Associated genetic polymorphisms and clinical manifestations in systemic lupus erythematosus in Asian populations - A systematic literature review

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic and life-threatening autoimmune disease. Its prevalence and clinical manifestations are known to be particularly severe in the Asian populations. Although genetics is known to play an important role in SLE susceptibility and clinical manifestations, the specific polymorphisms associated with these phenotypes in Asia are unclear. Therefore, we aim to review the association of SLE genetic polymorphisms with lupus manifestations across Asian populations and their role in the pathogenesis of SLE.

Methods: A systematic search was conducted on PubMed, EBSCOHost, and Web of Science. We identified 22 case-control studies that matched our inclusion and exclusion criteria. Information such as study characteristics, genetic polymorphisms associated with SLE, and organ manifestations was extracted and reported in this review.

Results: In total, 30 polymorphisms in 16 genes were found to be associated with SLE among Asians. All included polymorphisms also reported associations with various SLE clinical features. The association of rs1234315 in TNFSF4 linking to SLE susceptibility (P=4.17x10-17 OR=1.45 95% CI=1.34-1.59) and musculoskeletal manifestation (P=3.35x10-9, OR=1.37, 95%CI= 1.23–1.51) might be the most potential biomarkers to differentiate SLE between Asian and other populations. In fact, these associated genetic variants were found in loci that were implicated in immune systems, signal transduction, gene expression that play important roles in SLE pathogenesis.

Discussions and conclusions: This review summarized the potential correlation between 30 genetic polymorphisms associated with SLE and its clinical manifestations among Asians. More efforts in dissecting the functional implications and linkage disequilibrium of associated variants may be required to validate these findings.

KEYWORDS:
Systemic Lupus Erythematosus; Single Nucleotide Polymorphisms; Genetic Predisposition to Diseases; Phenotypes; Disease risk

INTRODUCTION

Systemic lupus erythematosus (SLE) is a debilitating disorder and genetically inheritable. The genetic contribution to the development of SLE is estimated to be 69% of heritability in monozygotic twin studies.[1] Majority of genetic association studies had suggested that the genetic risk for SLE shows modest effect sizes, ranging from 1.15-2.0.[2] Meanwhile, the key pathogenesis of SLE is the aberrant innate immune responses such as the defect in apoptosis and the loss of tolerance towards self-antigens. This has led to the auto-antibody formation and repository of immune complexes in the blood vessels, causing the infiltration of autoantibodies and deposition of inflammatory cells to affect various targeted organs.

The prevalence of SLE in Asians, particularly in the Eastern part of Asia, was reported to be two times higher compared to Caucasians (between 24.9 and 37.6/100,000 persons).[3] Asians with SLE are frequently at higher risk for severe with life-threatening complications such as renal and cardiovascular involvement.[4] However, the genetic predisposition of SLE in terms of disease susceptibility can vary according to different populations and ethnic groups.[5] The disparity in SLE genetics between populations may cause the Asians to be more severe than other Non-Asian populations.[6] Besides, the complexity of SLE genetics contributed to the penetrance of various targeted organ damage. Features such as lupus nephritis and cutaneous rashes are regularly found in SLE individuals.[7]

Although more than 100 SLE loci have been identified from the candidate gene approach and genome-wide association studies (GWAS) in European and Asian populations, there are high potential of biases in the association study of genetic polymorphism with SLE susceptibility and organ manifestation in Asia. The corroborations which featured Asians to have higher risk variant frequencies of SLE compared to Europeans/Caucasians might explain on why Asians are more severe than other Non-Asian populations. Therefore, this review will examine the best depiction of genotype-phenotype associations for SLE in Asians in comparison with Non-Asian populations and the functional implications of each locus in SLE.

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MATERIALS AND METHODS

2.1 Search Strategy

This review is registered in the PROSPERO database (CRD42020162670). The pipeline of this review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A broad search of the literature was performed on three renowned two databases, namely PubMed, EBSCOHost and Web of Science (WoS) from January of 2010 up to June of 2020. The main keywords of this study were adapted from Population-Exposure-Comparative-Outcome-Timeframe (PECOT) framework which is explained in the study design. From the framework, we decided to come up with 'Systemic Lupus Erythematosus', 'Polymorphisms' and 'Asians' as the main keywords for literature search. The synonyms of every keyword were obtained from the Medical Subject Headings (MeSH). All keywords and respective synonyms were used with truncation and standard Boolean Operators such as '*and*' and '*or*' where relevant.

2.2 Study Design Framework

The study design was devised based on the PECOT framework. P represented the population originated from Asia with SLE and their known complications; E represented the exposure of having the outcome; and C represented the comparable elements with the exposed group. O represented the outcome of interest of the study while T represented the timeframe of study from 2010 to 2020. The focus of this study was to determine the relationship between the genetic association underlying SLE and the organ manifestations in Asian populations. The case-control studies were included for further analyses.

