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PADI4 and IL-33 gene polymorphisms with susceptibility to systemic lupus erythematosus and juvenile idiopathic arthritis, a systematic review and meta-analysis

Bo Zheng, BM[a,*], Pingping Cai, BM[a], Yangjun Chen, BM[a], Yuechao Wu, BM[a], Hongyan Liu, BM[a]

Abstract

Background: This study evaluated the association between peptidyl arginine deiminase type IV (PADI4) and interleukin 33 (IL-33) with systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA).

Method: We searched the PubMed, Web of Science, Embase and Cochrane Library databases to retrieve articles published up to January 20, 2023. Stata/SE 17.0 (College Station, TX) software was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). The cohort study, case-control study focusing on the PADI4, IL-33 polymorphism, and SLE, JIA were retrieved. The data included basic information of each study and the genotypes and allele frequencies.

Results: Studies in PADI4 rs2240340 = 2 and 3 IL-33(rs1891385 = 3, rs10975498 = 2, rs1929992 = 4) were found in 6 articles. Overall, only the IL-33 rs1891385 show significant association between SLE in all 5 models. The results were OR (95% CI) = 1.528 (1.312, 1.778), P = .000 in Allele model (C vs A), OR (95% CI) =1.473 (1.092, 1.988), P = .000 in Dominant model (CC + CA vs AA), 2.302 (1.583, 3.349), P = .000 in Recessive model (CC vs CA + AA), 2.711 (1.845, 3.983), P = .000 in Homozygote model (CC vs AA), 5.568 (3.943, 7.863), P = .000 in Heterozygote model (CA vs AA). PADI4 rs2240340, IL-33 rs10975498, IL-33 rs1929992 were not found to be association with the risk of SLE and JIA. In gene model, statistically significant association was found between IL-33 rs1891385 and SLE in sensitivity analysis. Egger's publication bias plot showed there was no publication bias (P = .165). Only in recessive model the heterogeneity test was significant (I^2 = 57.9%, $P \leq .093$) of IL-33 rs1891385.

Conclusion: The current study suggests that in all 5 model, IL-33 rs1891385 polymorphism may be associated with genetic susceptibility to SLE. There was unclear association found between PADI4 rs2240340, IL-33 rs10975498, and IL-33 rs1929992 polymorphisms and SLE and JIA. Due to the limitations of included studies and the risk of heterogeneity, additional research is required to confirm our findings.

PROSPERO registration number: CRD42023391268.

Abbreviations: CI = confidential interval, IL-33 = Interleukin-33, JIA = juvenile idiopathic arthritis, JSLE = juvenile systemic lupus erythematosus, OR = odds ratio, SD = standard deviation, PADI4 = peptidyl arginine deiminase type IV, SLE = systemic lupus erythematosus.

Keywords: genetic polymorphism, IL-33, JIA, meta-analysis, PADI4, SLE, SNPs

1. Introduction

Systemic lupus erythematosus (SLE) and JSLE (juvenile systemic lupus erythematosus) are chronic autoimmune diseases with a wide spectrum of manifestations and severity both in children and adult.[1] Juvenile idiopathic arthritis (JIA) is a kind of chronic disease with joint swelling, and it may cause damage to other tissues and organs. Both SLE and JIA have the characteristics to damage the balance in lymphocyte subpopulations too.[2]

The etiopathology of SLE and JIA are still not fully clear, it was reported that maybe several factors including genetic and environmental factors have been associated with the initiation and the promotion of this complex disorder. The reports have demonstrated that genetic factors may play important roles in the development of SLE and JIA. Interleukin-33 (IL-33) is a novel cytokine which belongs to IL-1 family. It was associated with various biological functions, such as chronic inflammation, cancer and autoimmune disease.[3] ST2, which was the receptor

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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[a] Yuhuan People's Hospital, Taizhou, China.

