Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Meta-Analysis

Association between the functional PTPN22 G788A (R263Q) polymorphism and susceptibility to autoimmune diseases: A meta-analysis

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Received October 14, 2017; **Accepted** April 15, 2018; **Published** April 30, 2018

Doi: http://dx.doi.org/10.14715/cmb/2018.64.5.7

Abstract: This study explored whether the functional protein tyrosine phosphatase nonreceptor 22 (PTPN22) G788A (R263Q) polymorphism is associated with susceptibility to autoimmune diseases. A meta-analysis was conducted using 23 comparative studies with a total of 16,719 patients and 17,783 controls. The meta-analysis showed an association between the A allele of the PTPN22 G788A polymorphism and decreased risk of autoimmune diseases in all subjects ($p < 0.001$). Analysis after stratification by ethnicity indicated that the PTPN22 788A allele was significantly associated with autoimmune diseases in Europeans ($p < 0.001$) but not in Latin Americans. Meta-analysis by autoimmune disease type showed a significant negative association between the PTPN22 788A allele and systemic lupus erythematous (SLE) ($p = 001$), rheumatoid arthritis (RA) ($p = 0.008$), ulcerative colitis (UC) ($p = 0.016$), but not Crohn's disease (CD). A single study for each showed no association between the PTPN22 788A allele and systemic sclerosis, giant cell arteritis, Henoch-schonlein purpura, uveitis, and Grave's disease. This meta-analysis demonstrates that the PTPN22 G788A polymorphism confers protection against SLE, RA, and UC, supporting evidence of association of the PTPN22 gene with a subgroup of autoimmune diseases.

Key words: PTPN22; Autoimmune diseases; Meta-analysis.

Introduction

Autoimmune diseases are a diverse group of complex diseases characterized by the loss of self-tolerance, leading to immune-mediated tissue destruction (1). These diseases are multifactorial and are caused by interactions between genetic and environmental factors. Furthermore, these diseases share several characteristics, suggesting a common etiology. Particularly, their pathophysiology and co-occurrence in families suggest that these diseases share a genetic background (2). This hypothesis is strengthened by meta-analyses of whole-genome scans that show non-random clustering of disease susceptibility loci in patients with autoimmune diseases (3,4).

The protein tyrosine phosphatase nonreceptor 22 (PTPN22) gene maps to chromosome 1p13.3–p13.1 and encodes a lymphoid-specific phosphatase (Lyp). Its protein product is an intracellular protein tyrosine phosphate (PTP) that binds physically via its proline-rich motif to the SH3 domain of Csk kinase, an important suppressor of kinases that mediate T cell activation (5). The non-synonymous polymorphism of PTPN22 is rs33996649 (G788A), which maps to exon 10 within the catalytic domain of LYP. PTPN22 G788A polymorphism leads to a change of an arginine (R) to a glutamine (Q) at codon 263 (R263Q)(6). This functional PTPN22 A allele encodes for a loss-of-function variant of Lyp, causing reduced phosphatase activity, and might confer protection against autoimmunity (6). While the PTPN22 C1858T polymorphism is a gain-of-function mutant of LYP, the PTPN22 G788A is a loss-of-function variant of Lyp, a possible risk factor for autoimmunity.

A number of studies have examined the association between the PTPN22 G788A polymorphism and autoimmune diseases, but reported results have been contradictory (6-13). Taking into account these findings, we sought to assess whether the combined evidence shows an association between the functional PTPN22 G788A polymorphism and autoimmune diseases and to summarize, using meta-analysis, the effect size of the polymorphism associated with susceptibility to autoimmune diseases.

Materials and Methods

Identification of eligible studies and data extraction

We performed a search of studies that examined associations between the PTPN22 G788A polymorphism and autoimmune diseases. The literature was searched using MEDLINE, EMBASE, Cochrane library databases, and the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) conference proceedings to identify both published and unpublished articles in which the PTPN22 G788A polymorphism was analyzed in patients with autoimmune diseases. Combinations of keywords, such as, 'PTPN22 G788A,' 'PTPN22 R263Q,' 'polymorphism,' 'autoimmune diseases,' and the names of individual diseases were entered as Medical Subject Heading (MeSH) and text words. The references in identified studies were also investigated to identify additional studies