2.3 Article Screening

The filtering of selected evidence was executed in two consecutive phases: 1) Review of title and abstract information and 2) Review of full text. Full text of selected evidence was retrieved from Mendeley Web by adhering to the guideline from the University of Western Australia (https://guides.library.uwa.edu.au/mendeley). Once the literature filtering was completed, the total of final searched reports were narrowed down to prevent abundant searches and to eliminate biases, hence additional inclusion and exclusion criteria were incorporated. Published reports were included for quality assessment and data extraction if they matched with every aspect in the formulated inclusion criteria:

1. Case-control studies that were from original research article between 2010 and 2020
2. All texts were written in English
3. Cases and controls consisted of ethnic groups originating from all parts of Asia.
4. Cases and controls were classified using ACR/SLICC classification criteria.
5. Single nucleotide variant (SNV) was used as a marker in the genotyping analysis
6. Statistical outcomes such as OR and p-Value were included.
7. Genotype-phenotype association analysis was performed
8. There was no conflict of interest with any authorities.

We excluded papers that were

1. Published before the year of 2010
2. Not original research articles, such as mini reviews, case reports, meta-analyses, and editorials.

2.4 Methodological Quality

The quality of the texts and analyses was evaluated by risk of bias assessment tool before the identified publications were finalized and confirmed to be used in this study. The utilization of risk of bias assessment tool is to attain transparency of the data synthesis for an evidence and to detect if there are any potential bias that might affect the entirety of synthesis. In this study, the modified Newcastle-Ottawa Scale (NOS) was selected as the tool to determine the bias of our identified publications since NOS is regularly applied to assess the quality of case-control in genetic studies. For the assessment, an asterisk is marked for every points of view: (1) the selection of the study groups, (2) the comparability of the groups, and one or two asterisks were marked for the (3) ascertainment of either the exposure or outcome of interest. The score has a range between zero and nine. A score of 5 and higher was deemed reliable to be used after the quality assessment by conforming to the standards of the NOS, whereas the lower scores indicated high potential of bias. The quality assessment was carried out by two independent researchers and any disagreements were resolved through discussion.

2.5 Data Extraction

Data from selected evidences were independently extracted by two authors using a piloted extraction form implemented by University of Wisconsin, USA (https://researchguides.ebling.library.wisc.edu/systematic-reviews) from selected articles included: (1) first author's name and publication year, (2) countries, (3) ethnic or race, (4) disease type, (5) sample size of cases and controls with their mean ages, (6) associated SNPs, (7) minor allele frequencies (MAF), (8) statistical finding of genetic association analysis, (9) associated genes, and (10) genotype-phenotype association analysis. Data extraction was carried out by two independent researchers to minimize the rate of extraction errors and the time taken to complete the extraction, and any eventual disagreements were agreed upon by all the authors.

2.6 Data Analysis

Upon information extraction, meta-analysis was decided as an unlikely option to answer the research question. This was due to different polymorphisms/variants being found from the various study selection and outcome measurements among the included articles. Therefore, a narrative synthesis of the evidence was chosen to analyze these studies in which we tabulated every single nucleotide polymorphism (SNP) association with outcome (SLE) and disease risk information as a preliminary synthesis. In addition, we also correlated the association between outcome-associated SNP with SLE complication (gene-phenotype association) in a tabulated form to demonstrate the main objective of this study.

2.7 Genotype-phenotype Association Study

SLE-associated variants were made associated with most common organ manifestations. Risk effect (OR) >1 and

significant value of P<0.05 indicated that SNPs were to be associated with high risk of SLE, while risk effect (OR) <1 and significant value of P<0.05 indicated that SNPs were to be associated with low risk of SLE.

2.8 The Identification of SLE-associated Loci with Respective Biological Pathways

The interpretation of functional role for each locus were divided into five main biological pathway categories (Immune System, Signal Transduction, Metabolism, Gene Expression and Extracellular Matrix Organization) according to the Reactome pathway database (www.reactome.org).

RESULTS

3.1 Literature Search

The overall flow of work throughout the literature search is illustrated in Figure 1. In total, 22 articles were included for data synthesis. Unclear publications such as research reports, conference papers, dissertations and theses, clinical trials, government documents, census data, standards, patents, and other research outputs were excluded because they did not meet the formulated inclusion and exclusion criteria.

3.2 Study Characteristics

Most studies were carried out in mainland China (N=11), followed by Taiwan and India (N=3), Hong Kong and Korea (N=2), Japan (N=1) (Table I). The sample size varied greatly across the studies, ranging from 190 to 8,076 subjects (95 to 3,339 patients and 95 to 4,737 controls). The mean age of SLE patients ranged from 20.5 ± 10.9 years to 42.8 ±13.9 years, and the mean age of controls ranged from 29.2 ± 11.0 years to 40.0 ± 8.6 years. In total, 16 studies examined only one SNP, while the remaining six studies investigated multiple polymorphisms.

A total of 30 polymorphisms (located in/near 20 genes) were reviewed. Among these 30 polymorphisms, there were three polymorphisms significantly associated with lower SLE risk (OR<1.00), while the remaining 27 were positively associated with SLE risk (OR>1.00). All the included studies reported associations with various SLE phenotypes. The top three leading phenotypes were lupus nephritis/renal disorder, lupus arthritis and lupus rashes which were described in 19 studies. This was followed by photosensitivity, hematologic disorders, and vasculitis (two studies each), serositis (one study) and oral ulcers (one study).