**Correspondence: Bo Zheng, Yuhuan People's Hospital, 18 Changle Road, Taizhou 317600, China (e-mail: 370440859@qq.com).*

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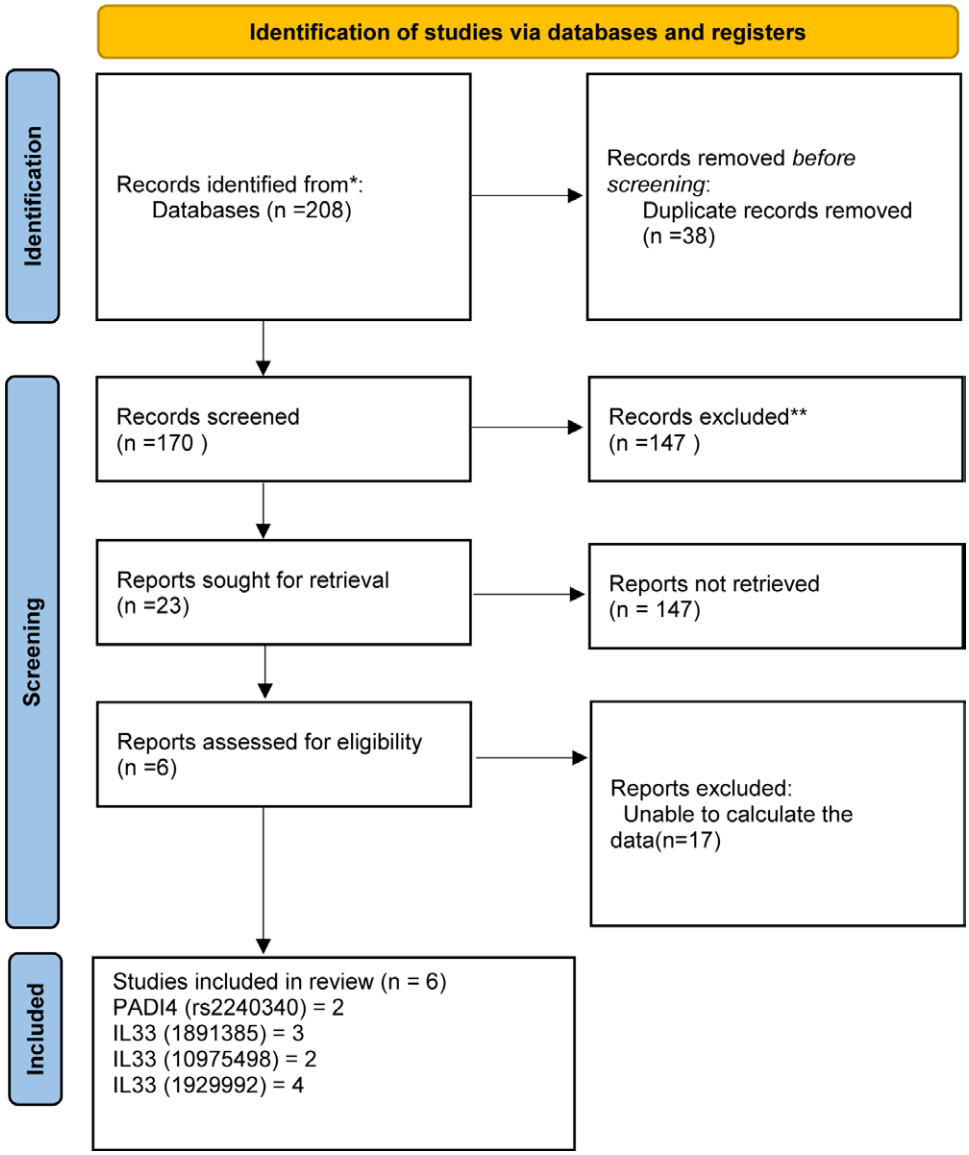

Figure 1. The PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

for IL-33, is expressed on the surface of Th2 cells and mediates important effector Th2 functions. By binding to ST2 receptors, IL-33 was reported to exert its biological functions, such as activating transduction cascade in IL-33 related diseases. The existing studies have shown that IL-33 is abnormally upregulated in asthma and SLE.[4]

The expression of the peptidyl arginine deiminase type IV (PADI4) gene is associated to effect macrophages and is associated with inflammation and immune response.[5] Genetic variants have potential associations with features of disease. The distribution of PADI4 genotype is compared with healthy controls in some kinds of autoimmune diseases. It had been reported about the association of PADI4 polymorphisms with Rheumatoid arthritis susceptibility in some ethnicities like Egyptians, French, Japanese, and Korean population.[6–8]

Many studies have found gene polymorphisms like IL-33 and PADI4 may play important roles in SLE and JIA. However, the findings are sometimes contradictory. As a result of our extensive literature search, we chose the 2 factors, IL-33 and PADI4, for further investigation. Therefore, we aimed to assess the association of polymorphisms of these genes and the risk of SLE and JIA in a meta-analysis of case-control studies and evaluating the genetic influences in children and adult.