not indexed by the electronic databases. No restrictions were placed on language, race, ethnicity, or geographic area. Autoimmune diseases were diagnosed according to classification criteria. Studies were included if (1) they were published before September 2017, (2) contained original data, and (3) provided sufficient genotype data to calculate odds ratios (ORs). The following were excluded: (1) studies containing overlapping data and (2) studies in which family members had been studied (for example, transmission disequilibrium tests, because the analyses conducted were based on linkage considerations). Data on methods and results were extracted from original studies by two independent reviewers. Any discrepancies between reviewers were resolved by the third person and the meta-analysis was conducted in accordance with PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines. The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics of subjects, numbers of cases and controls, the genotype and allele frequency of the PTPN22 G788A polymorphism, and the Hardy-Weinberg equilibrium (HWE) in control groups. We scored the quality of each included study based on the Newcastle–Ottawa Scale [17]. The highest score was nine. Scores ranging from 6–9 range were considered to indicate high methodological quality.

Evaluations of statistical associations

Meta-analyses were performed using allelic contrast (A versus G) for the PTPN22 G788A polymorphism. The weights for each original study were associated with sample size of each study. Point estimates of risks, ORs, and 95% confidence intervals (CI) were estimated for each study. Cochran's Q-statistic was used to assess within- and between-study variations and heterogeneities. This heterogeneity test assesses the null hypothesis that all studies evaluated the same effect. I^2 values were used to quantify the effect of heterogeneity, with values ranging between 0% and 100%, and represented the proportion of between-study variability attributable to heterogeneity rather than chance (14). I^2 values of 25%, 50%, and 75% were nominally defined as low, moderate, and high estimates. The fixed effects model assumes that a genetic factor has the same effect on disease susceptibility across all studies investigated and that observed variations between studies are caused by chance alone. The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance. When study groups are homogeneous, the two models are similar; however, if this is not the case, the random effects model usually provides wider CIs than the fixed effects model. Furthermore, the random effects model is used in the presence of significant between-study heterogeneity (15). P-values less than 0.05 were considered as significant. Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA).

Evaluation of heterogeneity, sensitivity, and publication bias

Subgroup analyses were performed by ethnicity and disease type to evaluate ethnic- and disease-specific effects and to examine the potential source of heterogeneity observed in the meta-analysis. Sensitivity analysis was also performed to assess the influence of each individual study on the pooled OR by omitting each individual study and to investigate statistically robust results from this meta-analysis. We compared the random and fixed effects models. Random and fixed effects model results provided the same interpretation, indicating that the results of this meta-analysis are robust. A funnel plot and the Egger's linear regression test were used to detect publication bias[18]. When asymmetry was indicated, we used the trim and fill method to adjust the summary estimate for the observed bias[19]. This method removes small studies until symmetry in the funnel plot is achieved by recalculating the center of the funnel before the removed studies are replaced with their missing mirror-image counterparts. A revised summary estimate is then calculated using all of the original studies, together with the hypothetical "filled" studies.

Results

Studies included in the meta-analysis

Electronic and manual searches identified 255 studies, of which ten were selected for full-text review based on their titles and abstracts. Two studies were excluded because of no autoimmune disease and a review. Thus, eight studies, which met the inclusion criteria, were included in the meta-analysis (6-13) (Table 1, Figure 1). In addition, two studies included data on six different groups, one study included data on four different groups, and one study included data on three different groups; these studies were analyzed independently. Thus, 23 separate studies involving 16,719 patients and 17,783 controls were included in the meta-analysis. These studies were performed on systemic lupus erythematosus (SLE, n = 5), rheumatoid arthritis (RA, n = 7), Crohn's disease (CD n = 3), ulcerative colitis (UC, n = 3), systemic sclerosis (SSc, n = 1), giant cell arteritis (GCA, n = 1), Henoch-Schonlein purpura (HSP; n = 1), uveitis (n = 1), and Grave's disease (GD, n