3.3 Study Quality Assessment

Nine studies[9,15,16,20,22,23,24,25,27] were classified as having a high methodological quality (8-10 stars) while the other 13 studies[8,10,11,12,13,14,17,18,19,21,26,28,29] reported moderate methodological quality (5-7 stars). In selection, it is obvious in most primary articles that case groups were selected upon self-reports or independent validation by several rheumatologists using the defined ACR or SLICC classification criteria. Besides, the reported cases were selected randomly in a consecutive time with lucid description. For controls, it was reported in most articles that controls were recruited from the same area as cases with a clear endpoint. In comparability, most authors clearly controlled the confounders such as age and gender, either in the study design, analysis, or both. The authors also claimed to be blinded by the detailed information of case and controls while performing genotyping and similar techniques used to genotype both cases and controls. In fact, there is a lack of clarity on the success rate of genotyping for both groups in most primary articles. This is crucial to be included as a high rate of more than 95% will provide higher inclination towards success genotyping and can eliminate potential biases.[12,20,23]

3.4 Genotype-Clinical Outcome Associations

Genetic polymorphisms associated with SLE were implicated in the association with clinical manifestations. Table II shows the details of study characteristics. The most reported clinical features were renal, musculoskeletal, and cutaneous involvements.

We further analyzed the implication of SLE-associated loci with the key pathways (Immune system, signal transduction and gene expression) that play role in the development of SLE autoimmunity (Figure 2). A total of 12 loci were linked with immune system, and 4 loci were linked with signal transduction and gene expression.

DISCUSSION

4.1 Exclusion Criteria for Literature Searching

Limits were applied because we intended only to report on the SNPs replicated in all Asian SLE studies since the inception of GWAS of SLE in Asia that was published in late 2009.[30] This was because prior studies before SLE GWAS were criticized for producing high rates of false positives which can bias in the genetic association of a particular or biologically known variant.

4.2 Synthesis of Research Findings

From the preliminary synthesis, rs1234315 in *TNFSF4* may be the most potential biomarkers to elucidate the genotype-phenotype association in Asian predominantly in East Asia. In fact, rs1234315 demonstrated genome-wide significance ($P<5x10^{-8}$) to both SLE susceptibility and musculoskeletal disorders is of a great implication for the reporting of genotype-phenotype association for SLE in Asia. Rs1234315 lies in a region about 2 kb distant from the 5'UTR of the *TNFSF4* gene which encodes for OX40L protein, a type II transmembrane protein expressed on several immune cells such as B and T lymphocytes. Increased OX40L-OX40 receptor binding would lead to abnormal signaling for the activation of cytokines and contribute to high plasma cell development in SLE. Of late, the genetic association of rs1234315 with SLE was only found in Chinese population with individuals harboring T risk allele were seen higher in SLE patients (51.2%) compared to healthy controls, according to Zhang and colleagues (32.5%).[17] Likewise, a subgroup analysis by ethnicity was found significant in Asian patients (P<0.01, OR=1.39, 95% CI= 1.32–1.46) but not in European (P=0.06, OR=0.84, 95% CI= 0.71-1.00) with different direction of genetic risk score.[31] A similar evidence was also shown in a meta-analysis study in which T allele of rs1234315 was significantly related to SLE susceptibility in Asian population (P<0.001, OR=1.39, 95% CI=1.33–1.46).[32] These two evidences have emphasized on the substantial difference between SLE genetics between Asian and Caucasian which remarks the

