Meta-Analysis of the Genetic Association between *PTPN22* and *CTLA-4* Variants and Risk of Uveitis

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Keywords

Uveitis · *PTPN22* · *CTLA-4* · Polymorphism · Meta-analysis

Abstract

Background: Though the risk of protein tyrosine phosphatase nonreceptor 22 (*PTPN22*) and cytotoxic T-lymphocyte antigen-4 (*CTLA-4*) genetic variants with uveitis have been developed, the combined results still remain uncertain and controversial. **Objectives:** The aim of this study was to perform a meta-analysis to estimate the precise association of *PTPN22* (rs2488457 and rs2476601) and *CTLA-4* (rs231775, rs5742909, rs4553808, and rs3087243) polymorphisms with uveitis susceptibility. **Method:** Five electronic databases (PubMed, Embase, Web of Science, China Biomedical Database, and China National Knowledge Infrastructure) were systematically searched for relevant literature up to July 20, 2021. All statistical analyses were evaluated by Stata 12.0 software and R programming language. **Results:** Our meta-results indicated that *PTPN22* rs2488457 conferred positive susceptibility to uveitis (odds ratio [OR] = 1.18, 95% confidence interval [CI] = 1.02–1.38, $p = 0.029$). In stratified analysis by ethnicity, the rs2488457 C allele had a growing tendency toward uveitis in the Asian region (OR = 1.21, 95%

CI = 1.00–1.45, $p = 0.046$). For *CTLA-4* rs231775, subgroup analysis based on ethnicity manifested a negative association among uveitis individuals in the Africa region (OR = 0.25, 95% CI = 0.19–0.33, $p < 0.001$). For *CTLA-4* rs4553808, subgroup analysis by the disease type revealed that the GG genotype was associated with an elevated risk of Behcet's disease (BD) (OR = 3.22, 95% CI = 1.05–9.90, $p = 0.042$). **Conclusions:** Our research revealed that *PTPN22* rs2488457 conferred strong susceptibility to uveitis in general, especially in the Asian region. *CTLA-4* rs231775 conveyed protection against uveitis in African populations, and *CTLA-4* rs4553808 displayed an increased risk of BD.

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Introduction

Uveitis, or inflammation of the uvea, is becoming a leading cause of visual loss. Uveitis can be clinically recognized with distinct phenotypes. Behcet's disease (BD) and Vogt-Koyanagi-Harada (VKH) syndrome have represented the most two common type of multisystem immune-mediated or inflammation-related uveitis [1, 2]. Although the pathophysiology of these phenotypes re-

mains to be elucidated, they are always characterized by immune hyperreactivity, mainly affecting elements of the immune system [3]. It is generally acknowledged that environmental and genetic factors are important components of the etiologies of BD, VKH syndrome, and other types of uveitis [4, 5]. Moreover, there is evidence of a strong association of the HLA allele with BD or VKH syndrome [6, 7]. However, mutations in HLA regions do not account for all uveitis individuals, indicating that non-HLA susceptibility genes also confer a genetic predisposition to these disorders.

A number of studies have revealed that an autoimmune response, in particular cellular immunity against T lymphocytes and tyrosinase family proteins, acts a pivotal part in the initiation and maintenance of uveitis [8–10]. Lymphoid tyrosine phosphatase (LYP) is a member of the protein tyrosine kinases family and expressed in T cells [11]. The LYP protein is encoded by the human protein tyrosine phosphatase nonreceptor 22 (*PTPN22*) gene on chromosome 1p13 [11], which plays a negative regulatory role in the T-cell signaling pathway. Dysfunction of *PTPN22* (i.e., increased activity) suppressed the T-cell receptor (TCR) signal transduction of regulatory T cells, thus weakening the regulation function of T cells and leading to autoimmune diseases [12]. Many functional mutations have been described and conferred either altered susceptibility to autoimmune diseases or appeared to influence the severity and clinical outcomes [13]. The most widely surveyed single-nucleotide polymorphisms (SNPs) of the *PTPN22* gene associated with uveitis were 1123G/C (rs2488457) and R620W (rs2476601).

Research has demonstrated that T-cell activation requires costimulatory signals involving CD28 and CD40 with B7-1 (CD80) and B7-2 (CD86) on antigen-presenting cells [14]. Cytotoxic T-lymphocyte antigen-4 (*CTLA-4*), a homolog of CD28, binds to CD80 and CD86 to negatively regulate T-cell activation [15]. Until now, the most shared SNPs of the *CTLA-4* gene reported in association with uveitis included 49A/G (rs231775), 318C/T (rs5742909), 1661A/G (rs4553808), and CT60G/A (rs3087243).

PTPN22 and *CTLA-4* genes, as susceptibility candidate locus involvement in inflammatory or immune-mediated disorders, have been commonly explored during the past decades. Quite a few meta-analyses of *CTLA-4* gene polymorphisms with BD risk have been performed [16, 17]; however, these research studies only focused on two SNPs (*CTLA-4* rs231775 and rs5742909). Several studies have shed light on the correlation of three SNPs (*CTLA-4* rs4553808, rs3087243, and *PTPN22* rs2476601) with uveitis [18, 19]. Although the relationships between

PTPN22 and *CTLA-4* genetic variants with uveitis have been comprehensively reported, the combined results are controversial and ambiguous. Another weakness in previous published articles is attributed to their relatively small sample size and few ethnic origins, suggesting insufficient power and inadequate evidences. To better clarify the genetic basis for the relationship between *PTPN22* (rs2488457 and rs2476601) and *CTLA-4* (rs231775, rs5742909, rs4553808, and rs3087243) toward the risk of uveitis in different races, a meta-analysis has been performed.

