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META-ANALYSIS

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Association Between Protein Tyrosine Phosphatase Non-Receptor Type 22 (*PTPN22*) Polymorphisms and Risk of Ankylosing Spondylitis: A Meta-analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AG Xiantao Meng
AG Weiming Wang
BC Yupeng Liu
CD Xiaojun Ma
DE Qian Zhang
EF Chunhui Li
CF Chenye Li
BD Liubao Ren

Department of Sports Medicine, Affiliated Zhongshan Hospital of Dalian University, Dalian, Liaoning, P.R. China

Corresponding Author: Weiming Wang, e-mail: xiaojduhfds@yeah.net
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Background: Ankylosing spondylitis (AS) is a chronic autoimmune disease that involves the imbalance of peripheral tolerance possibly caused by the negative signal of activated T cells. The polymorphisms in the human protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) gene have been pointed out to be related to the pathogenesis of AS, but conclusions over this issue remain contradictory. We attempted to give a more precise conclusion about the effects of *PTPN22* polymorphisms on AS risk by means of a meta-analysis.

Material/Methods: PubMed, Embase, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) were searched for relevant studies published in the English or Chinese language. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated with a fixed- or random-effects model to evaluate the correlation between *PTPN22* rs2488457, rs1217414, and rs2476601 polymorphisms and AS susceptibility. Sensitivity analysis was also carried out to detect the stability of the results.

Results: The present meta-analysis showed a positive correlation of both *PTPN22* rs2488457 and rs1217414 polymorphisms with AS risk under CC *vs.* GG, CC + GC *vs.* GG, CC *vs.* GC + GG, allele C *vs.* allele G (OR=1.39, 95% CI=1.04–1.85, *P*=0.646; OR=1.29, 95% CI=1.03–1.62, *P*=0.426; OR=1.26, 95% CI=1.02–1.56, *P*=0.971; OR=1.20, 95% CI=1.05–1.38, *P*=0.571), and TT *vs.* CC and TT *vs.* CT + CC models (OR=3.83, 95% CI=1.11–13.24, *P*=0.196; OR=3.83, 95% CI=1.09–13.42, *P*=0.244), respectively.

Conclusions: *PTPN22* rs2488457 and rs1217414 polymorphisms may be risk factors for AS occurrence.

MeSH Keywords: Polymorphism, Genetic • Risk • Spondylitis

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Background

Ankylosing spondylitis (AS) is a chronic autoimmune disease with inflammation in sacroiliac joints or the spine, and can lead to inflammatory back pain as well as limited motion range in both young and middle-aged men [1]. Two central features of AS are inflammation and formation of new bone in the spine, which can result in persistently forming new cartilage and capillaries and eventually can cause joint stiffness [2]. About 0.2% of the world population suffers from AS, and its incidence rate in Chinese, Caucasians, and Europeans is 0.2–0.54%, 0.86%, and 0.1–1.4%, respectively [1,3,4]. In addition, men are more susceptible to AS than women [5]. Although the exact mechanism underlying AS occurrence remains poorly understood, studies have pointed out that complex interactions between hereditary components, environmental factors, age, gender, and ethnicity play an important role in AS etiology. Additionally, familial clustering of AS can provide fine evidence for the significant impact of genetic factors on the etiology of the disease [6]. Among others, human leukocyte antigen (*HLA*) genes and the interleukin-1 (*IL-1*) family gene cluster have both been demonstrated to be closely correlated with AS [7–10], and they all can regulate the expression of immunomodulatory factors and cytokines [11,12]. However, these confirmed factors cannot explain all AS cases, indicating the possibility that there are other potential elements involved in the occurrence of the disease.

The human protein tyrosine phosphatase non-receptor 22 (*PTPN22*) gene located on chromosome 1p13 encodes a lymphoid tyrosine phosphatase (LYP) protein that belongs to the protein tyrosine kinases (PTKs) family [13,14]. The LYP protein is expressed in T cells and can complete the dephosphorylation of ZAP-70 and Src kinases as well as further inhibition of T-cell receptor (TCR) signaling [14–16]. Studies show that the number of circulating $CD4^+$ and $CD8^+$ T cells is higher in AS patients than in healthy persons [17,18]. Besides, TCR signal transduction of regulatory T cells can be suppressed by increased *PTPN22* activity, which may weaken T cell regulation function and further lead to the occurrence of autoimmune diseases [19]. Single nucleotide polymorphisms (SNPs) in the *PTPN22* gene have been proposed to be implicated in AS susceptibility through affecting the transcription and expression of *PTPN22*.

Previous studies have investigated the effects of *PTPN22* rs2488457, rs1217414, and rs2476601 polymorphisms on AS risk, but they have yielded conflicting results. Therefore, we performed this meta-analysis with the purpose of providing more definitive conclusions about this topic.