Table II: Genotype-phenotype Association in Study Characteristics

First Author (Year)	Country	Ethnics	Disease	Sample Size (Mean Age)		Associated Single Nucleotide Polymorphism (SNP)	Minor allele frequencies (MAF) (%)			Genetic associations			
				Case	Controls		Allele	Case	Controls	OR	95% CI	P-Value	Gene
Zhu, 2014[8]	China	Chinese	SLE	741 (37.87± 11.05 years)	731 (34.38± 12.42 years)	rs7396562 (C/T)	T	59.9	53.1	1.32	1.14-1.53	$1x10^{-3}$	Single immunoglobulin IL-1-related receptor *(SIGIRR)*
Liu, 2015[9]	China	Chinese	SLE/ LN	792 (38.37± 12.24 years)	777 (34.06 ± 11.28 years)	rs3788013 (C/A)	C	70	65.1	1.26	1.08-1.46	$3x10^{-3}$	Ubiquitin associated, central Src-homology 3 *(UBASH3A)*
Zhang, 2017[10]	China	Northern Han Chinese	SLE/ LN	500 (31.9 ± 11.2 years)	500 (40.0 ± 8.6 years)	rs1456896 (A/G)	A	25.45	33.17	0.69	0.52-0.91	$9.32x10^{-3}$	*IKAROS* family of zinc finger1 *(IKZF1)*
Kawasaki, 2010[11]	Japan	Japanese	SLE	364 (42.8 ± 13.9 years)	513 (34.1 ± 9.9 years)	rs7708392 (G/C)	C	76.5	23.5	1.40	1.13-1.74	$2x10^{-3}$	*TNFAIP3* interacting protein 1 *(TNIP1)* and TNF alpha-induced protein 3, *(TNFAIP3)*
Zhou, 2015[12]	China	Chinese	SLE	500 (32.06± 11.5 years)	900 (31.56± 8.4 years)	rs3093024 (A/G)	A	42.2	39.9	1.10	1.02–1.20	$1.57x10^{-2}$	C-C Motif Chemokine Receptor 6 *(CCR6)*
Yang, 2011[13]	Hong Kong	Chinese	SLE	612 (N/A)	1160 (N/A)	rs7329174 (A/G)	G	28.3	21.9	1.41	1.22–1.63	$7.18x10^{-6}$	E74-Like Factor 1 *(ELF1)*
Yu, 2010[14]	Taiwan	Taiwan Han Chinese	SLE	138 (20.5 ± 10.9 years)	138 (N/A)	rs2243250 (T/C)	C	24.5	16.7	1,65	1.06-2.56	$3x10^{-2}$	Interleukin-4 *(IL-4)*
						rs2070874 (T/C)	C	24.3	17.0	1.58	1.02-2.46	$4x10^{-2}$	
						rs2243291 (C/G)	G	25.9	17.2	1.73	1.12-2.68	$1x10^{-2}$	
Wen, 2017[15]	China	Han Chinese	SLE	1047 (34.02 ± ± 11.53 years)	1205 (34.75 ± 12.97 years)	rs7726414 (C/T)	T	9.23	6.78	6.78	1.16-1.30	***3.03x10**$^{-12}$	Intergenic of Transcription factor 7 *(TCF7)*
						rs244689 (A/G)	A	37.07	31.48	1.23	1.11-1.36	$6.75x10^{-5}$	Protein Phosphatase 2 Catalytic Subunit Alpha *(PPP2CA)*
Wang, 2015[16]	China	Han Chinese	SLE	2208 (33.58 years)	2208 (31.16 years)	rs4649038 (T/C)	T	42	39	1.10	1.01-1.20	$2.93x10^{-2}$	Runt-related transcription factor 1 *(RUNX3)*
Zhang, 2011[17]	China	Han Chinese	SLE	1344 (31.8 years)	4315 (31.8 years)	rs1234315 (C/T)	T	51.2	39.5	1.45	1.34-1.59	$*4.17x10^{-17}$	Tumour necrosis factor superfamily 4 *(TNFSF4)*
						rs1234315 (C/T)							
Li, 2012[18]	Hong Kong	Hong Kong Chinese	SLE	612 (N/A)	2193 (N/A)	rs704853 (A/C)	A	16.6	21.8	0.73	0.62-0.86	$6.94x10^{-5}$	CD247 *(CD3Z, TCRZ)*
Zhang, 2018[19]	China	Han Chinese	SLE	730 (36.06± 13.16 years)	779 (36.66± 12.74 years)	rs10491322 (A/G)	G	5.27	3.34	1.61	1.13–2.31	$9x10^{-3}$	Protein phosphatase 2CA *(PPP2CA)*
						rs7704116 (C/T)	T	7.33	4.75	1.59	1.17–2.15	$3x10^{-3}$	

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First Author (Year)	Country	Ethnics	Disease	Sample Size (Mean Age)		Associated Single Nucleotide Polymorphism (SNP)	Minor allele frequencies (MAF) (%)			Genetic associations			
				Case	Controls		Allele	Case	Controls	OR	95% CI	P-Value	Gene
Joo, 2013 [20]	Korea	Korean	SLE	601 (32.36 years)	984 (37.36 years)	rs3765456 (G/A)	A	N/A	N/A	1.34	1.09-1.66	$3x10^{-2}$	*CD40*
Li, 2018 [21]	China	Han Chinese	SLE	584 (37.14± 12.35 Years)	628 (36.63± 11.27 years)	rs1143679 (G/A)	A	0.94	0.24	3.97	1.11-14.28	$2x10^{-2}$	*CD11b/ITGAM*
Umare, 2019 [22]	India	Indian	SLE	200 (28.0± 10.0 years)	201 (29.2± 11 years)	IL-18 (-1297 T/C) (rs360719)	C	44.0	30.6	1.80	1.30-2.40	$2x10^{-3}$ (P corrected)	Interleukin-18 *(IL-18)*
Yang, 2017 [23]	China	Han Chinese	SLE	1470 (37.63 ± 14.54 years)	2283 (36.84 ± 14.67 years)	rs1042522 (G/C)	G	58.10	55.12	0.89	0.81-0.97	$1x10^{-2}$	Tumour protein p53 *(Tp53)*
Umare, 2017 [24]	India	Indian	SLE	200 (28 ± 10 years)	201(29.2 ± 11 years)	–2518 A/G (rs1024611)	G	35.0	22.1	1.9	1.30-3.00	$2.3x10^{-3}$	Monocyte Chemoattractant Protein-1 *(MCP-1)*
Cai, 2010 [25]	China	Han Chinese	SLE	1420 (30.44 years)	4461 (34.44 years)	rs2230926 (T/G)	G	7.2	4.5	1.65	1.39-1.99	$2.03x10^{-8}$	*TNFAIP3*
Chang, 2011 [26]	Taiwan	Taiwanese	SLE	N/A	N/A	c.1567 C/T	C	39.3	28.7	1.60	1.17-2.20	$3x10^{-3}$	Lumican *(LUM)*
Chen, 2020 [29]	Taiwan	Taiwanese	SLE	95 (33.7± 12.5 years)	95 (36.1± 14.3 years)	rs2844455 (G/A)	A	40.5	28.4	1.72	1.12-2.63	$1.3x10^{-2}$	Complement 2 *(C2)*
Baek, 2019 [28]	Korea	Korean	SLE	280 (35.7± 7.8 years)	260 (28.1± 7.4 years)	rs2271715 (C/T)	C	53.0	58.7	1.64	1.01-2.66	$3.6x10^{-2}$	Milk fat globule epidermal growth factor 8 *(MFGE8)*
						rs3743388 (G/C)	G	52.7	60.8	1.71	1.05-2.80		
Umare, 2020 [29]	India	Indian	SLE	200 (28± 10 years)	201 (29.2± 11 years)	rs1800896 (A/G)	G	28.0	19.2	1.60	1.18-2.28	$1.1x10^{-2}$	Interleukin 10 *(IL-10)*
						rs1800871 (C/T)	C	47.5	39.8	1.40	1.03-1.81	$9.8x10^{-2}$	
						rs1800872 (C/A)	A	46.8	33.2	1.70	1.30-2.30	$1x10^{-3}$	

