Meta-analysis of genome-wide association study identifies FBN2 as a novel locus associated with Systemic Lupus Erythematosus in Thai population

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Research article

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Abstract

Background: Differences in the expression of variants across ethnic groups in the Systemic Lupus Erythematosus (SLE) patients have been well documented. However, the genetic architecture in the Thai population has not been thoroughly examined. In this study, we carried out genome-wide association study (GWAS) in the Thai population.

Methods: Two GWAS cohorts were independently collected and genotyped: discovery dataset (487 SLE cases and 1,606 healthy controls) and replication dataset (405 SLE cases and 1,590 unrelated-disease controls). Data were imputed to the density of the 1,000 Genomes Project Phase 3. Association studies were performed based on different genetic models, and pathway enrichment analysis was further examined. In addition, the performance of disease risk estimation for individuals in Thai GWAS was assessed based on the polygenic risk score (PRS) model trained by other Asian populations.

Results: Previous findings on SLE susceptible alleles were well replicated in the two GWAS. The SNPs on HLA-class II (rs9270970, A>G, OR=1.82, p-value = 3.61E-26), STAT4 (rs7582694, C>G, OR=1.57, p-value = 8.21E-16), GTF2I (rs73366469, A>G, OR=1.73, p-value = 2.42E-11) and FAM167A-BLK allele (rs13277113, A>G, OR=0.68, p-value = 1.58E-09) were significantly associated with SLE in Thai population. Meta-analysis of the two GWAS identified a novel locus at the FBN2 that was specifically associated with SLE in the Thai population (rs74989671, A>G, OR=1.54, p-value = 1.61E-08). Functional analysis showed that rs74989671 resided in a peak of H3K36me3 derived from CD14+ monocytes and H3K4me1 from T-lymphocytes. In addition, we showed that the PRS model trained from the Chinese population could be applied in individuals of Thai ancestry, with the area under the receiver-operator curve (AUC) achieving 0.76 for this predictor.

Conclusions: We demonstrated the genetic architecture of SLE in the Thai population and identified a novel locus associated with SLE. Also, our study suggested a potential use of the PRS model from the Chinese population to estimate the disease risk for individuals of Thai ancestry.

Background

The systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by loss of tolerance to self-antigens, inappropriate immune activation, and inflammation [1]. The severity is various depending on affected organs [2]. Genetic susceptibility has been widely accepted as one of the critical factors driving disease development [2]. Recently, the genetic architecture of SLE has been examined worldwide [3]. Using GWAS, more than 90 loci have been found associated with SLE across at least four ethnic groups, including Han Chinese, European, North America, and Africa [4, 5]. The strongest signal was identified at the HLA-class II allele, which replicated in all of the different populations [4]. These findings indicate critical biological mechanisms underlying the disease, which will be the candidate in further functional studies [6].

However, heterogeneity of disease between different ethnicities drives a question of whether genetic background in different ancestries could affect the clinical manifestations. It is known that Asian SLE patients have higher disease severity compared to Europeans [2]. However, only a few studies on SLE associations, that were based on candidate genes were performed in the Thai population [7-11]. In this study, we conducted GWAS using the SLE samples collected from two tertiary referral hospitals in Thailand. We aim to replicate known SLE-associated variants in the Thai population and identify novel SNPs associated with SLE.

Methods

Sample collection & Preparation

We calculated the power of our study by using an online tool called Genetic association study (GAS) Power Calculator [12]. With 800 cases and 1,600 controls at 5E-08 significant level, we obtained 0.934 expected power for the study. The EDTA blood samples from SLE patients (n=487) were collected at King Chulalongkorn Memorial Hospital as cases for the discovery phase. All procedures were approved by the ethical committee from the Faculty of Medicine, Chulalongkorn University (COA no.923/2017). For the replication cohort, the samples (n=405) were collected from the Rheumatology clinic, Ramathibodi hospital, with ethical approval from the Faculty of Medicine, Mahidol University (MURA no. 2015/731, EC no. 590223, Protocol-ID 12-58-12). All patients were carefully recruited regarding the criteria from the American College of Rheumatology (ACR) [13]. Patients’ demographic data from both datasets have been summarized in Table 1. Healthy controls (n=1,606) and unrelated disease controls including breast cancer,
periodontitis, tuberculosis, drug-induced liver injury, epileptic encephalopathy, dengue haemorrhagic fever, thalassemia, and cardiomyopathy (n=1,590), data were provided from the Department of Medical Science, Ministry of Public Health, Thailand.