2. Methods

2.1. Search strategy

A systematic literature search was conducted using PubMed, Embase, Web of Science, and Cochrane Library, with articles published until January 20, 2023. For a comprehensive literature search, the reference lists of included studies and related reviews were manually searched and screened. There was no language restriction for this study. Two authors independently searched all databases using the following search terms: ("peptidyl arginine deiminase 4"[Title/Abstract] OR "PADI4"[Title/Abstract] OR "interleukin 33"[Title/Abstract] OR "IL-33"[Title/Abstract]) AND ("systemic lupus erythematosus"[Title/Abstract] OR "SLE"[Title/Abstract] OR "juvenile idiopathic arthritis"[Title/Abstract] OR "JIA"[Title/Abstract]).

2.2. Inclusion and exclusion criteria

The following were the inclusion criteria for our systematic review and meta-analysis: case-control or cohort studies; the case group of patients diagnosed with SLE or JIA, and the control group of term individuals without SLE and JIA; investigating the association between IL-33 and PADI4 polymorphisms and SLE or JIA; sufficient data supporting the genotype distribution

Table 1

Main characteristics of included studies.

First author, yr	Cases/controls	racial	Age (mean ± SD, yr)		Genotyping method	Cases			Controls			HWE (P) controls	Phenotype
			Cases	Controls		CC	CT	TT	CC	CT	TT		
PADI4 rs2240340													
Ali, 2022	150/160	British	10.5 (3.5)	10.1 (3)	Real-time PCR	65	50	35	88	56	16	0.1220	JIA
Zhou, 2022	159/302	Chinese	9.97	9.47	Multiplex PCR	52	71	36	106	137	59	0.47	JIA
First author, yr	Cases/controls	Racial	Age (mean ± SD, yr)		Genotyping method	Cases			Controls			HWE (P) controls	Phenotype
			Cases	Controls		CC	AC	AA	CC	AC	AA		
IL-33 rs1891385													
Guo, 2016	257/283	Chinese	36 ± 19.0	34 ± 18.9	PCR-SBE	22	85	150	6	97	180	0.0857	SLE
Zhu, 2019	421/425	Chinese	49.8 ± 11 7	48.6 ± 10 9	PCR	48	172	201	23	132	270	0.201	SLE
Zhou, 2022	159/302	Chinese	9.97	9.47	Multiplex PCR	14	58	72	19	114	167	0.99	JSLE
First author, yr	Cases/controls	Racial	Age (mean ± SD, yr)		Genotyping method	Cases			Controls			HWE (P) controls	Phenotype
			Cases	Controls		TT	CT	CC	TT	CT	CC		
IL-33 rs10975498													
Guo, 2016	257/283	Chinese	36 ± 19.0	34 ± 18.9	PCR-SBE	56	140	61	59	157	67	0.0632	SLE
Zhu, 2019	421/425	Chinese	49.8 ± 11 7	48.6 ± 10 9	PCR	35	162	224	26	150	249	0.593	SLE
First author, yr	Cases/controls	Racial	Age (mean ± SD, yr)		Genotyping method	Cases			Controls			HWE (P) controls	Phenotype
			Cases	Controls		GG	AG	AA	GG	AG	AA		
IL-33 rs1929992													
Guo, 2016	257/283	Chinese	36 ± 19.0	34 ± 18.9	PCR-SBE	41	126	90	38	152	93	0.0555	SLE
Xu, 2016	328/243	Chinese	34	33	PCR	60	178	133	77	219	112	0.0998	SLE
Zhu, 2019	421/425	Chinese	49.8 ± 11 7	48.6 ± 10 9	PCR	43	169	209	20	128	277	0.299	SLE
Zhou, 2022	159/302	Chinese	9.97	9.47	Multiplex PCR	35	70	39	70	145	84	0.6286	SLE

HWE = Hardy-Weinberg Equilibrium, JIA = juvenile idiopathic arthritis, JSLE = juvenile systemic lupus erythematosus, PCR = Polymerase chain reaction, PCR-SBE = polymerase chain reaction-single base extension, SD = standard deviation, SLE = systemic lupus erythematosus.