SLE, Systemic lupus erythematosus; LN, Lupus nephritis; OR, Odd-ratio; CI, Confidence Interval; N/A, Not available
*P-Value indicates significance if the value is less than 0.05

Table II: Genotype-phenotype Association in Study Characteristics

SLE feature	Description	Gene	Variant	Odds ratio	Population	References	PValue
Cutaneous	Malar rash	*SIGIRR*	rs7396562	1.36	Chinese	[8,16,25]	$5x10^{-2}$
		RUNX3	rs4649038	1.18	Han Chinese		$9x10^{-4}$
		TNIP3	rs2230926	1.58	Chinese		$3x10^{-5}$
Cutaneous	Photo sensitivity	*SIGIRR*	rs7396562	2.38	Chinese	[8,26,27]	$<1x10^{-3}$
		LUM	c.1567 C/T	2.05	Taiwanese		$3x10^{-2}$
		C2	rs2844455	2.00	Taiwanese		$5x10^{-2}$
Cutaneous	Discoid rash	*p53*	rs1042522	1.25	Chinese	[23]	$4x10^{-2}$
Oral ulcer	N/A	*CD247*	rs704853	0.78	Hong Kong	[18]	$5x10^{-2}$
Serositis		*IL-10*	rs1800896	2.7	India	[29]	$2x10^{-2}$
Renal	Lupus nephritis	*IKZF1*	rs1456896	0.80	Chinese	[10-14,16,20-22,24-26]	$2x10^{-3}$
		TNIP3	rs7708392	1.60	Japanese		$2x10^{-3}$
		CCR6	rs3093024	1.18	Chinese		$4x10^{-2}$
		ELF-1	rs7329174	1.27	Chinese		$2x10^{-2}$
		IL-4	rs2243250	0.38	Taiwanese		$4x10^{-2}$
		IL-4	rs2070874	0.31	Taiwanese		$2x10^{-2}$
		IL-4	rs2243291	0.36	Taiwanese		$4x10^{-2}$
		RUNX3	rs4649038	1.16	Han Chinese		$5x10^{-3}$
		CD40	rs3765456	0.47	Korean		$2x10^{-2}$
		Cd11b	rs1143679	N/A	Han Chinese		$5x10^{-2}$ ($P_{corrected}$)
		IL-18	rs360719	2.60	Indian		$2x10^{-2}$ ($P_{corrected}$)
		MCP-1	–2518 A/G	N/A	Indian		$1x10^{-4}$
		TNIP3	rs2230926	1.77	Han Chinese		$5x10^{-5}$
		MFGE8	rs2271715	N/A	Korean		$1x10^{-3}$
		MFGE8	rs3743388	N/A	Korean		$1x10^{-3}$
Musculo skeletal	Inflammatory Arthritis	*RUNX3*	rs4649038	1.13	Han Chinese	[16,17,19,20,26]	$9x10^{-3}$
		TNFSF4	rs1234315	1.37	Han Chinese		$**3x10^{-9}$
		PPP2CA	rs10491322	N/A	Han Chinese		$3x10^{-2}$
		CD40	rs3765456	2.46	Korean		$1x10^{-2}$($P_{corrected}$)
		TNIP3	rs2230926	1.77	Han Chinese		$**7x10^{-8}$
		LUM	c.1567 C/T	2.38	Taiwanese		$6.4x10^{-3}$
Vasculitis	N/A	*UBASH3A*	rs3788013	N/A	Chinese	[9,15]	$1x10^{-2}$
		Intergenic region between *TCF7* and *PPP2CA*	rs7726414 and rs244689	1.26	Han Chinese		$4x10^{-2}$
Hematologic disorder	N/A	*TNFAIP3*	rs2230926	1.57	Han Chinese	[18,25]	$1x10^{-5}$
		CD247	rs704853	0.57	Hong Kong		$3x10^{-2}$

