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rs2476601 polymorphism in *PTPN22* is associated with Crohn's disease but not with ulcerative colitis: a meta-analysis of 16,838 cases and 13,356 controls

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Abstract

Background Although the rs2476601 polymorphism of *PTPN22* has been reported to be a susceptibility gene for Crohn's disease (CD), results from different studies vary and remain inconclusive. Also, no association has been found between rs2476601 and the risk of ulcerative colitis (UC). The aim of this meta-analysis was to investigate the association between this *PTPN22* polymorphism (rs2476601) and the risk of inflammatory bowel disease, UC and CD.

Methods We performed a meta-analysis by identifying relevant candidate gene-based studies from EMBASE and MEDLINE. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the strength of associations between rs2476601 and inflammatory bowel diseases, using a fixed effect or random effect model. Publication bias was also assessed.

Results By pooling 14 different studies, 13,356 controls, 8182 patients with CD, and 8656 with UC were included. We found that the T allele of *PTPN22* was not significantly associated with a higher risk of developing UC (OR 1.06, 95%CI 0.98-1.14) but was associated with a decreased risk of developing CD (OR 1.28, 95%CI 1.17-1.40). The T allele in rs2476601 lowered the risk of CD by 22%.

Conclusion This study shows that *PTPN22* (rs2476601) is significantly associated with the risk of developing CD, but has no association with UC. This suggests that these diseases have different pathways involved in their pathophysiology.

Keywords Meta-analysis, candidate gene study, *PTPN22*, inflammatory bowel disease, polymorphism

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Conflict of Interest: None

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Introduction

Inflammatory bowel diseases (IBD), consisting of ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the gut that are probably the result of a dysregulated immune response to the gut microflora in genetically predisposed individuals, triggered by environment [1,2]. The annual incidence of UC varies from 0-19.2 per 100,000 in North America and from 0.6-24.3 per 100,000 in Europe, corresponding to a prevalence of 37.5-248.6 per 100,000 and 4.9-505 per 100,000, respectively. The incidence of CD is similar in western countries (0-20.2 per 100,000 in North America; 0.3-12.7 per 100,000 in Europe). The incidence and prevalence of IBD are increasing over time and in different regions around the world [3]. IBD are polygenic diseases for

which up to 163 genes have been found to increase the risk of susceptibility [4-6]. Previous reports indicated several single nucleotide polymorphisms (SNPs) in different regions of the genome increasing risk of IBD. One of the most important non-human leukocyte antigen (HLA) common susceptibility alleles for autoimmunity is the 1858C/T SNP of *protein tyrosine phosphatase non-receptor 22* (*PTPN22*) (rs2476601).

The *PTPN22* gene encodes a protein tyrosine phosphatase, non-receptor type 22 (PTPN22), located on chromosome 1p13. This 110-kDa lymphoid-specific phosphatase (Lyp) plays a critical role as a negative regulator of T-cell activation by dephosphorylating T-cell receptor activation dependent kinases (Csk kinase) [7], expressed exclusively in immune cells; therefore, this gene may be associated with autoimmunity [8].

SNPs within the *PTPN22* gene may affect the regulatory role of the Lyp. A non-synonymous SNP at position 1858 of *PTPN22* gene (rs2476601) changes the amino acid from an arginine to a tryptophan and affects the ability of Lyp to interact with the Csk kinase, thus avoiding the formation of the complex and the resulting suppression of T-cell activation. *In vitro* experiments have shown that the *PTPN22* 1858T allelic variant binds less efficiently to Csk than does the C allele. This suggests that individuals lacking the C allele of *PTPN22* may have a reduced capacity to downregulate T-cell responses and may therefore be more susceptible to autoimmunity. Several studies have investigated a potential association of *PTPN22* C1858T polymorphism with various autoimmune disorders, including rheumatoid arthritis [9], systemic lupus erythematosus [10], Grave's disease [11], and type 1 diabetes mellitus [12]. However, contradictory results have been published regarding the association of rs2476601 variant with either CD or UC. This inconsistency might be due to differences in sample size, patient ethnicity, or allele frequencies. Accordingly, given these results, we performed a meta-analysis to determine quantitatively the risk of CD and UC with the rs2476601 variant under an allelic, recessive, dominant and co-dominant model.

Materials and methods

Selection of eligible studies

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria [13]. The eligible studies were obtained by searching online databases, MEDLINE and EMBASE. The following keywords were used for searching: ("inflammatory bowel disease" OR "Crohn's disease" OR "ulcerative colitis") AND ("polymorphism∗ "OR "variant") AND ("protein tyrosine phosphatase nonreceptor" OR "PTPN22" OR "lymphoid protein tyrosine phosphatase"). The most recent research was performed on April 30th 2016, and there was no limitation on the research. The references of reviews and retrieved articles were also searched simultaneously to find additional eligible studies. Research was performed using the Entrez interface of the National Center for Biotechnology Information (ncbi) from the terminal of a Linux station (ubuntu 14.04.2) and through a graphical interface in EMBASE.