Table 2

Methodological scoring protocol based on quality assessment for genetic studies.

References	Genetic criteria										Score	Evidence*
	Control group	Hardy–Weinberg equilibrium	Case group	Primer	Reproducibility	Blinding	Power calculation	Statistics	Corrected statistics	Independent replication		
Xu, 2016	1	1	0	1	1	0	0	1	1	0	6	Medium
Guo, 2016	0	1	0	1	1	0	0	1	0	0	4	Medium
Massarenti, 2019	0	1	1	0	0	0	0	1	0	0	3	Low
Zhu, 2019	0	1	0	1	1	0	0	1	0	0	4	Medium
Ali, 2020	1	1	0	0	0	0	0	1	0	0	3	Low
Zhou, 2022	1	0	0	0	0	0	0	1	0	0	2	Low

*For the quantification of criteria: «1» means present, and «0» absent.

were provided for the calculation of odds ratios (ORs) and corresponding 95% confidence intervals (CIs), and full-text articles can be obtained. All 5 genetic model data can be obtained. The following were the exclusion criteria: studies that contained repeated data, and reviews, and short communications, special communications, conference proceedings.

2.3. Study selection and data extraction

Using Endnote20.4 (Bld 18004), duplicate studies were excluded during data selection. The titles and abstracts of studies were further screened, then the full text was reviewed using the inclusion and exclusion criteria. The following characteristics were extracted from each eligible literature by 2 authors independently following the preferred reporting items for systematic reviews and meta-analyses (2020 version PRISMA) guidance.[9] First author's surname, publication year, race, age of subjects, the phenotype of case group, single nucleotide polymorphism (SNP) genotyping method, numbers of cases, and controls, Hardy–Weinberg Equilibrium *P* value of controls and the genotype frequencies of IL-33 and PA DI4 gene polymorphisms in cases and controls. Discrepancies were resolved through discussion until consensus was reached, and if inconsistencies emerged, a third author was referred.

2.4. Quality assessment

An instrument was adapted to a 10-point scoring (control group, Hardy–Weinberg equilibrium, case group, primer, reproducibility, blinding, power calculation, Statistics, corrected statistics, independent replication) from a sheet used in genetic studies.[10] This tool makes 2 different criteria, ranging from 0 to 10 points (Yes = 1) or (no/undetermined = 0). The authors performed independently in the evaluation. Quality of studies are classified as low quality (up to 4 points), medium quality (5 to 7 points) and high quality (more than 7 points).

2.5. Assessment of heterogeneity and publication bias

According to Cochrane Q test, statistical heterogeneity was assessed using the standard χ^2 test (a = 0.1) and I^2 test. A

Table 3

Main results of the total and sensitivity analysis.