N/A, Not Available
**Genome-wide significant variant P<5x10-8

heterogeneity of SLE in terms of ethnic distribution. However, there is no functional validation to attest the implication of this variant in the pathogenesis of SLE which could serve as a gap for future studies. In addition, rs1234315 C/T predisposed high risk for arthritis in SLE patients ($P=3.35x10^{-9}$, OR=1.37, 95% CI= 1.23–1.51) might be the first demonstrated genotype-phenotype association of SLE in Asia.

Technically, all selected variants were associated with SLE susceptibility and clinical manifestations, regardless of the level of significance of p-value. Besides, genetic heterogeneity of SLE across different populations might give various risk impacts to disease susceptibility.[5] Some of those variants have also been demonstrated in non-Asian population. Other than rs1234315, risk allele A from rs1143679 *(Cd11b)* (OR=3.97) as studied by Li and colleagues had demonstrated to have similar effect sizes ranging from 1.65-1.8 and shared minor allele frequencies from several Non-Asian populations such as Brazilian and Central Mexican.[33,34] Similarly, in rs360719 *(IL-18)* (OR=1.80), the risk allele C has rendered a high risk for SLE with a range of effect sizes (OR=1.18-1.558) in several studies conducted across various European populations such as Spain, Italy, Argentina, and Polish.[35] However, risk allele frequencies of C allele was found higher in Asian SLE patients (the present study which has a frequency of 0.44) compared to the European SLE patients (0.2-0.35). However, all studies have high sample sizes which could indicate that the statistical association might be true according to the allele frequencies. The G allele from rs2230926 (TNFAIP3) (OR=1.65) as studied by Cai and colleagues has been consistently associated with high-risk for SLE in the latest genetics study in European SLE (OR=1.91).[25,36] In fact, a subgroup analysis from a meta-analysis study consisting of thousands of subjects has also demonstrated a similar OR in the minor G allele of rs2230926 between Caucasian (OR=1.675) and African (OR=1.324).[37] For rs1800896 *(IL10)* (OR=1.60), the minor G allele in our synthesis has also been associated in the dominant model of European Population (OR=1.375) but not in the African population.[38] Therefore, Asians have greater impact for SLE compared to Caucasians not just from the prevalence, socioeconomic status and clinical manifestations but also from genetic perspectives.

Another intriguing part of the data synthesis is that these 30 variants were significantly associated (P <0.05) with various clinical manifestations, of which 27 of them contributed to a higher risk (OR>1.00) and 3 of them have lower effects against these manifestations (OR<1.00). In fact, some of these variants such as rs2230926 *(TNFAIP3)*, rs4649038 *(RUNX3)* and rs3765456 *(CD40)* have rendered pleiotropic as they are