Data extraction

Relevant information from the articles were extracted from the studies independently by the first (AH) and second (CC) authors. Disagreements were resolved through discussion to reach consensus or were adjudicated by a third author. If genotype information was lacking, we tried to contact the corresponding authors in order to obtain the required data. If they did not provide data, those studies were excluded from our review. General characteristics (e.g. demography, genotyping method) of the included studies were extracted. We extracted the following information from each included study: first author's name, publication year, sample size, source of controls, ethnicity, genotyping method, matching variables of controls with cases, age, sex distribution, and counts of alleles and genotypes in both cases and controls. We restricted our meta-analysis to candidate gene studies. The included studies had to meet the following criteria: 1) they concerned the association between rs2476601 and IBD; 2) they were case-control design or cohort studies; 3) they reported genotype frequencies or allele frequencies of the rs2476601 polymorphism. The exclusion criteria were: 1) review-articles, case reports and comments; and 2) duplicate publications.

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) was examined in control groups using Fisher's exact test. If the study was found not to be in HWE with a P value less than 0.05, it was considered to be disequilibrium. Allele frequencies of the *PTPN22* rs2476601 polymorphisms in each of the studies were determined using the allele counting method. Allelic effect contrast was examined for the minor allele vs. the common allele. The genetic models evaluated for pooled ORs included allelic contrast (C vs. T), recessive models (CC vs. CT + TT), dominant models (CC + CT vs. TT), and the homozygote model (CC vs. TT). To evaluate the strength of association, the pooled ORs and their 95%CIs were determined for each study, and within- and between-study heterogeneity was assessed using Cochran's *Q* statistic [14]. The heterogeneity test was used to assess the probability of the null hypothesis that all studies were evaluating the same effect. The random-effects model was used for meta-analysis when a significant *Q* statistic ($P<0.10$) indicated heterogeneity across studies, while the fixed-effect model was used when heterogeneity was not indicated. The fixed-effect model assumes that genetic factors have similar effects on disease susceptibility across all studies and that observed variations between studies are caused by chance alone [15]. The random-effect model assumes that studies show substantial diversity, and assesses both within-study sampling errors and between-study variances [16]. When study groups are homogenous, the two models are similar, but if this is not the case, the random effects model

usually provides wider CIs than the fixed effects model. The random effects model is best used in the presence of significant between-study heterogeneity [16]. We quantified the effect of heterogeneity by using the recently developed I^2 measure, where $I^2 = 100\% \times (Q - df)/Q$, where df is degrees of freedom [17]. The I^2 measure ranges between 0% and 100% and represents the proportion of inter-study variability attributable to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% were defined as low, moderate, and high estimates, respectively. All statistical analyses were performed using the general package for meta-analysis (version 4.6-0, depends on R≥2.9.1).

Evaluation of publication bias

Finally, potential publication bias was assessed using a funnel plot and Egger's test, which measures funnel plot asymmetry on a natural logarithm scale of ORs [18]. Funnel plot should be interpreted with caution, as they usually require a large number of studies.

Results

Search strategy

According to the search strategy (Fig. 1), 34 studies were initially included; 15 papers were excluded after reading the title and abstract, 1 paper was not relevant to rs2476601, while 1 paper [19] included three different populations, which were treated as three different studies. Two studies [20,21] that presented a significant deviation from Hardy–Weinberg equilibrium in controls (P=0.041 and P=0.010) were excluded from the analysis (Table 1). One article [22] was excluded on the basis of a T recessive test, as the TT genotype was not reported in the population of interest.

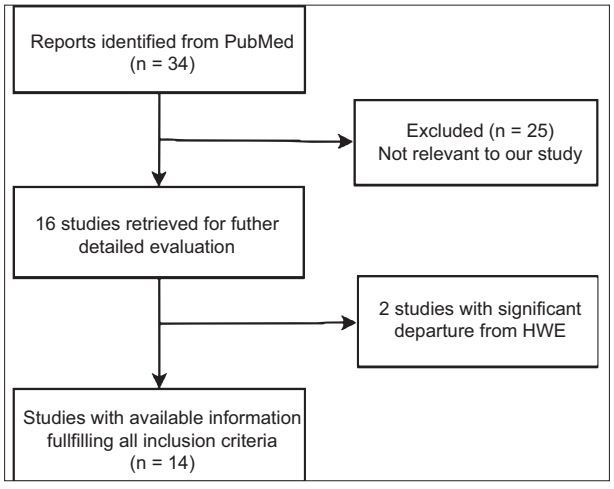

Figure 1 Flow chart showing selection of studies and specific reasons for exclusion from the study
HWE, Hardy-Weinberg equilibrium

A total of 14 studies [9,23-33] were thus included in the analysis (Tables 2 and 3) involving a total of 13,356 controls, 8182 patients with CD, and 8656 with UC. The methodological quality of the studies were also evaluated (Table 4).