Material and Methods

Literature search

A comprehensive search strategy was carried out in the electronic databases of PubMed, Medline, Web of Science, Embase, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) using terms "protein tyrosine phosphatase, non-receptor type 22" or "*PTPN22,*" "ankylosing spondylitis" or "AS," and "polymorphism" or "variation" or "mutation" or "SNP." A hand search of the reference lists of the relevant articles was performed for additional eligible studies. When the same study population was included in multiple publications, only the most complete and recent study was selected.

Selection criteria

The following criteria were used for study inclusion: (1) case-control studies evaluating the relationship between *PTPN22* rs2488457, rs1217414, and/or rs2476601 polymorphism(s) and AS susceptibility; (2) with available data for estimating odds ratios (ORs) and 95% confidence intervals (95% CIs); (3) published in the English or Chinese language; and (4) studies on humans. Studies with any one of the following characteristics were excluded: (1) no control population; (2) duplicate of previous articles; (3) insufficient information; and (4) abstracts, letters, or review articles.

Data extraction

The following information was independently collected from the included studies by two authors: first author's name, publication year, country of origin, ethnicity, control source, method of genotyping, total number of cases and controls, frequency of genotypes and alleles, and *P* value of Hardy-Weinberg Equilibrium (HWE) in controls. Discrepancies were resolved through discussion until a final consensus was reached.

Statistical analysis

The strength of associations between *PTPN22* rs2488457, rs1217414, and rs2476601 polymorphisms and AS risk was assessed with crude ORs and 95% CIs. The Z test was used to determine the significance of the summary ORs. The chi-square test was used to examine whether the genotype distribution in the control group was in accordance with HWE expectancy. The chi-square-based Q-statistical test was adopted for assessing between-study heterogeneity. A *P* value smaller than 0.05 in the Q test indicated the existence of significant heterogeneity, and pooled ORs were calculated with a random-effects model; otherwise, a fixed-effects model was applied. The stability of the final results was assessed with sensitivity analysis through deleting each included study in turn to observe

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alteration in the results as a whole. Publication bias across included studies was evaluated with Begg's funnel plots and Egger's linear regression test. All analyses were done utilizing STATA software (v. 12.0). *P*<0.05 was considered as the representative of statistical significance in all tests.

Results

Study characteristics

Figure 1 details the study selection process. Specifically, 87 reports were identified through database searching and from other sources. Then, 81 studies were removed because they were duplicates (n=1), were comments or letters (n=7), had irrelevant content (n=68), or presented unoriginal data (n=5). Consequently, a total of 1411 cases and 4167 controls were incorporated into the present meta-analysis [19–24]. Major information on the incorporated studies is listed in Table 1.

Meta-analysis results

Correlations between *PTPN22* rs2488457, rs1217414, and rs2476601 polymorphisms and AS susceptibility are shown in Table 2. Among the three single nucleotide polymorphisms (SNPs), rs2488457 increased the risk of AS under CC *vs.* GG (Figure 2), CC + GC *vs.* GG, CC *vs.* GC + GG, and allele C *vs.* allele G models (OR=1.39, 95% CI=1.04–1.85, *P*=0.646; OR=1.29, 95% CI=1.03–1.62, *P*=0.426; OR=1.26, 95% CI=1.02–1.56, *P*=0.971; OR=1.20, 95% CI=1.05–1.38, *P*=0.571); and a similar relationship was also shown for the rs1217414 polymorphism under TT vs. CC (Figure 2) and TT *vs.* CT + CC contrasts (OR=3.83, 95% CI=1.11–13.24, *P*=0.196; OR=3.83, 95% CI=1.09–13.42,

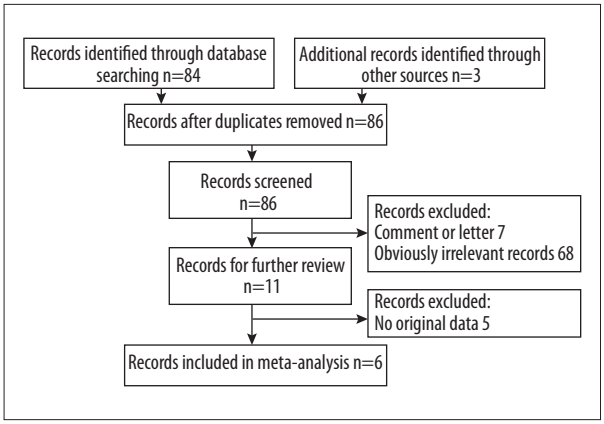

Figure 1. Flowchart of study selection.

Table 1. Principal characteristics of all included studies in the present meta-analysis.