Materials and Methods

This current meta-analysis was conducted and reported in accordance with the PRISMA guidelines [20] (see online suppl. Table 1; see www.karger.com/doi/10.1159/000521301 for all online suppl. material).

Search Strategy

A literature search of five common electronic databases (PubMed, Embase, Web of Science, China Biomedical Database, and China National Knowledge Infrastructure) was conducted to identify relevant studies published from the inception to July 20, 2021. Reference lists in the retrieved studies were also manually screened. Searches were retrieved using the following combined terms “uveitis,” “*PTPN22*,” “*CTLA-4*,” and “polymorphism” (see online suppl. Table 2). Two researchers (J.Z. and P.Z.) reviewed reports and dismissed irrelevant studies. Once uncertain conclusion arose, it would be solved by discussion with the third author.

Criteria for Identification

The inclusion criteria for an article were as follows: (1) it focused on the association between *PTPN22* and *CTLA-4* genetic polymorphisms and uveitis; (2) sufficient data of the alleles and genotypes in the comparison of case-control group; and (3) it focused on human subjects. The exclusion criteria were (1) not a case-control study; (2) genotype or allele frequency could not be extracted; (3) duplicates of previous publications; and (4) meta-analyses, letters, animal studies, reviews, and editorial articles. Only the study with the largest sample size or the most recent publication was enrolled, when the authors published several studies including the same subjects.

Quality Assessment

The quality evaluation of extracted studies was also reviewed by 2 authors (J.Z. and P.Z.) using the Newcastle-Ottawa scale [21]. In the case-control study, three items to assess potential bias in gene-disease associations were included: selection of cases and controls, comparability of cases and controls, and ascertainment of exposure. In the quality evaluation, each item was awarded a different number of stars: selection of cases and controls = 4 stars, comparability of cases and controls = 2 stars, and ascertainment of exposure = 3 stars. A study with more than 6 stars was regarded as high quality, and the one with 9 stars was regarded as the highest quality. Disagreements were resolved by discussion with a third reviewer (S.H.).

Fig. 1. Flow diagram of literature search and screening in current meta-analysis.

Data Extraction

Two reviewers (J.Z. and P.Z.) independently retrieved articles and extracted data from the eligible studies. The following information was collected from each record: the name of the first author, year of publication, country and ethnicity of the sample, characteristics and number of cases and controls, genotyping method, and the frequency of alleles and genotypes in cases and controls. To explore the differences between *PTPN22* and *CTLA-4* genetic susceptibility and various uveitis subtypes, we divided uveitis into a BD subtype and other types of uveitis. In the event of disagreement, 2 reviewers should examine the collected data and reached a consensus following a rigorous screening process. If consensus was not met, a third reviewer (S.H.) was asked to resolve the dispute in depth.

Statistical Analysis

Cochran's Q statistic was used to assess heterogeneity with a p value less than 0.1, indicating statistical significance. Quantitative I^2 was calculated to estimate inconsistency in the meta-analysis and represented the percentage of observed variability due to heterogeneity rather than chance (no heterogeneity, $I^2 = 0$ –25%; moderate heterogeneity, $I^2 = 25$ –50%; large heterogeneity, $I^2 > 50\%$) [22]. In case of no heterogeneity, a fixed-effects model was used for the meta-analysis; otherwise, a random-effects model was used. The odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and pooled ORs for each SNP were obtained from the meta-analysis using comparability analysis. The Hardy-Weinberg equilibrium (HWE) in controls was achieved by using a χ^2 test, and p value less than 0.05 suggested obvious deviation. A leave-one-out sensitivity analysis was conducted to explore the effect of each study on the pooled ORs. A funnel plot of publication

bias was evaluated by using Begg's funnel plots [23] and Egger's linear regression test [24]. Subgroup analysis was performed based on ethnicity and the disease subtype. Meta-regression by the restricted maximum likelihood approach was utilized to determine the potential source of heterogeneity in all populations. A p value of <0.05 was considered statistically significant in a two-tailed T test. The software Stata 12.0 (StataCorp LP, TX, USA) and R programming language were used for comprehensive meta-analyses. All results were checked separately by 2 reviewers (J.Z. and P.Z.).

Results

Literature Search

A detailed selection process for eligible studies was illustrated in Figure 1. A total of 143 articles were identified in the above electronic databases. Of these, 116 articles were excluded because 102 were duplicates, and 14 did not investigate the relationship between *PTPN22* and *CTLA-4* polymorphisms and the risk of uveitis. The remaining 27 records were eligible for inclusion in the study. Among these studies, one had depicted other *PTPN22* polymorphisms with VKH disease, and another six did not contain enough genotypic data. Finally, 20 published records with 5,320 cases and 8,839 controls were included in our meta-analysis [13, 16, 25–42].