Quantitative analysis of *PTPN22* rs2476601 and CD

They were 14 studies investigating the association between *PTPN22* and CD, which included a total of 13,370 patients and 16,888 controls (Table 2). The presence of the C allele significantly increased the risk of having CDs (OR 1.28, 95%CI 1.17-1.40). We could not find significant heterogeneity between the studies (I^2=37.5%, P=0.0835). The Funnel plot showed no asymmetry.

The CC genotype was compared with CT and TT assuming a recessive model for the C allele. The pooled OR was 1.34 (95%CI 1.20-1.49) and no significant between-study heterogeneity was found (I^2=3.5%, P=0.4077) (Fig. 2). Assuming a dominant model for C allele, we could not find a significant risk for having CD (OR 1.14, 95%CI 0.72-1.8). The between-study heterogeneity was low (I^2=14.5%, P=0.3094) (Fig. 2, Table 4).

Quantitative analysis of *PTPN22* rs2476601 and UC

Seven studies investigated the allelic risk of rs2476601, including a total number of 6971 patients with UC and 9715 controls. The results are summarized in a forest plot (Fig. 3). No significant association was found (OR 1.06, 05%CI 0.98-1.14), assuming a fixed effect model because of a low between-study heterogeneity (I^2=32.2%, P=0.1064). No association was found assuming a dominant effect for C allele (OR 0.92, 95%CI 0.64-1.31), or a recessive model for C allele: OR 1.09, 95%CI 0.97-1.22, and OR 1.11, 95%CI 0.94-1.31, assuming a fixed effect and a random effect model respectively (I^2=50%, P=0.0639). In addition, measuring the risk of carrying CC compared to TT allele on a co-dominant model, we could not find a significant increased risk of UC with either genotype (OR=0.84, 05%CI 0.55-1.28) assuming a fixed effect model.

Sensitivity analysis

We performed a sensitivity analysis for statistically significant results. For the association of the *PTPN22* rs2476601 polymorphism and CD or UC susceptibility among the overall populations, the observed significant result was not materially altered by sequentially excluding each study.

Publication bias

Egger's test indicated no significant publication bias in the allelic, dominant, recessive and co-dominant models for CD (P=0.48, P=0.75, P=0.78 and P=0.48, respectively). There was

Table 1 Hardy–Weinberg Equilibrium (HWE) deviation P-values in controls and cases

Author	Year	Ethnicity	Phenotype	CC	CT	TT	HWE-P-values
Bank	2014	Danish	Controls	588	166	11	0.123
Bank	2014	Danish	CD	533	85	2	0.072
Bank	2014	Danish	UC	338	68	4	0.093
Bank	2014	Danish	IBD	871	153	6	0.080
Chen	2013	Han Chinese	Controls	300	0	0	NC
Chen	2013	Han Chinese	UC	165	0	0	NC
Diaz	2011	Spanish	Controls	1467	209	9	0.067
Diaz	2011	Dutch	Controls	683	142	9	0.096
Diaz	2011	New Zealander	Controls	454	106	3	0.099
Diaz	2011	Spanish	CD	626	69	4	0.055
Diaz	2011	Dutch	CD	575	94	3	0.074
Diaz	2011	New Zealander	CD	414	60	3	0.069
Diaz	2011	Spanish	UC	571	81	6	0.071
Diaz	2011	Dutch	UC	468	67	4	0.070
Diaz	2011	New Zealander	UC	366	76	6	0.098
Diaz	2011	Spanish	IBD	1197	150	10	0.063
Diaz	2011	Dutch	IBD	1043	161	7	0.072
Diaz	2011	New Zealander	IBD	780	136	9	0.083
Hradsky	2008	Czech	controls	398	100	3	0.106
Hradsky	2008	Czech	CD	275	66	4	0.107
Latiano	2007	Italian	Controls	235	21	0	0.041
Latiano	2007	Italian	CD	283	18	0	0.030
Latiano	2007	Italian	UC	278	28	0	0.046
Latiano	2007	Italian	IBD	561	46	0	0.038
Martin	2005	Spanish	Controls	714	95	3	0.062
Martin	2005	Spanish	Controls	714	95	3	0.062
Martin	2005	Spanish	UC	474	67	3	0.067
Martin	2005	Spanish	CD	514	51	4	0.052
Morgan	2010	New Zealander	Controls	379	85	8	0.107
Morgan	2010	New Zealander	CD	260	52	3	0.092
Prescott	2005	British	Controls	312	61	1	0.084
Prescott	2005	British	Controls	312	61	1	0.084
Prescott	2005	British	Controls	312	61	1	0.084
Prescott	2005	British	CD	254	37	3	0.073
Prescott	2005	British	CD	254	37	3	0.073
Prescott	2005	British	UC	192	26	2	0.068
Sfar	2010	Tunisian	Controls	98	2	0	0.010
Sfar	2010	Tunisian	CD	68	37	0	0.176
Sfar	2010	Tunisian	UC	46	13	0	0.110
Sfar	2010	Tunisian	IBD	114	50	0	0.152
Skieceviciene	2013	Lithuanian	Controls	827	269	25	0.142
Skieceviciene	2013	Lithuanian	UC	308	117	11	0.159
Wagenleiter	2005	German	Controls	203	49	2	0.104
Wagenleiter	2005	German	CD	122	23	1	0.086