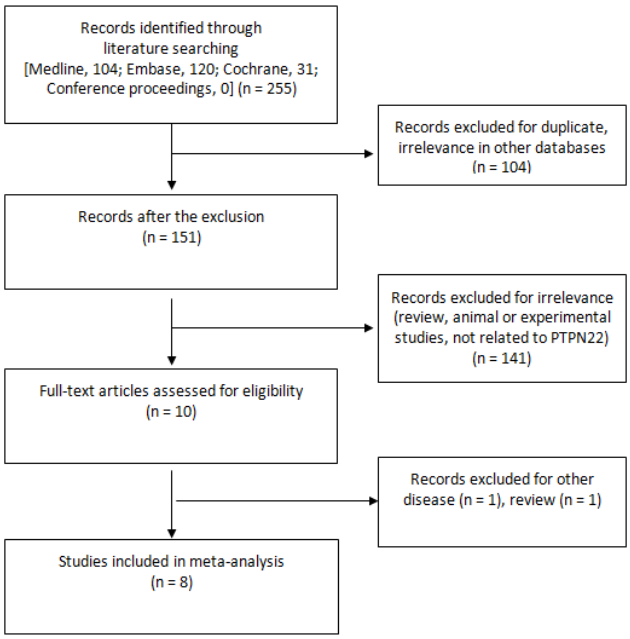

Figure 1. Flow diagram of the study selection process.

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

Author (Ref)	Country	Ethnicity	Disease	Numbers		Case			Control			Association p-value	Study Quality
				Case	Control	CC	CT	TT	CC	CT	TT		
Lopez-Cano-1, 2017(7)	Mexico	LA	SLE	405	336	404	1	0	327	9	0	0.023	7
Lopez-Cano-2, 2017(7)	Mexico	LA	RA	388	336	385	3	0	327	9	0	0.061	7
Lopez-Cano-3, 2017(7)	Mexico	LA	GD	83	336	79	4	0	327	9	0	0.325	7
Lopez-Mejias, 2017(13)	Spain	European	HSP	329	515	314	15	0	480	34	1	0.158	6
Serrano, 2013(8)	Spain	European	GCA	623	1729	583	39	1	1615	110	4	0.838	8
Cenit, 2013(9)	Spain	European	Uveitis	217	718	202	15	0	668	49	1	0.925	6
Diaz-Gallo-1, 2011(10)	Netherlands	European	CD	699	1685	640	59	0	1580	103	2	0.074	7
Diaz-Gallo-2, 2011(10)	Netherlands	European	UC	658	1685	632	26	0	1580	103	2	0.028	7
Diaz-Gallo-3, 2011(10)	Netherlands	European	CD	694	863	658	36	0	818	45	0	0.981	7
Diaz-Gallo-4, 2011(10)	Netherlands	European	UC	548	863	523	25	0	818	45	0	0.587	7
Diaz-Gallo-5, 2011(10)	NZ	European	CD	510	559	490	20	0	536	23	0	0.468	7
Diaz-Gallo-6, 2011(10)	NZ	European	UC	471	559	459	12	0	536	23	0	0.175	7
Rodriguez-1, 2011(11)	Spain	European	RA	1776	1906	1680	93	3	1776	129	1	0.110	8
Rodriguez-2 2011(11)	NZ	European	RA	735	555	715	20	0	532	23	0	0.165	8
Rodriguez-3, 2011(11)	UK	European	RA	995	632	955	40	0	606	26	0	0.926	8
Rodriguez-4, 2011(11)	Norway	European	RA	945	1106	919	26	0	1059	47	0	0.073	8
Rodriguez-5, 2011(11)	Netherlands	European	RA	940	908	898	40	2	863	45	0	0.785	8
Rodriguez-6, 2011(11)	Germany	European	RA	188	285	183	5	0	273	12	0	0.384	8
Diaz-Gallo, 2011(12)	Spain	European	SSc	3422	3638	3268	154	0	3445	193	0	0.123	8
Orru-1, 2009(6)	Spain	European	SLE	881	1133	846	35	0	1056	77	0	0.008	8
Orru-2, 2009(6)	Italy	European	SLE	357	371	344	13	0	348	23	0	0.120	8
Orru-3, 2009(6)	Argentina	European	SLE	276	277	268	8	0	265	12	0	0.374	8
Orru-4, 2009(6)	USA	European	SLE	579	567	564	15	0	550	17	0	0.678	8

Table 2. Meta-analysis of the association between the PTPN22 R263Q (G788A) polymorphism and autoimmune diseases.