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

Refs	Country	Ethnicity	Disease	Case	Control										Genotype method	HWE <i>p</i> value	Quality
PTPN22																	
rs2488457	China	Asian	BD	CC	CG	GG	C	G	CC	CG	GG	C	G	PCR-RFLP	0.0003	9	
	Spain	Caucasian	BD	191	250	75	632	400	227	376	87	830	550	TaqMan	0.58	9	
	China	Asian	VKH	185	88	5	458	98	998	460	58	2,456	576	PCR-RFLP	0.06	9	
	China	Asian	AS+AAU	102	454	449	658	1,352	691	1,009	310	2,391	1,629	PCR-RFLP	0.06	9	
rs2476601	China	Asian	AS+AAU	41	141	120	223	381	691	1,009	310	2,391	1,629	PCR-RFLP	0.06	9	
	Turkey	Middle East	BD	GG	GA	AA	G	A	GG	GA	AA	G	A	PCR-RFLP	0.73	8	
	Spain	Caucasian	BD	134	0	0	268	0	168	9	0	345	9	TaqMan	0.07	7	
	Spain	Caucasian	AAU	346	54	0	746	54	1,323	190	2	2,836	194	PCR-RFLP	0.89	7	
rs2311775	Spain	Caucasian	AAU	123	14	2	260	18	75	16	1	166	18	TaqMan	0.66	6	
	Spain	Caucasian	ENAU	186	28	1	400	30	628	89	4	1,345	97	PCR-RFLP	NA	8	
	UK	Caucasian	BD	NA	NA	NA	250	10	NA	NA	NA	308	30	PCR-RFLP	NA	7	
	Jordan	Middle East	BD	NA	NA	NA	275	5	NA	NA	NA	130	0	PCR-RFLP	NA	7	
CTLA-4																	
rs2311775	Turkey	Middle East	BD	GG	GA	AA	A	A	GG	GA	AA	G	A	PCR-RFLP	0.40	9	
	Korea	Asian	BD	5	59	26	69	177	19	71	89	109	249	PCR-RFLP	0.98	9	
	Tunisia	African	BD	144	115	30	403	167	140	121	26	401	173	PCR-RFLP	0.20	9	
	Turkey	Middle East	BD	4	25	30	33	85	7	49	43	63	135	PCR-RFLP	0.16	9	
rs5742909	Turkey	Middle East	BD	23	83	111	129	305	9	69	76	87	221	PCR-RFLP	0.19	8	
	China	Asian	BD	96	112	20	304	152	83	97	26	263	149	PCR-RFLP	0.78	8	
	Egypt	African	BD	8	21	31	37	83	36	38	21	110	80	PCR-RFLP	0.08	7	
	Germany	Caucasian	Fuchs	8	18	18	34	54	27	66	46	120	158	PCR-RFLP	0.70	9	
rs5742909	America	Caucasian	AAU	27	64	49	118	162	13	41	38	67	117	PCR-RFLP	0.72	9	
	Korea	Asian	SpA+U	5	5	1	15	7	49	27	8	125	43	PCR-RFLP	0.15	9	
	Spain	Caucasian	NAU	35	175	201	245	577	131	593	791	855	2,175	TaqMan	0.19	9	
	China	Asian	VKH	102	94	12	298	118	95	129	30	319	189	PCR-RFLP	0.17	9	
rs5742909	UK	Caucasian	BD	NA	NA	NA	50	72	NA	NA	NA	93	165	PCR-RFLP	NA	8	
	Jordan	Middle East	BD	NA	NA	NA	112	238	NA	NA	NA	30	72	PCR-RFLP	NA	8	
	Turkey	Middle East	BD	TT	TC	CC	T	C	TT	TC	CC	T	C	PCR-RFLP	0.45	9	
	Korea	Asian	BD	0	15	108	15	231	0	19	160	19	339	PCR-RFLP	0.02	9	
rs5742909	China	Asian	BD	3	69	213	75	495	2	87	198	91	483	PCR-RFLP	0.44	8	
	Germany	Caucasian	Fuchs	2	58	166	62	390	3	54	149	60	352	PCR-RFLP	0.31	8	
	America	Caucasian	AAU	0	16	28	16	72	0	22	117	22	256	PCR-RFLP	0.62	9	
	Korea	Asian	SpA+U	2	15	123	19	261	0	9	83	9	175	PCR-RFLP	0.01	9	
rs5742909	Spain	Caucasian	NAU	0	1	10	1	21	4	14	66	22	146	PCR-RFLP	0.49	6	
	China	Asian	VKH	8	63	331	79	725	18	271	1,226	307	2,723	TaqMan	0.64	9	
	UK	Caucasian	BD	2	45	162	49	369	6	60	189	72	438	PCR-RFLP	NA	8	
	Jordan	Middle East	BD	NA	NA	NA	15	107	NA	NA	NA	21	237	PCR-RFLP	NA	8	
rs4553808	Korea	Asian	BD	GG	GA	AA	G	A	GG	GA	AA	G	A	PCR-RFLP	0.08	9	
	China	Asian	BD	10	76	199	96	474	2	76	209	80	494	PCR-RFLP	0.23	8	
	China	Asian	VKH	3	58	165	64	388	2	54	149	58	352	PCR-RFLP	0.19	9	
	China	Asian	VKH	2	47	159	51	365	2	63	189	67	441	PCR-RFLP	0.75	8	
rs3087243	China	Asian	BD	AA	AG	GG	A	G	AA	GG	AA	G	A	PCR-RFLP	0.47	6	
	America	Caucasian	BD	9	81	138	99	357	11	70	126	92	322	PCR-RFLP	0.81	9	
	Touma et al. [32]	Caucasian	BD	8	26	8	42	42	10	23	20	43	63	NA	0.75	8	
	Du et al. [31]	Asian	VKH	2	72	135	76	342	15	91	150	121	391	PCR-RFLP	0.81	9	
BD, Behcet's disease; VKH, Vogt-Koyanagi-Harada; AS+AAU, acute anterior uveitis associated with ankylosing spondylitis; AAU, acute anterior uveitis; ENAU, endogenous nonanterior uveitis; SpA+U, spondyloarthritis; VKH, NAU, nonanterior uveitis; NA, not available; HWE, Hardy-Weinberg Equilibrium.																	