CD, Crohn's disease; *IBD, inflammatory bowel disease*; *UC, ulcerative colitis*

Table 2 Genotype and allelic distribution for rs2476601 in the selected studies

Ethnicity	Position	Study	Year	Phenotype	Total -controls	Total -cases	CC-controls	CT -controls	TT -controls	CC -cases	CT -cases	TT -cases	C -controls	Total -alleles -controls	C -cases	Total -alleles -cases
Danish	114089610	Bank	2014	CD	765	620	588	166	11	533	85	2	1342	1530	1151	1240
Danish	114089610	Bank	2014	UC	765	410	588	166	11	338	68	4	1342	1530	744	820
Spanish	114089610	Diaz	2011	CD	1685	699	1467	209	9	626	69	4	3143	3370	1321	1398
Dutch	114089610	Diaz	2011	CD	834	672	683	142	9	575	94	3	1508	1668	1244	1344
New Zealander	114089610	Diaz	2011	CD	563	477	454	106	3	414	60	3	1014	1126	888	954
Spanish	114089610	Diaz	2011	UC	1685	658	1467	209	9	571	81	6	3143	3370	1223	1316
Dutch	114089610	Diaz	2011	UC	834	539	683	142	9	468	67	4	1508	1668	1003	1078
New Zealander	114089610	Diaz	2011	UC	563	448	454	106	3	366	76	6	1014	1126	808	896
British	114089610	Prescott	2005	CD	374	294	312	61	1	254	37	3	685	748	545	588
Tunisia	114089610	Sfar	2010	CD	100	105	98	2	0	68	37	0	198	200	173	210
Tunisia	114089610	Sfar	2010	UC	100	59	98	2	0	46	13	0	198	200	105	118
German	114089610	Wagenleiter	2005	CD	254	146	203	49	2	122	23	1	455	508	267	292
Han Chinese	114089610	Chen	2013	UC	300	165	300	0	0	165	0	0	600	600	330	330
Czech	114089610	Hradsky	2008	CD	501	345	398	100	3	275	66	4	896	1002	616	690
Italy	114089610	Latiano	2007	CD	256	301	235	21	0	283	18	0	491	512	584	602
Italy	114089610	Latiano	2007	UC	256	306	235	21	0	278	28	0	491	512	584	612
New Zealander	114089610	Morgan	2010	CD	472	315	379	85	8	260	52	3	843	944	572	630
Spanish	114089610	Martin	2005	UC	812	544	714	95	3	474	67	3	1523	1624	1015	1088
Spanish	114089610	Martin	2005	CD	812	569	714	95	3	514	51	4	1523	1624	1079	1138
British	114089610	Prescott	2005	CD	374	294	312	61	1	254	37	3	685	748	545	588
British	114089610	Prescott	2005	UC	374	220	312	61	1	192	26	2	685	748	410	440
Lithuanian	114089611	Skieceviciene	2013	UC	1154	447	827	269	25	308	117	11	1923	2308	733	894
Canadian -Quebecois	114089610	De Jager	2005	CD	207	249	NR	NR	NR	NR	NR	NR	398	414	468	498
Canadian	114089610	Watterman	2011	CD	1057	1144	NR	NR	NR	NR	NR	NR	1932	2114	2144	2288
Canadian	114089610	Watterman	2011	UC	1057	1230	NR	NR	NR	NR	NR	NR	1931	2114	2263	2460
British	114089610	Anderson	2009	UC	2471	2483	NR	NR	NR	NR	NR	NR	4460	4942	4492	4966
Canadian	114089610	VanOene	2005	CD	190	455	NR	NR	NR	NR	NR	NR	355	380	842	910

