI: 1.15-2.77, P = 0.009) and additive models (OR = 1.87, 95%CI: 1.19-2.93, P = 0.007), but the *CD24* C170T polymorphism was not related to the risk for CD. Moreover, our results indicated the *CD24* TG1570*del* polymorphism was significantly associated with CD in the additive model (OR = 1.27, 95%CI: 1.01-1.58, P = 0.037). These results support the hypothesis that CD and UC are related but different in terms of some immunologic mechanisms[41]. Similar results have been reported for other autoimmune diseases. Zhou *et al*[42] reported that the expression of *CD24* on the peripheral blood T cells of CD24V/V MS patients is higher than that of *CD24* A/A genotype patients. Sánchez *et al*[24] demonstrated that the frequency of the CD24V/V genotype in SLE patients was higher than that in the controls in a Spanish cohort. The TG1527*del* genetic variant has been reported to reduce the constitutive levels of *CD24* mRNA by more than two-fold and to reduce the risks for MS and SLE[43]. Diaz-Gallo[26] also observed that the TG1527*del* genetic variant is a risk factor for CD, specifically for CD with an age of diagnosis between 17 and 40 years. Van Limbergen *et al*[27] did not have any association between the *CD24* TG1527*del* SNP and CD susceptibility, possibly due to a low number of subjects.

However, our study has some limitations that should be considered. First, heterogeneities among the studies involving *CD24* C170T were present and might have partially influenced the results of this study. Therefore, additional details are needed to analyze the source of the heterogeneity. Second, the numbers of included studies and patients were limited. We are looking forward to the availability of additional relevant studies to help us to understand this problem. Third, only studies published in English were selected for this meta-analysis, and these studies do not include unpublished documents. Thus, a selection bias might have been present. Finally, some publication bias was present because the population of included studies was not uniform. Therefore, additional studies with the same patient inclusion criteria or studies that perform analysis stratified by age, gender and race will help to decrease the publication bias.

In conclusion, this study suggests that the *CD24* C170T polymorphism is associated with an increased risk of UC and that the *CD24* TG1527*del* polymorphism has some influence on CD risk. A large number of cases and controls are required to enable us to make a more precise risk estimate and minimize the bias in this meta-analysis.

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COMMENTS

Background

Inflammatory bowel disease (IBD) is a nonspecific chronic intestinal inflammatory disorder, and its etiology has not been completely elucidated. In the last three decades, the prevalence of IBD has increased both in developed and developing regions. However, increasing evidence indicates that environmental, genetic and immunological factors play important roles in the

pathogenesis of IBD.

Research frontiers

CD24 is a GPI-anchored mucin-like cell surface glycoprotein and plays an important role in the immune system. Some studies have reported that polymorphisms of *CD24* are associated with the pathogeneses of autoimmune diseases. Recently, some studies have indicated that *CD24* polymorphisms are related to IBD. However, contradictory findings exist.

Innovations and breakthroughs

This is a first meta-analysis to focus on the association between *CD24* polymorphisms and IBD. Based on this meta-analysis, the *CD24* C170T polymorphism plays a significant role in the risk of UC, and the *CD24* TG1527*del* polymorphism exerts some influence on the CD risk.

Applications

The different loci of *CD24* polymorphisms might be associated with the phenotypes of IBD. An exploration of the mechanisms might be useful for reducing the risk of IBD.

Terminology

Stata SE12 software was used to calculate the pooled odds ratios with 95% confidence intervals based on the available data from each article. Cochran's *Q*-statistic and the I^2 test were used to test the heterogeneity. Begg's funnel plots and Egger's tests were used to detect publication biases.

Peer-review

This is a well-performed meta-analysis of currently available studies about the associations between *CD24* gene polymorphisms and IBD risk. The authors found that the *CD24* polymorphisms C170T (rs8734) and TG1527*del* (rs3838646) are associated with the risk of UC and CD. This meta-analysis utilized appropriate methods for the literature search, data extraction and quality assessment of the literature.

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