Locus		rs2488457		rs1217414		rs2476601		
First author		Huang	Zhang	Meng	Tang	Orozco	Li	Tang
Year		2014	2014	2015	2014	2006	2010	2014
Region		Taiwan	China	China	China	Spain	China	China
Ethnicity		Asian	Asian	Asian	Asian	Caucasian	Asian	Asian
Case	Sample size	391	302	120	180	197	131	90
	11	138	41	84	170	166	131	90
	12	194	141	24	10	28	0	0
	22	59	120	12	0	3	0	0
Control	Sample size	391	2010	100	359	551	576	180
	11	169	310	81	284	462	576	180
	12	174	1009	17	74	84	0	0
	22	48	691	2	1	5	0	0
Control source		HB	PB	HB	PB	PB	PB	PB
Genotyping method		PCR-RFLP	Real-time PCR	PCR-RFLP	PCR-RFLP	TaqManSNP	AS-PCR	PCR-RFLP
PHWE		0.756	0.063	0.340	0.092	0.588	/	/

11 – wild homozygote; 12 – heterozygote; 22 – variant homozygote; PCR – polymerase chain reaction; PCR-RFLP – PCR-restriction fragment length polymorphism; AS-PCR – allele-specific PCR; HB – hospital based; PB – population based; P_{HWE} – *P* value for Hardy-Weinberg Equilibrium test.

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Table 2. *PTPN22* polymorphisms and AS risk.

SNP	Analysis	22 *vs.* 11	22 + 12 *vs.* 11	22 *vs.* 11+12	2 *vs.* 1	12 *vs.* 11
rs2488457						
	OR (95% CI)	1.39 (1.04, 1.85)	1.29 (1.03, 1.62)	1.26 (1.02, 1.56)	1.20 (1.05, 1.38)	1.23 (0.97, 1.56)
	Ph	0.646	0.426	0.971	0.571	0.294
rs1217414						
	OR (95% CI)	3.83 (1.11, 13.24)	0.64 (0.08, 5.14)	3.83 (1.09, 13.42)	0.72 (0.08, 6.27)	0.55 (0.09, 3.28)
	Ph	0.196	0.000	0.244	0.000	0.000
rs2476601						
	OR (95% CI)	1.67 (0.39, 7.06)	0.97 (0.62, 1.51)	1.69 (0.40, 7.13)	1.01 (0.67, 1.53)	0.93 (0.58, 1.47)
	Ph	/	/	/	/	/

Ph – *P* value of heterogeneity; 11 – wild homozygote; 12 – heterozygote; 22 – rare homozygote; 1 – major allele; 2 – rare allele.

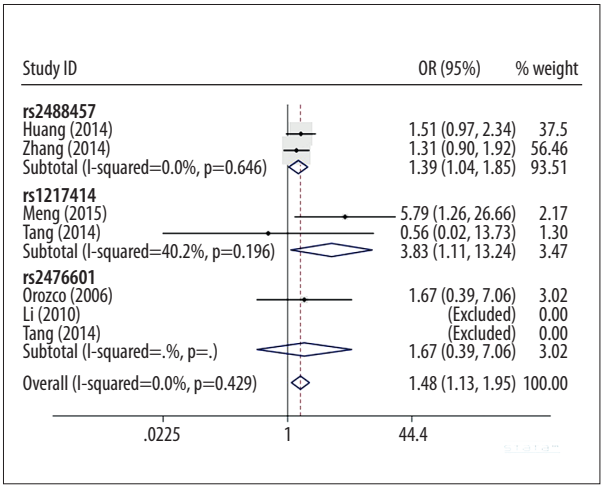

Figure 2. Forest plot for the association between *PTPN22* polymorphisms and risk of AS under rare homozygote *vs.* wild homozygote.

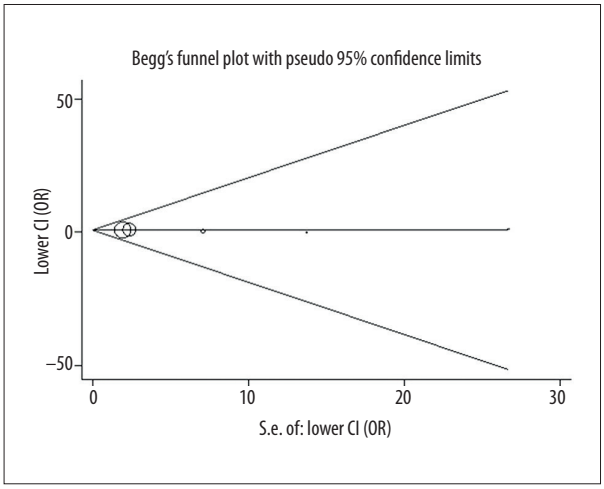

Figure 3. Begg's funnel plot of publication bias.

P=0.244). However, no significant relationship was observed between the rs2476601 polymorphism and AS susceptibility.