	C-allele vs T-allele		CC vs TT		CT vs TT		CC vs TT + CT		CT + CC vs TT	
Study groups	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
PADI4 rs2240340 for JIA										
Overall	0.345 [0.033, 3.551]	.371	0.535 [0.229, 1.249]	.148	0.615 [0.301, 1.254]	.181	0.763 [0.565, 1.032]	.128	0.567 [0.254, 1.265]	.166
Sensitivity analysis										
Ali, 2022 year	1.11 [0.85, 1.47]	–	0.80 [0.47, 1.36]	–	0.84 [0.51, 1.40]	–	0.89 [0.59, 1.34]	–	0.82 [0.51, 1.32]	–
Zhou, 2022	0.10 [0.05, 0.18]	–	0.33 [0.17, 0.66]	–	0.40 [0.20, 0.82]	–	0.62[0.39, 0.97]	–	0.36 [0.19, 0.69]	–
Study groups	C-allele vs A-allele		CC vs AA		AC vs AA		CC vs AA + AC		AC + CC vs AA	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
IL-33 rs1891385 for SLE and JSLE										
Overall	1.528 [1.312, 1.778]	.000	2.711 [1.845, 3.983]	.000	5.568 [3.943, 7.863]	.000	2.302 [1.583, 3.349]	.000	1.473 [1.092, 1.988]	.011
Sensitivity analysis										
Guo, 2016	1.57 [1.31, 1.88]	–	2.39 [1.56, 3.67]	–	9.161 [3.937, 21.270]	–	1.97 [1.30, 2.98]	–	1.247 [0.882, 1.762]	–
Zhu, 2019	1.33 [1.07, 1.64]	–	2.60 [1.48, 4.56]	–	4.911 [3.026, 7.967]	–	2.36 [1.37, 4.07]	–	1.907 [1.449, 2.509]	–
Zhou, 2022	1.62 [1.36, 1.93]	–	3.16 [2.00, 5.00]	–	4.833 [2.673, 8.731]	–	2.67 [1.70, 4.18]	–	1.256 [0.844, 1.868]	–
Study groups	T-allele vs C-allele		TT vs CC		CT vs CC		TT vs CC + CT		TT + CT vs CC	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
IL-33 rs10975498 for SLE										
Overall	1.123 [0.956, 1.320]	.157	1.235 [0.856, 1.782]	.26	1.124 [0.888, 1.423]	.330	1.175 [0.850, 1.624]	.329	1.159 [0.926, 1.451]	.197
Sensitivity analysis										
Guo, 2016	1.22 [0.98, 1.51]	–	1.49 [0.87, 2.56]	–	0.979 [0.647, 1.482]	–	1.39 [0.82, 2.35]	–	1.24 [0.94, 1.63]	–
Zhu, 2019	1.01 [0.80, 1.29]	–	1.04 [0.62, 1.72]	–	1.201 [0.902, 1.598]	–	1.05 [0.70, 1.59]	–	0.99 [0.67, 1.48]	–
Study groups	G-allele vs A-allele		GG vs AA		AG vs AA		GG vs AA + AG		GG + AG vs AA	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
IL-33 rs1929992 for SLE										
Overall	1.091 [0.973, 1.225]	.137	1.123 [0.877, 1.437]	.359	1.021 [0.646, 1.613]	.930	1.148 [0.919, 1.434]	.224	1.106 [0.940, 1.302]	.225
Sensitivity analysis										
Guo, 2016	1.13 [0.69, 1.86]	–	1.24 [0.52, 2.92]	–	0.857 [0.590, 1.244]	–	1.22 [0.69, 2.16]	–	1.10 [0.56, 2.17]	–
Xu, 2016	1.23 [0.84, 1.79]	–	1.50 [0.80, 2.78]	–	0.684 [0.497, 0.942]	–	1.40 [0.89, 2.20]	–	1.23 [0.75, 2.03]	–
Zhu, 2019	0.92 [0.77, 1.09]	–	0.89 [0.62, 1.27]	–	1.750 [1.308, 2.341]	–	0.98 [0.76, 1.26]	–	0.83 [0.64, 1.07]	–
Zhou, 2022	1.12 [0.69, 1.80]	–	1.25 [0.54, 2.91]	–	1.040 [0.648, 1.669]	–	1.29 [0.72, 2.28]	–	1.05 [0.55, 2.01]	–

CI = confidence interval, JIA = juvenile idiopathic arthritis, JSLE = juvenile systemic lupus erythematosus, OR = odds ratio, SLE = systemic lupus erythematosus.

fixed-effects model (Mantel–Haenszel method) was used to confirm collective effectiveness when $P \geq .1$ and $I^2 \leq 50\%$ were met. Random-effects models was used if $P < .1$ or $I^2 > 50\%$ were met. Eggers's publication bias plot was used to represent the publication bias graphically for all 5 genetic models. Publication bias ($P < .05$) was carefully discussed in our discussion section and listed as one of the limitations of our meta-analysis.