BD, Behcet's disease; VKH, Vogt-Koyanagi-Harada; AS+AAU, acute anterior uveitis associated with ankylosing spondylitis; ENAU, endogenous nonanterior uveitis; SpA+U, spondyloarthropathies uveitis; NAU, nonanterior uveitis; NA, not available; HWE, Hardy-Weinberg Equilibrium.

Table 2. Heterogeneity statistics and publication bias analysis

SNP	Polymorphism	No.	Test of heterogeneity			Publication bias	
			I^2 , %	p value	model	Begg's test	Egger's test
PTPN22							
rs2488457	C versus G (allele)	4	70.1	0.018	R	0.734	0.176
	CC versus GG (homozygote)	4	72.5	0.012	R	1.000	0.808
	CG versus GG (heterozygote)	4	66.6	0.029	R	1.000	0.871
	CC+CG versus GG (dominant)	4	73.0	0.011	R	1.000	0.975
	CC versus CG+GG (recessive)	4	61.4	0.051	R	0.308	0.033
rs2476601	G versus A (allele)	6	56.5	0.043	R	0.452	0.359
	GG versus AA (homozygote)	4	0.0	0.965	F	1.000	0.810
	GA versus AA (heterozygote)	4	0.0	0.781	F	1.000	0.928
	GG+GA versus AA (dominant)	4	0.0	0.947	F	1.000	0.829
	GG versus GA+AA (recessive)	4	49.6	0.114	F	0.089	0.036
CTLA-4							
rs231775	G versus A (allele)	14	87.8	<0.001	R	0.037	0.289
	GG versus AA (homozygote)	12	87.0	<0.001	R	0.244	0.399
	GA versus AA (heterozygote)	12	77.0	<0.001	R	0.193	0.336
	GG+GA versus AA (dominant)	12	85.1	<0.001	R	0.244	0.344
	GG versus GA+AA (recessive)	12	80.2	<0.001	R	0.193	0.173
rs5742909	T versus C (allele)	10	36.4	0.117	F	0.592	0.258
	TT versus CC (homozygote)	8	0.0	0.611	F	1.000	0.540
	TC versus CC (heterozygote)	8	41.9	0.121	F	0.389	0.316
	TT+TC versus CC (dominant)	8	43.7	0.087	F	0.386	0.392
	TT versus TC+CC (recessive)	8	0.0	0.613	F	1.000	0.556
rs4553808	G versus A (allele)	3	0.0	0.451	F	0.296	0.107
	GG versus AA (homozygote)	3	0.0	0.384	F	0.296	0.179
	GA versus AA (heterozygote)	3	0.0	0.844	F	0.296	0.322
	GG+GA versus AA (dominant)	3	0.0	0.653	F	0.296	0.201
	GG versus GA+AA (recessive)	3	0.0	0.399	F	0.296	0.186
rs3087243	A versus G (allele)	3	58.7	0.089	R	1.000	0.403
	AA versus GG (homozygote)	3	72.0	0.028	R	1.000	0.729
	AG versus GG (heterozygote)	3	56.7	0.099	R	0.296	0.167
	AA+AG versus GG (dominant)	3	63.4	0.065	R	0.296	0.258
	AA versus AG+GG (recessive)	3	55.5	0.106	F	1.000	0.326

No., number of studies; F, fixed-effects model; R, random-effects model.

General Characteristics of the Included Studies

Various types of uveitis including BD, VKH, acute anterior uveitis, nonanterior uveitis, acute anterior uveitis associated with ankylosing spondylitis, endogenous non-anterior uveitis, and spondyloarthropathies uveitis were included in our research. The characteristics of each study were presented in Table 1. Different genotyping methods, including polymerase chain reaction-restriction fragment length polymorphism, polymerase chain reaction-sequence-specific primer, and TaqMan SNP genotyping, assays were applied. The genotypic distribution from all studies was in agreement with the HWE ($p > 0.05$) except for 3 studies [25, 35, 37]. The quality assessments for all selected articles are manifested in Table 1. Furthermore,

all studies were of high quality (i.e., they were awarded more than 6 stars) according to the Newcastle-Ottawa scale.