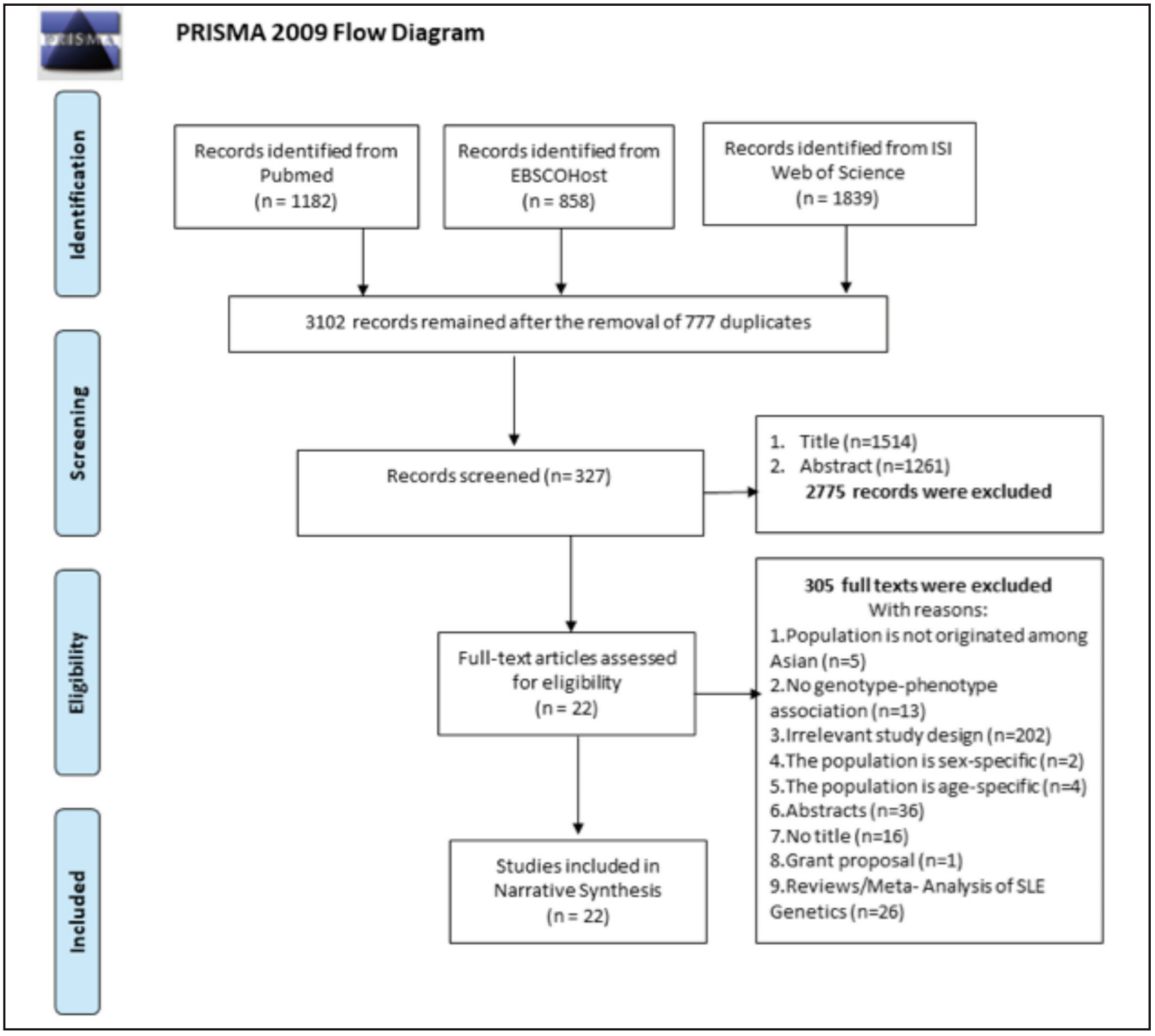

Fig. 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram.

associated with more than a manifestation. The pleiotropy of a variant comes from its ability to regulate the transcription of other genes, which is an important mediator in general biological functions. For example, rs2230926 demonstrated by Cai and colleagues shows higher risk for multiple manifestations including renal, musculoskeletal, malar rash and hematologic disorder.[25] Normally, *TNFAIP3* encoded into an A20 protein which is known as ubiquitin-editing enzyme and a negative regulator of the NF-κB signalling pathway including TNF and Toll-like receptors.[25] However, in SLE, changes in the rs2230926 T>G led to decrease of the ability of *TNFAIP3* to suppress A20 protein expression which results in autoimmunity throughout the constant stimulation of autoantibodies by NF-κB hyperactivation.

The most reported manifestation that was associated with SLE susceptibility genes is lupus nephritis (LN) that affected up to 40% of adults and 80% of children with SLE. LN was shown to be the major cause of morbidity and mortality of every population in the world. Most studies that interrogated SLE/LN associated genes, were also correlated with LN presentations such as high proteinuria in urine and presence of immune complexes upon renal biopsy. In terms of genetic risk of LN by ethnicity, few variants from the present data are in concordance with case-control studies of LN in other populations. For variant rs7708392, the genetic association of the minor allele C with high risk for LN in present data has been simultaneously found in almost every population.[39] In fact, variant rs1143679 in *Cd11b* has also been reported to be associated with high risk for renal disorder from several populations including Asians.[40] Therefore, most SLE-associated genes contributed a pivotal role in LN development, regardless of population types.

Fundamentally, the key pathways related to SLE are the immune system, signal transduction and gene expression.

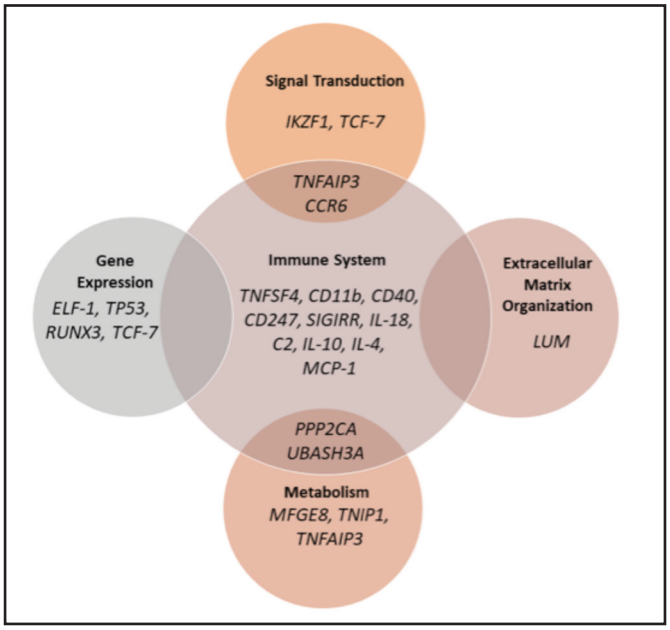

Fig. 2: Biological pathways of genes associated with SLE.