2.6. Statistical analysis

The meta-analysis was performed using Stata/SE 17.0 (College Station, TX) software. ORs and 95% CIs were calculated to assess the association between IL-33 rs1891385, PADI4 rs2240340, IL-33 rs10975498, and IL-33 rs1929992 with SLE and JIA in 5 genetic model, which include allele model, dominant model, recessive model, homozygote model, and heterozygote model, respectively. Subgroup analysis is not available in this study as the papers for polymorphism are few. The goodness-of-fit χ^2 test assessed the control group's Hardy–Weinberg Equilibrium deviation. We performed sensitivity analysis to analyze the robustness of our findings. For sensitivity analysis, a leave-one-out meta-analysis was used. A P value < .05 was deemed statistically significant.

3. Results

3.1. Study selection

According to PRISMA flow diagram, a systematic literature search of PubMed, Embase, Web of Science, and Cochrane library

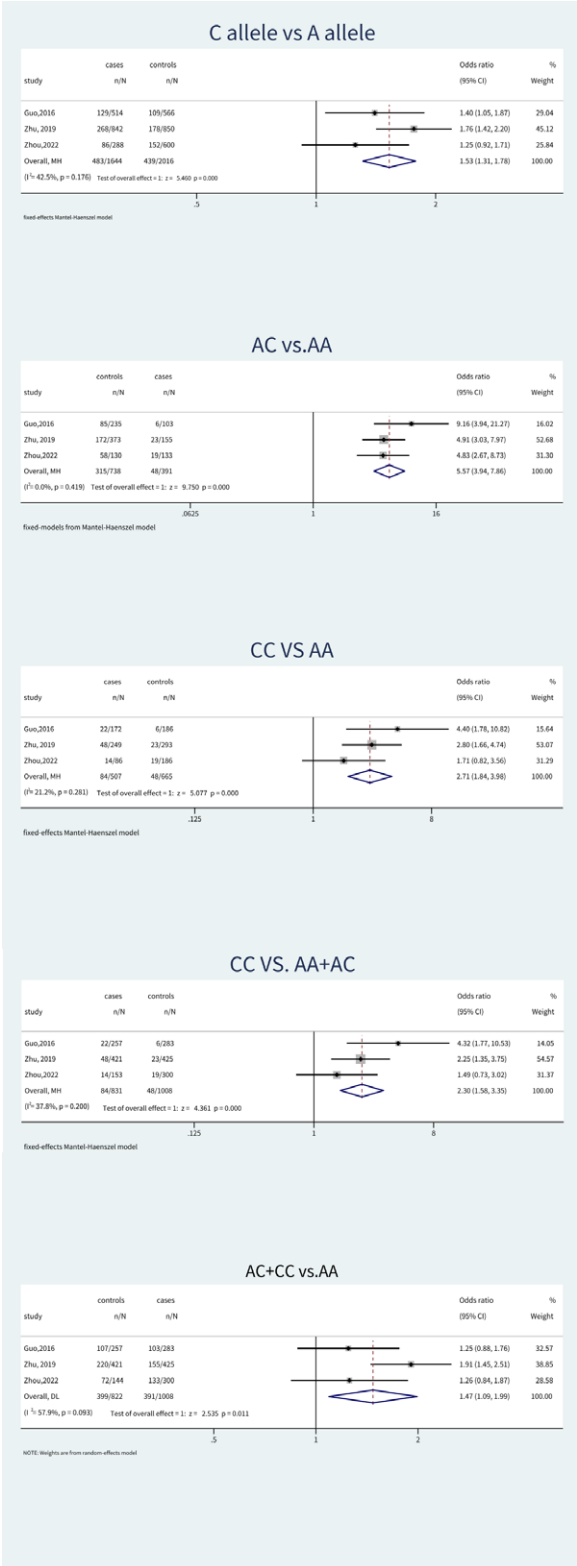

Figure 2. Forest plots of IL-33 rs1891385 polymorphism and SLE. The Allele model (C vs A), Dominant model (CC + CA vs AA), Recessive model (CC vs CA + AA), Homozygote model (CC vs AA), Heterozygote model (CA vs AA). The count for genotypes, weight, OR 95% confidence interval for each study. The fixed effect and random effect models were respectively utilized according to heterogeneity. SLE = systemic lupus erythematosus.

yielded 208 studies, including 38 duplicate records (Fig. 1). We excluded 147 studies after reviewing the titles and abstracts of 23 non-duplicate articles. Of the remaining 23 studies, 17 were excluded because they lacked eligible data. Finally, 6 eligible studies were included in this study. These studies included SLE or JIA cases as well as healthy controls. Using these studies, we investigated the relationship between alleles and genotypes of the IL-33 rs1891385, PADI4 rs2240340, IL-33 rs10975498, and IL-33 rs1929992 genetic polymorphisms and the risk of SLE and JIA.