Polymorphism	Population	No. of studies	Numbers		Test of association			Test of heterogeneity		
			Case	Control	OR	95% CI	P-val	Model	p-val	I^2
PTPN22 R263Q (G788A) A vs. G	Overall	23	16,719	21,562	0.829	0.753-0.912	<0.001	F	0.140	24.5
	European	20	15,843	20,554	0.833	0.756-0.918	<0.001	F	0.361	7.64
	Latin American	3	876	1,008	0.418	0.078-2.234	0.308	R	0.021	74.1
	SLE	5	2,498	2,684	0.605	0.452-0.811	0.001	F	0.365	7.37
	RA	7	5,967	5,728	0.788	0.661-0.939	0.008	F	0.546	0
	CD	3	1,903	3,107	1.148	0.897-1.468	0.272	F	0.285	20.4
	UC	3	1,677	3,107	0.696	0.518-0.936	0.016	F	0.540	0
	SSc	1	3,422	3,638	0.845	0.682-1.047	0.123	NA	NA	NA
	GCA	1	623	1,729	0.963	0.671-1.382	0.838	NA	NA	NA
	HSP	1	329	515	0.644	0.350-1.186	0.158	NA	NA	NA
	Uveitis	1	217	718	0.972	0.541-1.747	0.925	NA	NA	NA
	GD	1	83	336	1.819	0.553-5.980	0.325	NA	NA	NA

F: Fixed effects model, R: Random effects model, p-val: p-value, NA: Not available, SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, CD: Crohn's disease, UC: ulcerative colitis, SSc: Systemic sclerosis, GCA: Giant cell arteritis, HSP: Henoch-Schonlein purpura, GD: Grave's disease.

= 1). Disease-specific meta-analysis was performed for SLE, RA, CD, and UC, and ethnicity-specific meta-analysis was performed for European and Latin American populations. The quality assessment score of each study ranged from 6 to 8. The selected characteristics of these studies on the association between the PTPN22 G788A polymorphism and autoimmune diseases are summarized in Table 1.

Meta-analysis of the functional PTPN22 G788A polymorphism in autoimmune disease

Meta-analysis was performed on all patients with autoimmune diseases and on patients in each ethnic group. Meta-analysis showed an association between the A allele of the functional PTPN22 G788A polymorphism and decreased risk of autoimmune diseases in all subjects (OR = 0.829, 95% CI = 0.753–0.912, $p < 0.001$) (Table 2, Figure 2). Analysis after stratification by ethnicity indicated that the PTPN22 788A allele was significantly associated with autoimmune diseases in Europeans (OR = 0.833, 95% CI = 0.756–0.918, $p < 0.001$), but not in Latin Americans (Table 2).

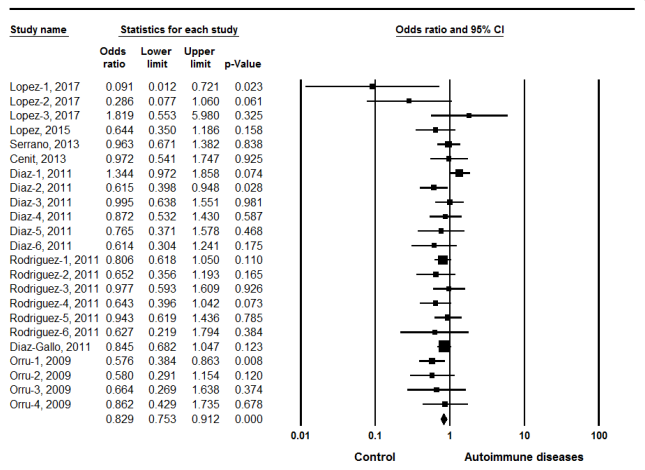

Figure 2. ORs and 95% CIs of individual studies and pooled data for the association of the PTPN22 788A allele and autoimmune diseases.

Meta-analysis of relations between the PTPN22 G788A polymorphism and autoimmune disease type

Meta-analysis by autoimmune disease type showed a significant negative association between the PTPN22 788A allele and SLE (OR = 0.605, 95% CI = 0.452–0.811, p = 001), RA (OR = 0.788, 95% CI = 0.661–0.939, $p = 0.008$), UC (OR = 0.696, 95% CI = 0.518–0.936, $p = 0.016$), but not CD and SSc (Table 2, Figure 3). A single study showed no association between the PTPN22 788A allele and GCA, HSP, uveitis, and GD (Table 2).