Association between *PTPN22* Gene Polymorphisms and Uveitis

Totally, ten eligible studies that described common SNPs of the *PTPN22* gene (rs2488457 and rs2476601) as association with uveitis were included in our meta-analysis. Analysis of the association of rs2488457 polymorphism and uveitis susceptibility was based on 4 studies. As delineated in Table 2, significant heterogeneity was identified in all genotypic models ($p < 0.1$), and a random-effects model was applied. A significantly positive relation-

Table 3. Summary of pooled ORs in the meta-analysis

Subgroup	Studies, <i>N</i> <i>n</i>	Allele model		Homozygote model		Heterozygote model		Dominant model		Recessive model	
		case	control	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
PTPN22 rs2488457 (associated allele vs. reference allele: C vs. G)											
Overall	4	2,101	6,226	1.18 (1.02, 1.38)	0.029	1.46 (0.99, 2.15)	0.054	1.13 (0.81, 1.59)	0.472	1.27 (0.88, 1.82)	0.204
BD	2	794	2,206	1.06 (0.93, 1.22)	0.378	1.29 (0.61, 2.71)	0.506	1.19 (0.43, 3.32)	0.737	1.23 (0.50, 3.03)	0.658
Other	2	1,307	4,020	1.29 (1.08, 1.55)	0.005	1.65 (1.11, 2.46)	0.013	1.25 (0.98, 1.59)	0.072	1.41 (1.02, 1.93)	0.037
Ethnicity											
Caucasian	1	278	1,516	1.10 (0.87, 1.39)	0.447	2.15 (0.85, 5.43)	0.105	2.22 (0.87, 5.69)	0.097	2.17 (0.86, 5.46)	0.099
Asian	3	1,823	4,710	1.21 (1.00, 1.45)	0.046	1.38 (0.90, 2.14)	0.141	1.05 (0.75, 1.49)	0.767	1.18 (0.80, 1.75)	0.398
PTPN22 rs2476601 (associated allele vs. reference allele: G vs. A)											
Overall	6	1,158	2,739	1.27 (0.83, 1.96)	0.273	1.07 (0.26, 4.34)	0.927	0.91 (0.23, 3.61)	0.891	1.04 (0.25, 4.35)	0.959
BD	4	804	1,926	1.50 (0.57, 3.95)	0.413	1.31 (0.06, 27.3)	0.862	1.43 (0.07, 30.2)	0.818	1.32 (0.06, 27.6)	0.857
Other	2	354	813	1.14 (0.72, 1.79)	0.578	1.00 (0.20, 4.94)	0.995	0.79 (0.16, 3.80)	0.769	0.97 (0.19, 4.92)	0.970
Ethnicity											
Caucasian	4	884	2,497	1.22 (0.84, 1.78)	0.296	1.07 (0.26, 4.34)	0.927	0.91 (0.23, 3.61)	0.891	1.04 (0.25, 4.35)	0.959
Middle East	2	274	242	1.70 (0.02, 122)	0.808	—	—	—	—	—	—
CTLA-4 rs231775 (associated allele vs. reference allele: G vs. A)											
Overall	14	2,157	3,435	0.87 (0.65, 1.16)	0.303	0.72 (0.38, 1.36)	0.312	0.85 (0.60, 1.20)	0.346	0.80 (0.54, 1.21)	0.292
BD	9	1,343	1,351	0.77 (0.52, 1.14)	0.195	0.48 (0.17, 1.36)	0.166	0.68 (0.40, 1.18)	0.171	0.62 (0.32, 1.17)	0.140
Other	5	814	2,084	1.15 (0.94, 1.41)	0.165	1.33 (0.85, 2.09)	0.211	1.17 (0.96, 1.42)	0.122	1.20 (0.91, 1.58)	0.198
Ethnicity											
Caucasian	4	656	1,875	1.09 (0.95, 1.26)	0.204	1.09 (0.78, 1.53)	0.608	1.12 (0.92, 1.38)	0.262	1.12 (0.92, 1.36)	0.253
Asian	4	732	831	1.18 (1.02, 1.38)	0.031	1.50 (1.04, 2.16)	0.029	1.34 (0.93, 1.93)	0.133	1.41 (0.99, 2.00)	0.053
Middle East	4	574	483	0.98 (0.81, 1.20)	0.870	0.87 (0.34, 2.22)	0.767	0.94 (0.69, 1.28)	0.690	0.94 (0.71, 1.24)	0.663
African	2	195	246	0.25 (0.19, 0.33)	<0.001	0.08 (0.02, 0.27)	<0.001	0.23 (0.09, 0.57)	0.001	0.16 (0.06, 0.41)	<0.001
CTLA-4 rs5742909 (associated allele vs. reference allele: T vs. C)											
Overall	10	1,676	2,937	0.98 (0.84, 1.13)	0.758	1.11 (0.61, 2.03)	0.735	0.98 (0.76, 1.26)	0.881	0.99 (0.77, 1.27)	0.937
BD	5	870	852	0.95 (0.77, 1.18)	0.658	0.91 (0.26, 3.18)	0.888	0.87 (0.67, 1.12)	0.278	0.87 (0.67, 1.12)	0.278
Other	5	806	2,085	1.00 (0.82, 1.22)	0.988	1.18 (0.59, 2.34)	0.639	1.11 (0.71, 1.74)	0.648	1.12 (0.72, 1.76)	0.611
Ethnicity											
Caucasian	4	647	1,875	1.14 (0.92, 1.42)	0.232	1.77 (0.80, 3.95)	0.161	1.37 (0.63, 2.99)	0.431	1.44 (0.68, 3.04)	0.337
Asian	4	731	832	0.83 (0.67, 1.02)	0.077	0.65 (0.26, 1.63)	0.359	0.83 (0.66, 1.06)	0.131	0.82 (0.65, 1.04)	0.096
Middle East	2	298	230	1.21 (0.67, 2.17)	0.529	—	—	1.17 (0.57, 2.40)	0.068	1.17 (0.57, 2.40)	0.670
CTLA-4 rs4553808 (associated allele vs. reference allele: G vs. A)											
Overall	3	719	746	1.07 (0.87, 1.32)	0.510	2.58 (0.99, 6.71)	0.052	0.97 (0.77, 1.23)	0.833	1.02 (0.81, 1.29)	0.849
BD	2	511	492	1.14 (0.89, 1.46)	0.296	3.22 (1.05, 9.90)	0.042	1.02 (0.77, 1.35)	0.917	1.08 (0.82, 1.42)	0.580
Other	1	208	254	0.92 (0.62, 1.36)	0.674	1.19 (0.17, 8.53)	0.864	0.89 (0.58, 1.37)	0.586	0.90 (0.58, 1.37)	0.614
CTLA-4 rs3087243 (associated allele vs. reference allele: A vs. G)											
Overall	3	479	516	0.95 (0.67, 1.34)	0.758	0.65 (0.17, 2.39)	0.513	1.14 (0.72, 1.79)	0.574	1.07 (0.66, 1.72)	0.787
BD	2	270	260	1.11 (0.76, 1.62)	0.592	1.11 (0.43, 2.87)	0.823	1.55 (0.60, 3.97)	0.362	1.46 (0.60, 3.54)	0.409
Other	1	209	256	0.72 (0.52, 0.99)	0.043	0.15 (0.03, 0.66)	0.012	0.88 (0.60, 1.29)	0.514	0.78 (0.53, 1.13)	0.187
Ethnicity											
Caucasian	1	42	53	1.47 (0.82, 2.61)	0.195	2.00 (0.58, 6.91)	0.273	2.83 (1.05, 7.63)	0.04	2.58 (1.00, 6.66)	0.051
Asian	2	437	463	0.83 (0.62, 1.12)	0.231	0.37 (0.07, 1.84)	0.225	0.96 (0.73, 1.27)	0.777	0.88 (0.68, 1.16)	0.372