**DNA extraction**

Buffy coats were extracted using the QIAGEN® EZ1® DNA blood kit (QIAGEN GmbH, Hilden, Germany). We used 200 μL of a buffy coat as recommended by the manufacturer's instruction. Buffy coat samples were transferred into tube or sample cartridge for EZ1 Advanced XL (QIAGEN GmbH, Hilden, Germany) and extracted using EZ1® Advanced XL DNA Buffy coat protocol. From this protocol, DNA was eluted at 200 ul. DNA was diluted and quantitated using Qubit™ dsDNA BR Assay Kit according to manufacturing protocol (Invitrogen, Thermo Fisher Scientific, MA, USA).

**Genotyping and quality control**

Genotyping was performed using Infinium Asian Screening Array-24 v1.0 BeadChip with 659,184 SNPs (Illumina, San Diego, CA, USA) at the Department of Medical Sciences (DMSC, Ministry of Public Health, Thailand) based on the protocol recommended by the manufacturer. The Genome Studio data analysis software v2011.1 (Illumina, San Diego, CA, USA) was used for calling genotypes. Samples and SNP markers were tested for quality control (QC) using PLINK genomic analysis software (v1.90b5.4) [14]. Individuals with autosomal genotype call rate ≤ 0.98, gender inconsistency based on heterozygosity rate of X chromosome (maleTh = 0.8, femaleTh = 0.2) and genome-wide estimates of identity-by-descent (pihat) ≥ 0.185 (3rd generation) were excluded from analysis. SNPs with more than 5% missing genotyping rate or significant deviation of Hardy-Weinberg equilibrium (p-value ≤ 1 x 10^{-8}) were also removed. After quality control (QC), we obtained a dataset of 2,041 individuals with 421,909 variants for the discovery phase and 1,955 individuals with 446,139 variants for replication. The flow diagram of the analysis process was shown in Figure 1A.

**GWAS data imputation**

Pre-phasing was performed using SHAPEIT [15]. After that, genotype data for individuals was imputed to the density of the 1,000 Genomes Project Phase 3 reference using IMPUTE2 [16]. After all the QC processing, 6,657,806 were left for further analysis. The processed data were publicly available at http://2anp.2.vu/GWAS_SLE_Thailand.

**Association study, meta-analysis, and statistical analysis**

The association studies were conducted by using SNPTEST [17], and the factored spectrally transformed linear mixed models (FaST-LMM v.0.2.32) program [18]. The results from FaST-LMM were analysed and visualized by RStudio to obtain genomic inflation factor (λ), quantile-quantile plot, and Manhattan plot [19]. The SNPs with p-value ≤ 1x10^{-5} were plotted to obtain the regional plot by using LocusZoom [20]. Haplotype block and linkage disequilibrium structure were analysed by Haploview software version 4.2 [21]. The characterized SLE susceptible loci were downloaded from a previous study [22] and GWAS catalogue (The NHGRI-EBI catalogue of published genome-wide association studies). Meta-analysis was studied based on the inverse variant strategy in the METAL program [23]. The genetic inheritance pattern was calculated from the frequency of different genotyping on risk alleles using R-Bioconductor. Simultaneously, functional annotation was predicted by using SNP-nexus, which applied data from the Reactome database [24]. The histone markers and transcription factor binding sites were predicted from an online tool called HaploReg V4.1 [25].

**Polygenic risk score calculation**

Lassosum [26] was used to calculated PRS for individuals. The summary statistics for SLE association in East Asians [27], involving 2,618 cases and 7,446 controls with Chinese ancestry, were used to train the model. The area under the ROC curve (AUC) was calculated using R package pROC [28].

**Results**

**Known SLE associations found in the Thai population**
In the discovery dataset, the association studies were initially performed using healthy controls (n = 1,606) and SLE patients (n = 487) collected from King Chulalongkorn Memorial Hospital. Regarding the result, we found that variants at the HLA class II regions were strongly associated with SLE (p-value < 5E-08). Similarly, GWAS from 405 SLE cases and 1,590 non-immune mediated disease controls found variants at the HLA class II regions reached the genome-wide significant threshold (p-value < 5E-08). Our findings were consistent with previous reports in other ethnic groups [29]. Inflation factors from both datasets were calculated as reported in Supplementary figure 1.