Determination of association between these variants with SLE pathogenesis is crucial to understand the key pathways leading to diversity in the clinical heterogeneity of SLE. The dramatic increase in the genetic information of SLE over the passing years has allowed the depth understanding of SLE related to the pathogenesis stemming from the aberrancies in the downstream signaling pathways which affect the normal immune response. The substantial pathways culminating in several autoimmune events such as continuous production of autoantibodies, higher inflammatory cytokine production, and impaired tolerance has been progressively delineating the mechanistic pathways of SLE pathogenesis in cellular function. In fact, suppression of these pathologic events might be new targets for SLE treatments. However, little or no information of these perspectives has yet to be translated into new therapeutic strategies.

4.3 Limitations of preliminary synthesis

At this point, many studies have identified genetic variants associated with SLE and organ manifestations. However, the association is spurious due to limitations such as lower sample sizes. Smaller sample size would be a major factor of GWAS failure as it would lead to a discovery of false-positive results. In fact, most studies do not apply a multiple testing correction on the statistical value which is extremely important to obtain higher confidence on the statistical outcome as it will eliminate the false discovery rate (FDR). However, most genotype-phenotype associations from the synthesis are inconsistent as some variants fall below genome-wide significance when associated with disease susceptibility, but they reached genome-wide significance when associated with clinical manifestations. Thus, these variants are not reliable as potential biomarkers for disease susceptibility. Furthermore, certain novel variants that were recently discovered, had augmented the difficulty to search for supporting evidence. Many reviews had attempted to conduct a meta-analysis on these novel variants but due to the lack of relevant evidence, it would not be feasible to obtain significant association for these novel variants due to lower sample sizes.

4.4 Strength of Systematic Review

Despite the above limitations, the preliminary synthesis has benefitted the main question in correspondence to the emphasis on associated variants with the disease susceptibility and organ manifestations that reached genome-wide significance threshold ($P<5x10^{-8}$) particularly rs1234315 in *TNFSF4*. Higher genetic risk load of rs1234315 in Asian compared to European has eventually answered why SLE is more prevalent in Asian compared to European despite both continental populations share the same loci across the genome. Although no multiple testing was conducted in this literature search, given the supporting evidences such as meta-analyses and difference allelic distribution between Caucasian and Asian, study by Zhang and colleagues already provided high quality as a potential marker of lupus in Asia.[17] In terms of the effect sizes in study by Zhang and colleagues, rs1234315 has a 1.45 times higher risk to develop SLE and 1.36 times higher risk to form arthritis, which confer modest effect sizes (OR<1.5) and account about 30% of the total genetic susceptibility to the disease.[17] This explains the missing heritability such as gene-gene and gene-environment interaction that might increase the polygenic prediction risk score of rs1234315 in SLE susceptibility, which potentially serves the gap for future study. However, other candidate gene markers may have contributed to a promising genotype-phenotype association of SLE as well, but well-designed parameters such as larger sample sizes and different subgroups should be employed to increase the significance of a study.

CONCLUSION

In summary, we found that *TNFSF4, CD11b, Cd40, CD247, SIGIRR, IL-18, C2, IL-10, IL-4, MCP-1, IKZF-1, TCF-7, PPP2CA,* and *UBASH3A* may contribute to the genotype-phenotype association in Asia, with rs1234315 in TNFSF4 as the highly potential risk biomarker in Asian lupus particularly musculoskeletal involvement. In terms of functional perspective, these genes have been implicated with various roles in the pathogenesis of SLE such as autoimmunity and altered signal transduction and gene expression signature which culminates in loss of tolerance and production of autoantibodies. This might entail an insight on future target therapies which can be tailored to the management of SLE in Asian populations. Our study may suggest that Asians have more severe risk for SLE compared to Caucasians in terms of genetics. However, there are still gaps of ongoing genetic studies of novel variants in Asia that should be replicated in non-Asian populations to ascertain the SLE heterogeneity across different populations. In fact, an effort to define the association of these variants in accordance with their functional implications may be required to propose new therapeutic strategies. Identification of linkage disequilibrium of associated variants that account for gene-gene interaction may as well be necessary to unfold the missing heritability of SLE, especially due to small contribution of risk prediction by certain variants.

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DECLARATION OF INTEREST

The authors declare that there is no competing interest.

AUTHOR CONTRIBUTIONS

Conceptualization, N.A.A.M. and S.C.T.; methodology, A.K.A.A.T. and S.C.T.; formal analysis, A.K.A.A.T.; investigation, A.K.A.A.T., N.A.A.M. and S.C.T.; resources, A.K.A.A.T. and S.C.T.; data curation, N.A.A.M. and S.C.T.; writing original draft preparation, A.K.A.A.T.; writing review and editing, N.A.A.M., E.A.A., S.C.T. and S.S.S.; visualization, A.K.A.A.T.; supervision, N.A.A.M., E.A.A., R.J. and S.S.S.; project administration, N.A.A.M., E.A.A., R.J. and S.S.S.; funding acquisition, S.S.S. All authors have read and agreed to the published version of the manuscript.

ETHICS STATEMENT

Not applicable.

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