BD, Behcet's disease; OR, odds ratio; CI, confidence interval.

Fig. 2. Forest plots of studies reporting the associations between *CTLA-4* rs231775 and risk of uveitis. Each square indicates a study, and the area of squares is proportional to the weight of the study. The diamond represents the summary OR and 95% CI.

ship was observed between rs2488457 polymorphisms and uveitis susceptibility (C vs. G, OR = 1.18, 95% CI = 1.02–1.38, $p = 0.029$ and CC vs. CG+GG, OR = 1.27, 95% CI = 1.06–1.52, $p = 0.009$; Table 3). In addition, disease type-stratified analysis demonstrated that the C allele was not correlated with greater prevalence of BD in any model ($p > 0.05$) but with other uveitis subtypes (C vs. G, OR = 1.29, 95% CI = 1.08–1.55, $p = 0.005$; CC vs. GG, OR = 1.65, 95% CI = 1.11–2.46, $p = 0.013$; CC+CG vs. GG, OR = 1.41, 95% CI = 1.02–1.93, $p = 0.037$; and CC vs. CG+GG, OR = 1.43, 95% CI = 1.18–1.73, $p < 0.001$). Subsequently, in terms of the subgroup analysis of the ethnicity, C allele conferred significantly increased susceptibility to uveitis in the Asian region (C vs. G, OR = 1.21, 95% CI = 1.00–1.45, $p = 0.046$ and CC vs. CG+GG, OR = 1.36, 95% CI = 1.15–1.60, $p < 0.001$).

Moreover, the pooled results between *PTPN22* rs2476601 and uveitis risk declined the presence of sig-

nificant association in our meta-analysis ($p > 0.05$, Table 3).

Association between *CTLA-4* Gene Polymorphisms and Uveitis

Four polymorphic sites (rs231775, rs5742909, rs4553808, and rs3087243) in the *CTLA-4* gene were commonly reported to investigate potential susceptibility to uveitis. For *CTLA-4* rs231775, fourteen studies in thirteen articles were enrolled and reanalyzed. Obvious heterogeneity was detected in the genetic models; thus, a random-effects model was used (Table 2). There was no evidence of association between rs231775 and uveitis in general for any model ($p > 0.05$, Table 3). Subgroup analysis based on ethnicity also did not reveal any risk of uveitis among Caucasian and Middle-East regions. A marginally increased risk of uveitis was discovered in the Asian group (G vs. A, OR = 1.18, 95% CI = 1.02–1.38, $p =$

Fig. 3. Leave-one-out sensitivity analysis of the association between *CTLA-4* rs231775 and risk of uveitis. The three vertical lines indicate the summary effect and its 95% CI. Each horizontal line shows the summary effect and its 95% CI after elimination of the included study in turn.

0.031 and GG vs. AA, OR = 1.50, 95% CI = 1.04–2.16, $p = 0.029$). However, a significantly negative correlation was observed in the Africa group (G vs. A, OR = 0.25, 95% CI = 0.19–0.33, $p < 0.001$, Fig. 2; GG vs. AA, OR = 0.08, 95% CI = 0.02–0.27, $p < 0.001$; GA vs. AA, OR = 0.23, 95% CI = 0.09–0.57, $p < 0.001$; GG+GA vs. AA, OR = 0.16, 95% CI = 0.06–0.41, $p < 0.001$; and GG vs. GA+AA, OR = 0.18, 95% CI = 0.11–0.31, $p < 0.001$; Table 3).