CD, Crohn's disease; NR, not reported; UC, ulcerative colitis

Table 3 Demographic and baseline characteristics of the selected studies

Study-year	Method	Ethnicity	Controls		UC		CD		Quality of the study
			Mean	Male (%)	Mean Age	Male (%)	Mean	Male (%)	
Bank, 2014	Kasp	Danish	43 (median)	52	42 (median)	49	37 (median)	44	9
	TaqMan	Spanish	NR	NR	NR	NR	NR	NR	
Diaz, 2011	TaqMan	Dutch	NR	NR	NR	NR	NR	NR	9
	TaqMan	New Zealander	NR	NR	NR	NR	NR	NR	
Prescott, 2005	TaqMan	British	NR	NR	NR	NR	NR	NR	2
Sfar, 2010	RFLP-PCR	Tunisian	NR	52	38	30	36	52	9
Wagenleiter, 2005	RFLP-PCR	German	38	72%	NR	NR	NR	NR	8
Chen, 2013	RFLP-PCR	Han Chinese	NS	NS	41.3	57.6	43.7	55	11
Hradsky, 2008	TaqMan	Czech	20.27 (median)	64%	NS	NS	21	44	11
Latiano, 2007	TaqMan	Italian	NR	NR	35	52%	35	57	10
Morgan, 2010	MALDI-TOF	New Zealander	NR	66.5	NS	NS	NR	31.4	11
Martin, 2005	TaqMan	Spanish	NR	NR	NR	NR	NR	NR	9
Skieceviciene, 2013	TaqMan	Lithuanian	40.2	NR	44.4	NR	NS	NS	10
De Jager, 2005	SeqenomMassArray	Canadian-Quebecois	NR	NR	NS	NS	NR	NR	6
Watterman, 2011	IlluminaGoldenGate	Canadian	NR	35.8	NR	49.2	NR	52.7	9
Criswell, 2005	PSQHS96APyrosequencer	American	NR	NR	NR	NR	NR	NR	8
Anderson, 2009	iPLEX	British	NR	NR	NR	50%	NR	39%	11
Van Oene, 2005	MALDITOF	Canadian	NR	NR	NS	NS	NR	NR	9

NR, not reported; NS, not studied; CD, Crohn's disease; UC, ulcerative colitis

also no significant publication bias in the allelic, dominant, recessive and co-dominant models for UC (P=0.49, P=0.6, P=0.91 and P=0.49, respectively). The funnel plots were symmetrical for all tests.

Discussion

The incidence of IBD is increasing worldwide and the rising prevalence of immune diseases is thought to be influenced by genetic and environmental factors [1,2]. *PTPN22* encodes the gatekeeper of T-cell receptor signaling, cytoplasmic Lyp and as such is a likely candidate risk factor for UC because of its role in down-regulation of T-cell activity [34].

So far, genome-wide association studies have found more than 163 genes that are associated with IBD in a Caucasian population from. Of these genes, 110 have been shown to be significantly associated with both UC and CD, but 23 showed risk effects that were UC specific and 30 were CD-only loci [5]. This suggests that there are different biological pathways in these two diseases that are well reflected by the different phenotypes and still need to be explored. There have been conflicting results, with some studies showing an increased risk associated with the T allele [19], whereas other studies, such as the one conducted by Silverberg *et al* [35], did not report any significantly increased risk. Most studies have failed to show a significant association and this could be due to a lack of power. A meta-analysis is a powerful tool that can improve the statistical performance by combining the results of multiple studies. Therefore, in the present study, we investigated whether the *PTPN22* 1858C/T polymorphism contributes to IBD susceptibility, using a meta-analysis approach.

We pooled data from 14 individual studies results to determine the effect of a non-synonymous SNP at position 1858 of the *PTPN22* gene (rs2476601) on CD and UC, This is the first meta-analysis of candidate gene studies exploring the variant rs2476601 of *PTPN22*. We determined that individuals carrying minor allele C in rs2476601 have a greater risk of developing CD (OR 1.28, 95%CI 1.17-1.40) relative to those carrying the T allele, while carrying the C allele does not significantly change the risk of developing UC. Genotypic effects were also estimated for *PTPN22* and the risk of CD was greater (OR 1.34, 95%CI 1.20-1.49) with CC genotype compared to CT or TT. In our study we did not detect significant between-study heterogeneity among the case-control studies included. Interestingly, the T allele was associated with a lower risk of CD, but an increased risk for other immune diseases, such as type 1 diabetes mellitus, or rheumatoid arthritis [10,12].

The rs2476601 polymorphism disrupts the interaction between Lck and Lyp, leading to reduced phosphorylation of Lyp, which ultimately contributes to gain-of-function

Table 4 Methodological quality of included studies

Criteria	Score	Bank 2014	Diaz 2011	Prescott 2005	Sfar, 2011	Wagenleiter, 2005	Chen, 2013	Hardsky, 2008	Latiano, 2007	Morgan, 2010	Martin, 2005	Skiecevicience, 2013	De jager, 2005	Watterman, 2011	Criswell, 2005	Anderson, 2009	VanOene, 2005
Representativeness of cases																	
Selection from population or hospital	2	x	x			x	x		x	x	x	x		x	x	x	x
Selected from any gastroenterology department	1				x			x									
Selected without clearly defined inclusion /exclusion criteria	0			x									x				
Credibility of controls																	
Population-based	3				x			x									
Blood donors or volunteers	2	x					x		x	x	x	x				x	x
Hospital-based	1						x							x			
Not described	0		x	x		x							x		x		
Ascertainment of inflammatory bowel disease																	
Standard clinical, radiological, endoscopic and pathology	2		x		x	x	x	x	x	x	x	x	x	x	x	x	x
By patient medical records	1	x															
Not described	0			x													
Genotyping examination																	
Genotyping checked	1	x	x				x	x		x	x	x	x	x	x		x
Not mentioned	0			x	x	x			x		x	x	x	x	x		x