As shown in Table 2, there was no significant heterogeneity for the *PTPN22* rs2488457 polymorphism, and only one included study on the rs2476601 successfully underwent association analysis, so the fixed-effects model was adopted to calculate pooled ORs for these two polymorphisms. As for the *PTPN22* rs1217414 polymorphism, the presence or absence of significant heterogeneity varied under different genetic models; therefore, which model would be chosen for calculating ORs was determined according to the standard described above.

Sensitivity analysis

The effect of individual studies on pooled ORs and 95% CIs was evaluated by excluding one single study each time. The pooled results were not apparently changed during the omission of any single study, which indicated that the meta-analysis results were reliable and statistically robust.

Publication bias

Begg's funnel plots and Egger's test were applied to evaluate the publication bias. The funnel plots showed symmetrical shapes (Figure 3), and statistical data were detected by Egger's test as well (*P*=0.268). Therefore, publication bias between the included studies was not significant.

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Discussion

As a common inflammatory disorder, AS can lead to asymmetrical peripheral oligoarthritis, enthesitis, specific organ attacks associated with psoriasis, acute anterior uveitis (AAU), and chronic inflammatory bowel disease, even complete fusion and rigidity of the spine [1,25]. Generally, AS occurs in people aged from 25 to 45 years [1,26], thus producing a heavy sociological burden and health care cost. Therefore, it is an urgent task to deeply understand AS pathology so as to explore effective treatment methods [27]. The concordance rate of developing AS for monozygotic twins is more than 90% [4], showing an important role of hereditary factors in the disease. In addition, the regulation of T cell response has also been demonstrated to be a critical point in AS pathogenesis [28]. Since the LYP protein encoded by the *PTPN22* gene acts as a negative regulator of activation of T cells [15], the *PTPN22* gene has been suggested to be a candidate gene for autoimmune diseases including type 1 diabetes (T1D), systematic lupus erythematous (SLE), rheumatoid arthritis (RA), giant cell arteritis (GCA), Graves' disease, and AS [21,29–34]. Three SNPs of rs2488457, rs1217414, and rs2476601 in the *PTPN22* gene have been discussed in regard to their relationship with AS susceptibility, but inconsistent conclusions have been drawn.

Huang et al. evaluated the impact of the *PTPN22* rs2488457 polymorphism on AS occurrence, and found that carriers of CC and GC genotypes of the SNP had a higher AS occurrence risk than those with the GG genotype [20]. Zhang et al. revealed that the SNP was not significantly different between acute anterior uveitis $(AAU)^+$ AS^+ patients and controls, though they observed impaired cell proliferation and decreased *PTPN22* expression in CC genotype carriers compared with GG genotype carriers [23]. For the association of the *PTPN22* rs1217414 polymorphism with AS susceptibility, Meng et al. suggested that the T allele of the polymorphism possibly was a risk factor for AS [19], but Tang et al. reached a contradictory conclusion that the T allele might be a protective marker against AS occurrence [22]. For the third SNP rs2476601 in the *PTPN22* gene, Orozco et al. found no apparent differences in genotypic or allelic frequencies between cases and controls [21]. However, in two other studies by Tang et al. and Li et al., respectively, the variant allele was not detected either in cases or in controls, so the linkage analysis was not performed [22,24].

The above discordant results may be due to several factors. Firstly, an SNP may have different distribution in people of different ethnic lines. Secondly, the study preciseness may be weakened by a small sample size. Thirdly, other potentially relevant factors such as age and gender that may affect AS risk were not adjusted in all these studies.

To statistically combine these inconsistent findings, we performed this meta-analysis containing 1411 cases and 4167 controls, and observed a risk-increasing effect of *PTPN22* rs2488457 and rs1217414 polymorphisms on AS occurrence under CC *vs.* GG, CC + GC *vs.* GG, CC *vs.* GC + GG, and allele C *vs.* allele G, and TT *vs.* CC and TT *vs.* CT + CC comparisons, respectively. However, the rs2476601 polymorphism neither increased nor decreased the risk of AS under any genetic contrast in our study.

Inclusion of a larger number of cases and controls was one of the advantages in the present meta-analysis compared with the above mentioned studies. Nevertheless, some limitations in our study still should be acknowledged. First of all, only articles published in English and Chinese were included, which might lead to some possible publication bias not revealed even with Begg's funnel plot or Egger's test. Also, the number of included studies was relatively small, thus probably affecting the authoritativeness of our results. Last but not least, potential influences of interfering factors such as age, gender, and other pathological aspects were not incorporated into the present meta-analysis.

Conclusions

All in all, the present meta-analysis suggested that *PTPN22* rs2488457 and rs1217414 polymorphisms may contribute to increase AS risk. Due to the above limitations, more studies are needed to verify our finding in different populations.

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