Meta-analysis of ten studies was performed to investigate the association of rs5742909 polymorphism with uveitis. A pooled result of all genetic models implied that there was no obvious correlation among them ($p > 0.05$, Table 3). Subgroup analysis based on ethnicity and the disease type also failed to find any relationship (Table 3).

Only three studies were focused on *CTLA-4* rs4553808 with uveitis in Asian populations. No evidence of between-study heterogeneity under the five genetic models was observed, and a fixed-effects model was added ($p > 0.1$, Table 2). Subgroup analysis based on the disease type revealed that the rs4553808 GG genotype conferred an elevated risk of BD (GG vs. AA, OR = 3.22, 95% CI = 1.05–9.90, $p = 0.042$ and GG vs. GA+AA, OR = 3.20, 95% CI = 1.04–9.84, $p = 0.042$).

For *CTLA-4* rs3087243 G>A polymorphism, 3 studies examined the predisposition to uveitis in Caucasian and Asian populations. Overall, the A allele could not convey any risk of uveitis in all genetic models ($p > 0.05$). Subgroup analysis based on ethnicity suggested a positive relationship between the heterozygote model and Cauca-

sian region (AG vs. GG, OR = 2.83, 95% CI = 1.05–7.63, $p = 0.04$).

Sensitivity Analysis

In the sensitivity analysis of the effect of each study on the pooled ORs, each study was omitted in turn. Although 3 studies [25, 35, 37] showed evident deviation from the HWE ($p < 0.05$), excluding each of the studies in turn did not affect the pooled ORs (rs231775 G vs. A, Fig. 3), which inferred that the combined results of present meta-analysis were relatively robust.

Publication Bias

A series of Begg's funnel plots and Egger's regression tests were applied to examine potential publication bias in the studies of the association of the *PTPN22* and *CTLA-4* polymorphisms with uveitis. As shown in Table 2, no obvious publication biases were discovered, with the shape of the funnel plots of each polymorphism site nearly symmetrical (rs231775 G vs. A, Fig. 4).

Meta-Regression Analysis

Significant heterogeneity was identified for our model comparisons, so meta-regression analysis was used to explore the potential heterogeneity in turn. The ethnicity, disease type, genotypic method, and sample size were thoroughly regarded as independent covariate factors. As delineated in Table 4, meta-regression indicated that the disease type was the source of between-study heterogene-

Fig. 4. Begg's funnel plot of the association between *CTLA-4* rs231775 and risk of uveitis. The x-axis is the SE of log(OR), and the y-axis is the natural logarithm of OR. SE, standard error.

ity (95% CI = 1.73–2.14, $p = 0.003$) in rs231775. Simultaneously, we found that none of the other potential confounding factors contributed to the source of heterogeneity.

Discussion

In this systematic meta-analysis of 20 case-control studies, 6 SNPs from *PTPN22* and *CTLA-4* gene were delineated to investigate the association with uveitis. Three variants were shared across uveitis and could confer genetic predisposition to uveitis.

PTPN22 belongs to a family of genes encoding protein tyrosine phosphatases, which play a negative role in the TCR signal pathway via dephosphorylation of protein tyrosine kinases. These kinases, which contain the Src family (Lck and Fyn being the most important) and the Syk family (ZAP-70 being the most important), cause phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs). ITAMs of the TCR-associated CD3 γ -chain induce several intracellular signaling pathways [43]. Functional studies derived from human and mouse cells indicated that *PTPN22* knockdown or pharmacological inhibition could enhance TCR signaling [44–46].

Although increasing studies have investigated the correlation between *PTPN22* genetic mutation and autoimmune diseases, the functional consequences of a single

Table 4. Meta-regression for the heterogeneity of *PTPN22* and *CTLA-4* genetic polymorphisms

Covariate factor	Exp (b)	Std. err	p value	95% CI
<i>PTPN22</i> rs2488457				
Disease type	0.82	0.09	0.210	0.51–1.32
Ethnicity	0.91	0.18	0.681	0.38–2.16
Genotypic method	0.91	0.18	0.681	0.38–2.16
Cases, n	1.00	0.0001	0.165	0.99–1.00
<i>PTPN22</i> rs2476601				
Disease type	0.84	0.54	0.796	0.14–5.05
Ethnicity	0.71	1.03	0.826	0.01–39.76
Genotypic method	0.08	0.13	0.203	0.0008–8.04
Cases, n	0.99	0.002	0.302	0.99–1.00
<i>CTLA-4</i> rs231775				
Disease type	1.26	0.73	0.003	1.73–2.14
Ethnicity	0.70	0.23	0.300	0.35–1.43
Genotypic method	1.53	0.48	0.202	0.77–3.04
Cases, n	1.00	0.001	0.242	0.99–1.00
<i>CTLA-4</i> rs3087243				
Disease type	0.65	0.19	0.388	0.01–30.5
Ethnicity	1.75	0.63	0.361	0.02–165.2
Genotypic method	1.75	0.63	0.361	0.02–165.2
Cases, n	0.99	0.002	0.415	0.97–1.03

Exp, exponential; Std. err, standard error; CI, confidence interval.