(*Contd...*)

Table 4 (*Continued...*)

Criteria	Score	Bank 2014	Diaz 2011	Prescott 2005	Sfar, 2011	Wagenleiter, 2005	Chen, 2013	Hardsky, 2008	Latiano, 2007	Morgan, 2010	Martin, 2005	Skiecevicience, 2013	De jager, 2005	Watterman, 2011	Criswell, 2005	Anderson, 2009	VanOene, 2005
Hardy–Weinberg equilibrium																	
Equilibrium in controls	2	x	x	x		x		x	x	x	x	x	x	x	x	x	x
Disequilibrium in controls	1				x	x	x										
Not checked	0																
Association assessment																	
Appropriate statistics	2		x		x	x		x	x	x	x	x	x	x	x	x	x
Logistic regression	1	x															x
Inappropriate/ not mentioned	0			x													
Total (/13)		9	9	2	9	8	11	11	10	11	9	10	6	9	8	11	9

inhibition of T-cell activation [36]. Despite the promising role for *PTPN22* mutation in the risk of UC, we were unable to find a significant association in our meta-analysis. Interestingly, other polymorphisms, such as -1123G/C, located in the promoter region of *PTPN22* have been shown to be correlated with other autoimmune diseases [37,38]. Another polymorphism, +788G/A in exon 10 of *PTPN22*, has been found to be associated with UC [22] in a Chinese population but remains to be further explored in the Caucasian population.

More recently, Spalinger *et al* [39] investigated the association between *PTPN22* rs2476601 polymorphism and clinical features in 2028 IBD patients. They found that TT and CT genotypes were associated with less use of steroids and antibiotics and a lower prevalence of vitamin D and calcium deficiency in CD, which again indicates a protective role for the T allele. Interestingly, the authors found that TT and CT genotypes were significantly associated with an increased use of azathioprine and anti-tumor necrosis factor antibodies in UC, suggesting more severe clinical manifestations, and therefore opposite effects on disease severity compared to CD. However, in our study, we could not identify a significantly higher risk of UC with rs2476601 after pooling data from 6971 individuals. However, given the much smaller number of patients compared to those with CD, there may have been insufficient statistical power to detect a possible difference.

Several limitations in our study should be considered. First we could not perform a stratified analysis because of the lack of data on other ethnic groups. Most of the studies involved a Caucasian population. Gene polymorphism variation among different ethnicities was not explored. According to the study of Chen *et al* [22], the T allele was absent in rs2476601, suggesting that the protective effect on CD is exclusive to non-Asian ethnic groups. In addition, clinical subtypes of IBD, especially relating to the severity of the diseases, could not be taken into account due to insufficient data.

Nevertheless, the present meta-analysis also had several strengths. First, no publication biases were detected, indicating that the results may be unbiased. Second, a significant number of cases and controls were included in the current study by using an effective and efficient search strategy to increase the statistical power of the analysis. Third, to our knowledge, this is the first meta-analysis to assess the association between *PTPN22* and IBD.

In conclusion, the present meta-analysis pooled both statistically significant and non-significant findings from individual studies to improve the statistical performance and generate a precise conclusion. The findings of this meta-analysis demonstrate that rs2476601 polymorphism is an important risk factor for CD but not for UC. However, larger and well-designed multicenter studies, particularly addressing the Asian population group, stratified by gene–gene and gene–environment interactions, are warranted to validate our findings.