3.2. Study characteristics

Table 1 summarizes the key characteristics of included studies in our systematic review meta-analysis. Until 20th January 2023, these studies included 309 cases and 462 controls for PADI4 rs2240340, 837 cases and 1010 controls for IL-33 rs1891385, 668 cases and 708 controls for IL-33 rs10975498 and 1165 cases and 1253 controls for IL-33 rs1929992, respectively. Table 2 shows the methodological scoring, 3 studies had low scores,[5,11,12] and 3 studies had medium scores.[13–15]

3.3. Results of meta-analysis

Two studies evaluated the relationship between PADI4 rs2240340 polymorphism and JIA. No significant association was found between the overall risk of JIA and rs2240340 under different genetic factors models (Table 3; Figure S1, Supplemental Digital Content, http://links.lww.com/MD/I917). A sensitivity analysis revealed no significant association between SLE and PADI4 rs2240340 polymorphism under different genetic models.

Three studies evaluated the relationship between IL-33 rs1891385 polymorphism and SLE. Significant association was found between the overall risk of SLE and IL-33 rs1891385 under all 5 genetic models like allele model (C vs A), homozygote model (CC vs AA), heterozygote model (AC vs AA), recessive model (CC vs AA + AC), dominant model (CC + AC vs AA) (Table 3; Fig. 2). A sensitivity analysis revealed significant association between SLE and IL-33 rs1891385 polymorphism under different genetic models.

Two studies in our review investigated the association between IL-33 rs10975498 polymorphism and SLE. No significant association was found between the overall risk of SLE and IL-33 rs10975498 under different genetic models. A sensitivity analysis revealed no association between SLE and IL-33 rs10975498 polymorphism under different genetic models. (Table 3; Figure S2, Supplemental Digital Content, http://links.lww.com/MD/I918)

Four studies were included to investigate the relationship between IL-33 rs1929992 polymorphism and SLE, and no significant association was found between the overall risk of SLE and IL-33 rs1929992 under different genetic models (Table 3; Figure S3, Supplemental Digital Content, http://links.lww.com/MD/I919). A sensitivity analysis revealed no significant association between SLE and IL-33 rs1929992 polymorphism under different genetic models.

In terms of IL-33 rs1891385 publication bias, there was no obvious bias. For allele model, the *P* value for publication bias was .165, for other 4 genetic model, the *P* value was .692 (Fig. 3; Figure S4, Supplemental Digital Content, http://links.lww.com/MD/I920).

4. Discussion

In this systematic review and meta-analysis, all 5 genetic models revealed significant associations between IL-33 rs1891385 polymorphism and SLE. Furthermore, due to an insufficient number of studies for meta-analysis, many other IL-33 and PADI4 gene polymorphisms were excluded from this study.

It has been widely accepted that there is individual susceptibility to autoimmune diseases for SLE and JIA even with the