Subsequently, a meta-analysis of the two Thai GWAS was carried out, and we systematically examined associations across the 90 known SLE-associated loci, which were collected from the GWAS Catalogue (https://www.ebi.ac.uk/gwas/) and previous review articles [22]. Of these loci, the HLA-DQA1, HLA-DRB1, STAT4, FAM167A-BLK, and GTF2I loci have reached the genome-wide significant threshold (p-value < 5E-08; Figure 1B, Table 2) in Thai population, and the variants at the PROS1C1, NOTCH4, HCP5, C6orf10, TAP2, TNFSF4, RasGRP3, TERT, TNPO3-IRF5, CXCR5, GPR19, SLC15A4, and ITGAM loci showed suggestive evidence of associations with SLE (p-value < 5E-05, Supplementary Table 1). These loci have been found in several ancestries, including Han Chinese, Korean, North American, European, African, and Hispanic populations [30, 31].

We noticed that some of the previously characterized nonsynonymous polymorphisms also showed certain evidence of association (p-value < 0.05) in Thai population, such as rs11235604 (ATG16L2, R58W), rs13306575 (NCF2, R395W), rs1990760 (IFIH1, A946T), rs3734266 (UHRF1BP1, Q454L), rs2841280 (PLD4, E27Q) and rs2230926 (TNFAIP3, F127S). Details of these associations were summarized in Table 3. All significant variants were calculated for Hardy-Weinberg equilibrium, as reported in Supplementary Table 2.

Identification of novel loci associated with SLE

Excluding the variants at the known SLE-associated loci, we discovered a novel variant on FNB2 (rs74989671, OR=1.54, p-value=1.61E-08) specifically associated with SLE in Thai population (Figure 1B and Figure 2A, Table 2) when comparing the association in Europeans (OR=0.998, p-value=0.979) and in Chinese populations (OR=0.982, p-value=0.692) [27]. Further analyses based on different genetic inheritance models suggested that the disease risk was associated with the copy number of risk alleles that the individuals carried (additive model) (Table 4). Three SNPs on FBN2 loci (rs74989671, rs3598344, rs6595836) showed linkage disequilibrium (LD r^2 = 0.82) (Figure 2B, Supplementary Table 1). Of these variants, rs74989671 was found to locate within the peak of H3K36me3 derived from CD14 positive monocytes and H3K4me1 (associated with active enhancers) derived from the primary T cells (Figure 2C).

In addition, we found variants at the ATP6V1B1, MIR4472-2, MYO5C, ADCY5, and DGKG, showing suggestive evidence of associations with SLE in Thai population (p-value < 5E-05) (Supplementary Figure 2, Supplementary Table 1). Though these polymorphisms are likely to associate with Thai SLE patients, an independent GWAS dataset of SLE patients with Thai background is needed for further validation.

In silico functional annotation of SLE-associated variants in Thai population

To understand the biological meaning underlying the SLE-associated loci in the Thai population, we performed the pathway analysis using the SNP-nexus program [24]. Variants with p-value < 5E-05 were involved in this study. Notably, we found that 50% of all-variants were located within the coding region, by which 10% is non-synonymous polymorphisms. Pathway analysis results revealed that SLE-associated variants were highly enriched in the regulation of interferon signalling, PD-1 signalling, MHC-class II antigen presentation, TCR/BCR signalling, cytokine signalling, TNF-signalling, NOTCH4 signalling, calcium-activated potassium channels, and cell-cell junction organization pathways. Furthermore, we found that extracellular matrix organization was significant in our results (Figure 3). It indicated that Thai SLE patients might have a higher risk of fibrosis-associated inflammation.

Polygenic risk score prediction for the individuals

To apply the GWAS result to predict the Thai SLE outcome, we also tested the hypothesis of whether the PRS models trained by individuals with Chinese ancestry could be applied for Thai SLE patients. We calculated PRS for individuals in the Thai GWAS, based on the training data from the Chinese population (2,618 cases and 7,446 controls) [27]. Significantly, the PRS for SLE cases were higher than controls (mean difference = 0.89; p-value = 2.2E-16; Figure 4A), and the area under the receiver-operator curve
patients. Although we did not recognize polymorphisms on chromosome 11q23.3 (rs11603023 on association with Japanese and Korean background [59]. Thus, this implies the specificity of these variants to the Thai SLE background was a pivotal factor driving a severe LN among Thai SLE patients. Taken together, these pieces of evidence could justify the link between genetic variants and clinical involvement in Thai SLE patients.