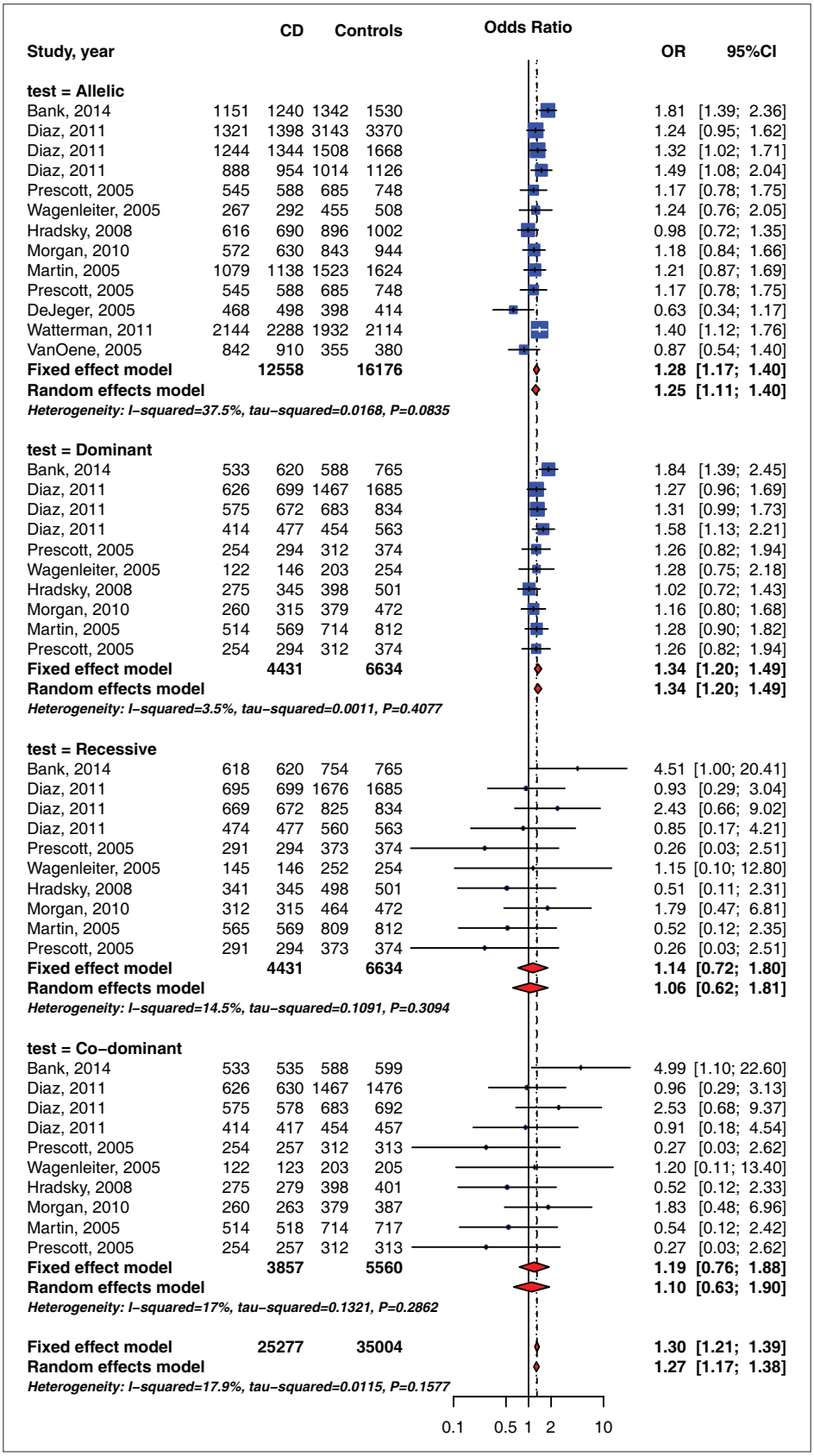

Figure 2 Risk of Crohn's disease associate with C allele, assuming an allelic, dominant, recessive, and co-dominant model
CD, Crohn's disease; OR, odds ratio; 95%CI, 95% confidence interval