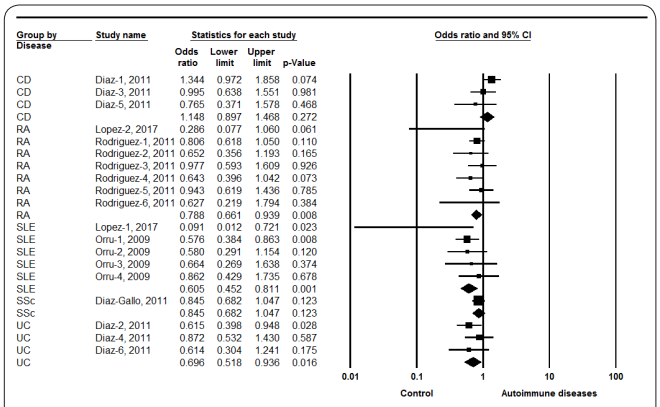

Figure 3. ORs and 95% CIs of individual studies and pooled data for the association of the PTPN22 788A allele and SLE, RA, CD, UC, and SSc.

Heterogeneity, sensitivity, and publication bias

The distribution of genotypes in normal control groups was consistent with HWE in all studies. Between-study heterogeneity was not found during the meta-analyses of the relation between the PTPN22 G788A polymorphism and autoimmune diseases, except for Latin Americans (Table 2). Sensitivity analysis showed that no individual study significantly affected the pooled OR, indicating statistically robust results from this meta-analysis. We pooled the data of different diseases from Lopez-Cano's study (7) and Diaz-Gallo's study (10), and then pooled the data from different original studies. The analyses did not significantly affect the pooled SMDs It was found to be difficult to correlate the funnel plot, which is usually used to detect publication bias because the number of studies included in the analysis was relatively small. Egger's regression test showed evidence of publication bias (Egger's regression test p-value < 0.1) and the funnel plot showed asymmetry. Therefore, the 'trim and fill' method was used to adjust for publication bias. However, after adjustment, significant ORs remained significant (Figure 4).

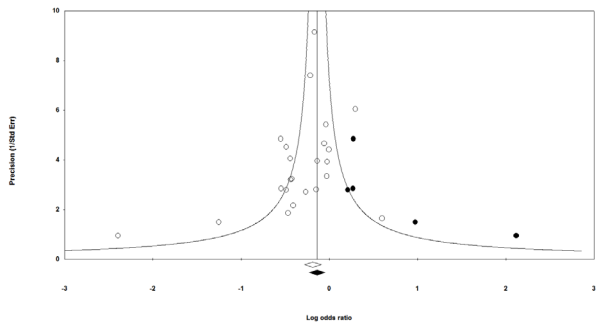

Figure 4. Funnel plot of studies that examined the association between the PTPN22 788A allele and autoimmune diseases (Egger's regression *p*-value = 0.060). The filled circles represent studies that showed publication bias. The diamonds at the bottom of the figure show summary effect estimates before (open) and after (filled) publication bias adjustment.

Discussion

Accumulating evidence suggests the presence of common genetic factors that predispose a person to autoimmunity (2). The PTPN22 gene has been considered as a potential common genetic factor shared for different autoimmune disorders because of its crucial role in T cell activation and its linkage to autoimmune diseases(16-18). We combined evidence on the association of the PTPN22 G788A polymorphism and susceptibility to autoimmune diseases. The results of this meta-analysis provide strong evidence of an association of the PTPN22 missense polymorphism with autoimmune diseases, including SLE, RA, and UC. The PTPN22 G788A polymorphism was associated with protection against SLE, RA, and UC. In contrast, our results suggested that this polymorphism was not associated with protection against or susceptibility to SSc, CD, GCA, HSP, uveitis, and GD.

The result of our study that the PTPN22 788A allele confers protection against SLE, RA, and UC is consistent with the functional effect of the PTPN22 G788A polymorphism (6). The PTPN22 788A allele was less efficient compared to the 788G allele (6) in reducing the phosphorylation of a mediator of TCR signaling downstream of LYP and inhibiting TCR-induced activation. The protective effect of the PTPN22 788A allele with SLE, RA, and UC may be explained by the less efficient reduction of TCR signaling, PTPase activity, and T-cell function. Our data support that the loss-of-function allele of the PTPN22 R263Q polymorphism may have a protective effect against autoimmunity and that Lyp, encoded by the *PTPN22* gene, is a major regulator of autoimmunity important in the negative control of activation and development of T-cells. The result that PTPN22 788A allele was a protective factor against SLE, RA and UC does not reply for Latin Americans, because the result came not from Latin American, but from all study subjects. The PTPN22 788A allele was significantly associated with autoimmune diseases in Europeans, but not in Latin Americans. The results of the ethnicity-based stratification analysis need further explanation. There were three comparison studies on SLE, RA, and GD in Latin Americans; a significant negative association between the PTPN22 788A allele and SLE, a trend of negative association between the PTPN22 788A allele and RA, but no association between the PTPN22 788A allele and GD. Thus no association between the PTPN22 788A allele and AD in Latin Americans may be not due to ethnicity, but different kinds of ADs.