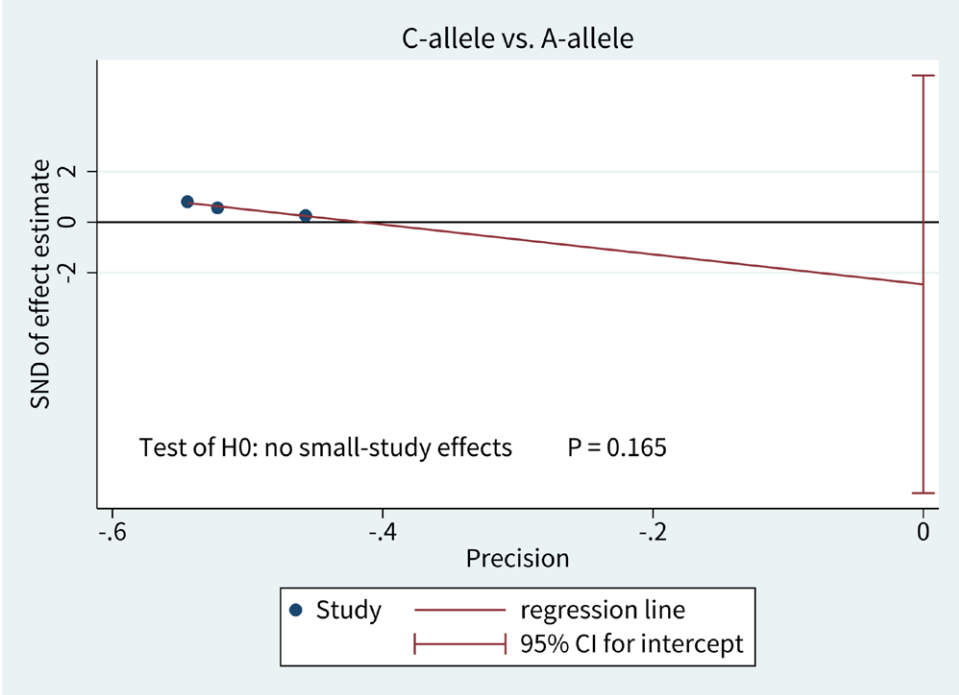

Figure 3. The Eggers publication bias plot for IL-33 rs1891385.

same environmental exposure. Host factors like polymorphisms of genes, might have accounted for this difference. Therefore, genetic susceptibility to autoimmune diseases has been a research factor in the scientific community.

Some papers have reported rs2240340 of PAD14 in different variants of JIA. Although its association with SLE has been reported, but the results were confused as in many reports, there were no significant links detected compared to adult with JIA and SLE.[16] In this study, no definite associations between rs2240340 genotypes or alleles and severe disability were found.

It has been reported that patients with SLE showed correlation of IL-33 with ESR, CRP, and by multivariate logistic regressions, patients with SLE showed independent association of IL-33 with thrombocytopenia and anti-SSB antibody.[17] Their results indicated that IL-33 may play a role in acute phase of SLE. IL-33 may be an indicator for disease activity in SLE.[18] This meta-analysis found significant association between IL-33 rs1891385 gene polymorphism and SLE. However, IL-33 (rs10975498, rs1929992) was regarding no relationship with SLE and JIA. Our sensitivity analysis also found significant link between IL-33 rs1891385 gene polymorphism and SLE. No subgroup analysis was made due to the small number of included studies, which requires to be confirmed by further research.

5. Limitation and conclusion

Our study has some limitations as well. First, the number of studies involving PADI4 rs2240340, IL-33 rs1891385, IL-33 rs10975498, and IL-33 rs1929992 are small. Second, we did not analyze among different races in countries, which may have obscured the correlation caused by race differences. Third, there was a risk of heterogeneity for IL-33 rs1891385 which may be caused as one study was for children,[19] when other 2 studies were for adult.[5,14] And the last, the Methodological scoring for these studies were low.

In conclusion, our findings suggest that IL-33 rs1891385 polymorphism may be associated with genetic susceptibility to SLE. On the other hand, PADI4 rs2240340, IL-33 rs10975498, and IL-33 rs1929992) polymorphisms are unrelated to SLE and JIA. Due to the limitations of included studies and the risk of heterogeneity, future studies in larger populations are required to confirm our findings.

Author contributions

Conceptualization: Bo Zheng.
Data curation: Pingping Cai.
Formal analysis: Pingping Cai, Yangjun Chen.
Funding acquisition: Yangjun Chen.
Investigation: Pingping Cai.
Methodology: Yangjun Chen.
Project administration: Yangjun Chen, Hongyan Liu.
Resources: Hongyan Liu.
Software: Bo Zheng, Hongyan Liu.
Supervision: Bo Zheng, Yuechao Wu.
Validation: Bo Zheng, Yuechao Wu.
Visualization: Bo Zheng, Yuechao Wu.
Writing—original draft: Hongyan Liu, Yuechao Wu.
Writing—review & editing: Bo Zheng.

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