base change at the DNA level remain to be clarified. The present meta-analysis examined the literature on two SNPs (rs2488457 and rs2476601) of the *PTPN22* gene with uveitis. *PTPN22* rs2488457 is located in the promot-

er region containing the core motif of the transcription factor AP-4 binding consensus sequence. Our meta-analysis was the first to confirm the association between rs2488457 and uveitis risk. Especially, the C allele was a risk factor for other autoimmune uveitis types and in the Asian group but not BD. The inconsistency may be attributed to different immune-mediated pathways in these uveitis entities. It has been commonly believed that BD is considered as an autoinflammatory disease, which differs from other type of uveitis [47, 48]. The common *PTPN22* polymorphism rs2476601 (1858C>T) encodes an arginine-to-tryptophan substitution (amino acid 620, Arg-620Trp) in the first proline-rich motif of the *PTPN22* protein. Trp620 is known to prevent LYP from binding to at least one of its adapter molecules such as Csk kinase. Thus, LYP containing Trp instead of Arg at this position cannot complex with Csk so that abrogates inhibition of T-cell activation [49]. The failure of T-cell inhibition following an immune attack on the body could lead to extensive T-cell proliferation and autoimmune phenotype ultimately, which would be potentially fatal [50]. This hypothesis was confirmed by a comprehensive meta-analysis of 12 autoimmune diseases, in which rs2476601C>T was strongly correlated with rheumatoid arthritis and systemic lupus erythematosus risk [19]. However, the pooled ORs of *PTPN22* rs2476601 did not imply any association with uveitis in our current meta-analysis. The remarkable difference between our data and the earlier meta-analyses may be explained by the disease-specific nature.

The gene *CTLA-4*, located on chromosome 2q33, is a crucial negative regulator of T-cell activation. However, the exact mechanisms involved in how *CTLA-4* restrains T-cell activation are still not confirmed. One hypothesis suggested that *CTLA-4* might successfully compete with CD28 for its CD80/86 ligands. CD28, which is constitutively expressed on the surface of T cells, plays an important role in signaling following T-cell binding to antigen-presenting cells [51]. Thus, combining with CD80/86 ligands, *CTLA-4* could inhibit the costimulatory effect of CD28 and T-cell activation. A second hypothesis proposed that *CTLA-4* might interact with Lck, Fyn, and ZAP-70 protein kinases through SHP1 phosphatases and exert its inhibition effect by acting on downstream signal pathways [52]. According to a third hypothesis, *CTLA-4* could directly interact with TCR ITAM and disrupt the cascade of biochemical signals that lead to activation of T cells [53]. Lastly, a recent study showed that *CTLA-4* could regulate the Cbl family molecule as a possible mechanism for aberrant T-cell activation for the occurrence of autoimmunity [54].

The present meta-analysis investigated the potential correlation between *CTLA-4* genetic variants and uveitis. Combined results of rs231775 polymorphism revealed a reduced trend toward uveitis in an ethnic stratification analysis. Additionally, our combined results revealed significantly positive association between rs4553808 and uveitis risk. These results differ from previous meta-analysis, which did not find any positive relationship [17, 18]. This discrepancy could be attributed to much more studies and larger populations. Therefore, it is certain that these findings are more accurate than before.

In our meta-analysis, further subgroup analysis based on ethnicity indicated distinctive associations between rs2488457 and rs231775 polymorphisms and uveitis. The reasons for this discrepancy could be explained by genetic backgrounds with different allele frequency among populations, living environments, and matching criteria. Besides, the results of our meta-regression analysis have shown that the disease type may be the major source of heterogeneity between studies, but ethnicity, genotypic method, and sample size could not explain obvious heterogeneity, suggesting that these confounding factors may not cause statistical bias. These disparate conclusions may be attributed by the relatively small sample size, resulting in substantial estimation errors.

There are several limitations in this meta-analysis. First, the subgroup analysis revealed disease type-induced heterogeneity in the association of *CTLA-4* rs231775 with uveitis. However, the overall effect cannot be affected in the examination of sensitivity analysis and meta-regression analysis. Second, the sample size in each study was relatively small. Further records with much larger populations and different ethnic groups are encouraged. Third, the ethnic origins from patients and controls were not specified in all the studies, and different criteria were used for the inclusion of controls, which may result in potential heterogeneity. Fourth, the current research should be registered in the PROSPERO or Cochrane system. We have tried our best and failed to register as soon as possible, which could result in bias. But our meta-analysis was performed strictly in accordance with the process of systematic review. Fifth, the information of sex differences was not available in uveitis subtypes, thus the potential heterogeneity by sex could not be evaluated. Finally, all eligible studies were retrieved from English and Chinese language records. This would result in selection bias in this meta-analysis.

Conclusion

In summary, the results of this comprehensive meta-analysis demonstrated that *PTPN22* rs2488457 conferred strong susceptibility to uveitis, especially in the Asian region. The *CTLA-4* rs231775 polymorphism convey potential protection against uveitis in African populations; otherwise, *CTLA-4* rs4553808 displayed an elevated risk of BD. Although our results revealed *PTPN22* and *CTLA-4* could be prioritizing candidate genes for uveitis, further well-designed independent studies with larger case-control individuals are required to validate these findings.

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Statement of Ethics

All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to this work.

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Author Contributions

J.Q. conceived the study. J.Z. and P.Z. performed and checked the available information from eligible articles in this meta-analysis. P.Z. analyzed the data. S.H. prepared Figures 1–4 and Tables 1–4. J.Z. wrote the main manuscript text. J.Q. reviewed and revised the manuscript. All the authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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