Our analysis found several LN-susceptible loci such as IRF5 [37, 38], ITGAM [9, 39], IKZF1 [40], and TNFSF4 [41]. While IKZF1 is a co-transcription factor with STAT4 mediated Th1 lymphocyte differentiation and interferon pathways [42], the TNFSF4 locus, also called OX40L, encoded for the TNF superfamily ligand, which actively stimulates CD4+ T-cells activation [41]. Study in the Finnish and Swedish SLE patients found the correlation of ITGAM with cutaneous discoid lupus erythematosus (DLE) and LN as well as Ro/SSA auto-antibody positive [43]. Not only LN, but we also found several loci that have been verified in the specific sub-phenotype of SLE patients. For example, our result found a variant on ETS1, which previously showed association with juvenile SLE, as well as a variant on RasGRP3, which was involved in malar rash or discoid rash [40]. The recent SLE susceptible loci identified in the cardiac manifestation of neonatal lupus, NOTCH4, was found in our results [44].

Note that we found some of the known SNPs which are nonsynonymous variants such as NCF2 [45], IFIH1 [46], TNFAIP3 [47], UHRF1BP1[48], ATG16L2 [49], and PLD4 [50]. A few pieces of evidence have revealed the impact of those variants on various pathways including, neutrophil extracellular traps (NETs) formation [51], sensor molecule to detect viral genome inside cells [52], a negative regulator for NF-kB transcription factors [53], a negative regulator of cell growth [54]. These pathways resembled with our functional enrichment pathways analysis. Interestingly, our results found extracellular matrix organization (ECM) pathways associated with Thai SLE patients. Previously, single-cell transcriptome analysis in non-responder LN patients highlighted the upregulated genes in the ECM pathway correlated with treatment failure [55]. The ECM reflected the active fibrotic process, which was a marker of poor prognosis LN [56]. Remarkably, the prevalence of severe LN was high in the South East Asian ethnic included Thai [57]. Regards to our SLE patients' demographic data, we found that the frequency of clinical phenotype was roughly similar to other ethnic [58]. The LN was the highest abundance found among Thai SLE patients. Thus, our results supported that genetic background was a pivotal factor driving a severe LN among Thai SLE patients. Taken together, these pieces of evidence could justify the link between genetic variants and clinical involvement in Thai SLE patients.

The study of known SNPs showed most of the polymorphisms resembled with previous reports in Thais, such as ARID5B, TNFSF4, BANK1, TNFAIP3, CXCR5 SLC15A, ITGAM, WDFY4, ETS1, and BLK [7-11]. It confirmed that our analysis processes were reliable. Noticeably, The allele frequency of ITGAM was higher among Thai SLE when compared to Chinese Hong Kong [9], but has no association with Japanese and Korean background [59]. Thus, this implies the specificity of these variants to the Thai SLE patients. Although we did not recognize polymorphisms on chromosome 11q23.3 (rs11603023 on PHLD1 and rs638893 on
DDX6), which has been identified in the Thais’ SLE, our meta-analysis enhanced signal from rs10845606 on GPR19 allele which does not correlate with Thai SLE patients previously [8].

It is noteworthy that meta-analysis in the Thai population discovered novel SLE susceptible variants on FBN2. The FBN2 allele is located on a chromosome 5 encoded protein called fibrillin-2 [60]. Fibrillins-2 is one of the glycoprotein components incorporated extracellularly on microfibrils and is essential in bone, muscle, and extracellular matrix formation [61]. It is well known that mutation of FBN2 leads to dominant heritable connective tissue disorders [62]. Importantly, a recent review article has gained insight on fibrillin-2 as a critical mediator that binds to transforming growth factor-beta (TGF-β) during extracellular matrix formation [63]. The TLR9/TGF-β1/PDGF-β pathway was excessively activated in peripheral mononuclear cells isolated from LN patients [64]. Besides, the upregulation of FBN2 correlated with fibrosis prevalence in the spontaneous LN developed mouse model (SWR X NZB1 F1) [65]. Although the function of FBN2 in SLE is unclear, collective evidence led us to hypothesize that this variant might drive either fibrosis-associated inflammation or inflammatory induction during disease pathogenesis. Due to whole-genome sequencing data in the Thai population is lacking, further study using FBN2 target sequencing, whole-genome sequencing, and variant functional characterization in a large cohort is needed. This knowledge could be useful to identify rare coding variants and genetic propensity eliciting SLE pathogenesis in Thais.