Considering that the PTPN22 R620W polymorphism predisposes individuals to several autoimmune diseases, it is likely that the PTPN22 R263Q polymorphism is associated with decreased risk of multiple autoimmune diseases. We previously revealed that the functional PTPN22 R620W polymorphism is associated with increased risk of multiple autoimmune diseases, suggesting involvement of the humoral component in the association (19). In contrast, SLE and RA showed an opposite association with the PTPN22 G788A polymorphism in this meta-analysis. Reduced TCR signaling is considered to be a major factor in the development of autoimmunity (19). The bi-directional association of PTPN22 with autoimmunity has potentially important implications since inhibition of LYP activity, which would enhance TCR signaling, could help prevent or treat autoimmune diseases.

Our results do not support association between the PTPN22 G788A polymorphism and SSc, CD, GCA, HSP, uveitis, and GD. The lack of association between the PTPN22 G788A polymorphism and these disorders suggests that the *PTPN22*-associated diseases share a common underlying mechanism that may not be important in the pathogenesis of all autoimmune diseases. However, we could not rule out the possibility that autoimmune diseases not associated with the PTPN22 G788A polymorphism could be due to a lack of power to detect a true association. Although the pooled OR showed a protective trend in the meta-analysis for the PTPN22 788A variant and SSc, the PTPN22 G788A polymorphism was not associated with SSc, in contrast to the R620W polymorphism that was associated with increased risk for SSc (19). The PTPN22 788A loss-of-function variant is a protective factor for UC, with no association with CD, supporting the idea that UC and CD differ in some genetic risk factors and the involvement of different immunological mechanisms.

The present study has some limitations that require consideration. First, heterogeneity, confounding factors, and publication bias may have distorted the analysis. In particular, publication bias could have affected our findings because studies that produced negative results may not have been published or may have been missed. Second, our ethnicity-specific meta-analysis included data from European and Latin American patients and, thus, our results are applicable only to these ethnic groups. Further studies are required in different ethnic populations. Third, the PTPN22 polymorphism may be associated with specific clinical manifestations in addition to disease susceptibility. We did not stratify and analyze many factors, such as sex or clinical and environmental variables because of a lack of data. Fourth, several diseases, such as SSc, GCA, HSP, uveitis, and GD, were not fully analyzed in the present meta-analysis study since they were represented by only 1 study each. While the number of studies included in these analyses was small, so the statistically insignificant results may result from the limited test power. Hence, such negative results were not conclusive. Thus, additional studies are required warranted to explore the associations between these autoimmune diseases and the PTPN22 polymorphism. Fifth, the meta-analysis is not just pooling studies and its results should be interpreted carefully, rigorously and comprehensively. Lopez-Cano-1, 2017 (7) and Orru-3, 2009 (6) found contrary results about SLE. Lopez-Cano-2, 2017 (7) and Lopez-Cano-3, 2017 (7) found negative results about RA and GD, respectively. No studies in Latin Americans about UC has been included. By this token, the meta-analysis results about RA and UC only apply for Europeans, while the conclusions were not limited to ethnicity.

In conclusion, this meta-analysis demonstrates that the PTPN22 G788A polymorphism confers protection against SLE, RA, and UC and suggests that the PTPN22 788A allele may have no or only a negligible effect on SSc, CD, GCA, HSP, uveitis, and GD. The former result also suggests that the PTPN22 G788A polymorphism may modulate the development of multiple autoimmune diseases. This meta-analysis provides further evidence that the PTPN22 gene plays a significant role in the etiology of a subgroup of autoimmune diseases and common autoimmune susceptibility alleles may be not shared among all autoimmune diseases but rather among subgroups of these conditions. Further studies are required to clarify the role of the PTPN22 gene in autoimmune pathogenesis.

Funding

This study was supported in part by NRF-2017M3A9B4050335, Republic of Korea.

Declaration of Conflicting Interests

The authors have no financial or non-financial conflict of interest to declare.

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