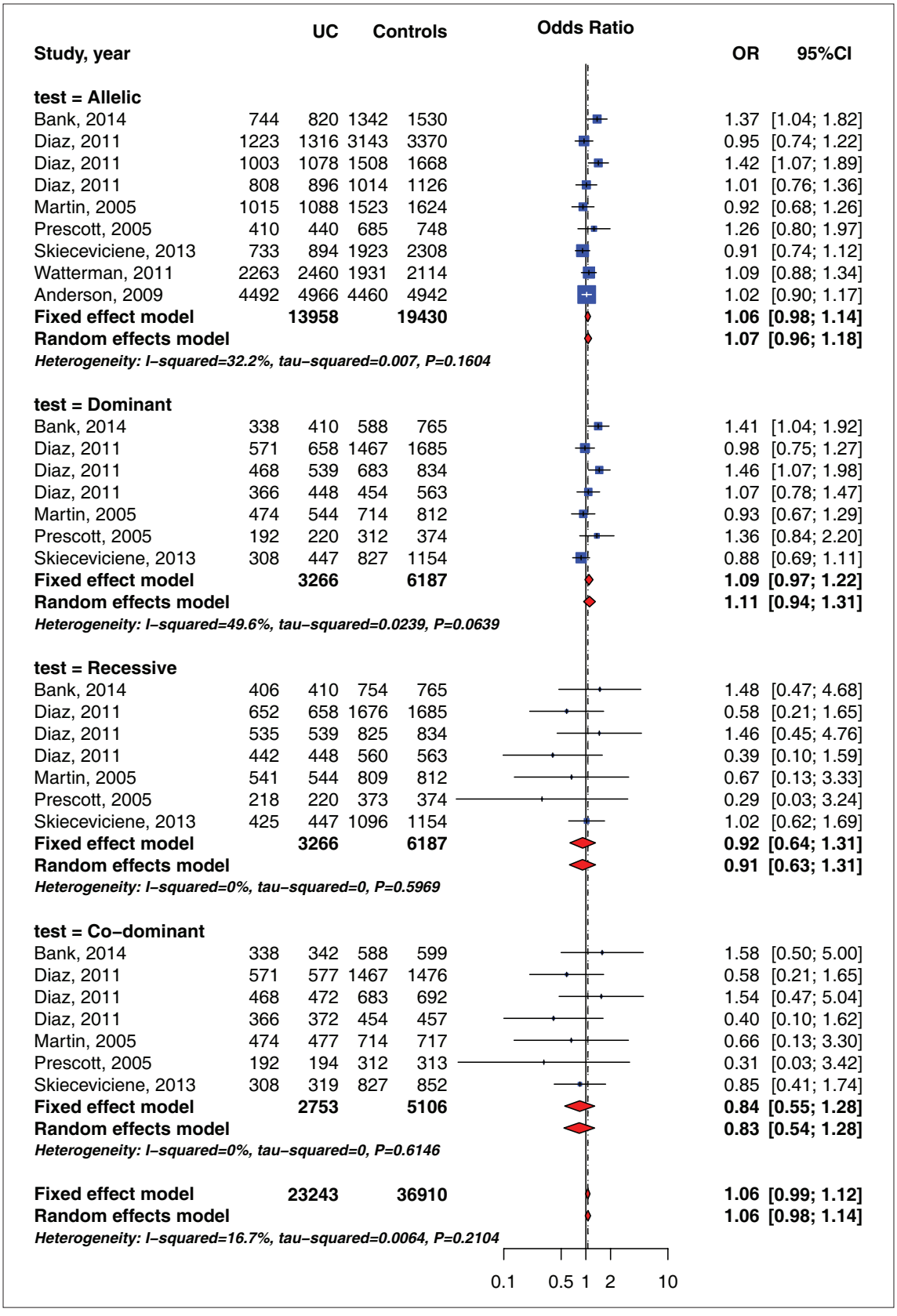

Figure 3 Risk of ulcerative colitis, assuming an allelic, dominant, recessive and co-dominant model
CD, Crohn's disease; OR, odds ratio; 95%CI, 95% confidence interval

Table 5 Summary statistics for Crohn's disease (CD) and ulcerative colitis (UC)

Trait	Number of studies	Model	Test	N (cases)	N (controls)	Test for heterogeneity			Test for association					Test for publication bias	
						Q	I2 (%)	P-value	Model	OR	LCI	UCI	P-value	t	P-value
CD	13	Allelic	T vs. C	6279	8088	19.21	37.54	0.08	Fixed	1.28	1.17	1.4	8.48e-08	-0.73	0.48
CD	10	Dominant	CC vs. TT + TC	4431	6634	9.33	3.5	0.41	Fixed	1.34	1.2	1.49	1.05e-07	0.34	0.75
CD	10	Recessive	TT vs. TC+CC	4431	6634	10.53	14.52	0.31	Fixed	1.14	0.72	1.8	0.57	-0.28	0.78
CD	10	Codominant	TT vs. CC	4431	6634	10.85	17.05	0.29	Fixed	1.19	0.76	1.88	0.45	-0.73	0.48
UC	9	Allelic	T vs. C	6979	9715	11.8	32.2	0.16	Fixed	1.06	0.98	1.14	0.16	0.72	0.49
UC	7	Dominant	CC vs. TT + TC	3255	6154	11.91	49.64	0.06	Random	1.11	0.94	1.11	0.22	0.55	0.6
UC	7	Recessive	TT vs. TC+CC	3255	6154	4.59	0	0.6	Fixed	0.92	0.64	1.31	0.63	-0.12	0.91
UC	7	Codominant	TT vs. CC	2753	5106	4.46	0	0.61	Fixed	0.84	0.55	1.28	0.42	0.72	0.49

LCI, lower bound of 95% confidence interval; OR, odds ratio; UCI, upper bound of 95% confidence interval

Summary Box

What is already known:

- The incidence and prevalence of inflammatory bowel diseases (IBD) are increasing over time and in different regions around the world, but their etiology remains unknown
- One of the most important non-HLA common susceptibility alleles for autoimmunity is the 1858C/T single nucleotide polymorphism of protein tyrosine phosphatase non-receptor 22 (*PTPN22*) (rs2476601)
- The *PTPN22* gene is located on chromosome 1p13.3-p13.1 and encodes a lymphoid-specific phosphatase
- The association between *PTPN22* R620W polymorphism and IBD is inconsistent among candidate gene studies

What the new findings are:

- Individuals carrying minor allele C in rs2476601 have a greater risk of developing Crohn's disease relative to those carrying T allele, under an allelic and dominant model
- No significant results were found concerning ulcerative colitis, suggesting different underlying biological pathways
- No significant risk association could be identified under the recessive or co-dominant model for ulcerative colitis and Crohn's disease. Studies were not heterogeneous and no publication bias has been identified

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