Note that some of the variants were previously characterized in other autoimmune diseases, including rheumatoid arthritis and primary Sjögren Syndrome (pSS). It, therefore, indicates the sharing of underlying genetic factors between autoimmune disease. However, predisposing factors which could affect clinical manifestation driving different autoimmune disease outcome has not been elucidated yet. Recently, the GRS (genetic risk score) has been widely adopted to predict disease outcomes from genetic variants [66]. The previous studies in SLE showed that overall mortality was higher in the striking GRS SLE patients; also, the high cumulative genetic risk could predict the specific organ damages such as proliferative nephritis and cardiovascular disease [67]. Our study showed a high sensitivity for using polygenic risk scored as a marker for SLE disease development in the Thai population. It is exciting for further study to calculate the genetics risk score and specific clinical manifestation among Thai SLE patients.

**Conclusions**

In conclusion, our study reported susceptible loci of SLE patients in Thai ancestry, which were variants on the HLA class II allele, STAT4, GTF2I, and BLK. Additionally, we confirmed those variants which had been reported previously in the Thai populations, which were ARID5B, TNFSF4, BANK1, TNFAIP3, CXCR5 SLC15A, ITGAM, WDFY4, and ETS1. Interestingly, we identified novel variants associated with the Thai SLE patients, which were on the FNB2 allele. Summary loci associated with the Thai SLE were seen in Figure 4B. Functional annotation analysis highlighted extracellular matrix organization pathways specific to the Thai population. The PRS using GWAS data is useful for SLE prediction with sensitivity and specificity of more than 70%. Further whole-genome sequencing study with a large sample size might help to validate our results. Finally, our finding provides the necessary genetic background susceptible to SLE disease, expanding the number of molecular targets for treatment options.

**Abbreviations**

GWAS  
Genome-wide association study  
SLE  
Systemic lupus erythematosus  
SNP  
Single nucleotide polymorphism  
HLA  
Human leukocyte antigen  
MHC  
Major Histocompatibility  
CHR  
Chromosome
MAF
Minor allele frequency
OR
Odds ratio
CI
Confidence interval
bp
Base pair
BCR
B cell receptor
TCR
T cell receptor
IL
interleukin
PD
Program cell death
MDA
Melanoma differentiation-associated gene 5

Declarations

Ethics and approval and consent to participate
All the procedures were followed in compliance with the principles of the Declaration of Helsinki, and informed consent was obtained from all participants. The study and the consent procedures were reviewed and approved by the local institutional review board including the ethical committee from the Faculty of Medicine, Chulalongkorn University (COA no.923/2017), and the Faculty of Medicine, Mahidol University (MURA no. 2015/731, EC no. 590223, Protocol-ID 12-58-12).

Consent for publication
Not applicable

Availability of data and materials
The complete results from the two Thai GWAS datasets and the GWAS meta-analysis are publicly available for download at http://2anp.2.vu/GWAS_SLE_Thailand.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
NH, PP, and SM conceived the study. WYF and WW performed genetic data imputation. PT CT and PK performed the statistical analysis and function annotation with all figures. NH, PP, JW, SM, DC, and PR provided Thai SLE samples. TS, TC, SK, and NS
carried out DNA extraction and genotyping. PT, CT, WYF, and NH wrote the first draft of the manuscript. All authors contributed to the revision of the manuscript and approved the final manuscript.

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**Tables**

**Table 1** SLE patients’ characteristics of both observatory and replication datasets
### Patients’ characteristics

| Clinical cases | Observatory cohort n = 455 | Replication cohort n = 371 |
|----------------|---------------------------|---------------------------|
|                | a (%)                     | n (%)                     |

#### Ages of onset (mean ± SD)

- **Observatory cohort**: 30.38 ± 13.68
- **Replication cohort**: 30.39 ± 11.43

#### Sex

|                | Observatory cohort | Replication cohort |
|----------------|--------------------|--------------------|
| Female         | 425 (93.41%)       | 337 (90.84%)       |
| Male           | 26 (5.71%)         | 27 (7.28%)         |

#### Clinical aspects

|                                | Observatory cohort | Replication cohort |
|--------------------------------|--------------------|--------------------|
| Hematologic disorders          | 243 (53.41%)       | 136 (36.66%)       |
| Neurological disorders         | 62 (13.63%)        | 33 (8.89%)         |
| Ulcer                          | 115 (25.27%)       | 52 (14.02%)        |
| Discoid rash                   | 161 (35.38%)       | 49 (13.21%)        |
| Malar rash                     | 142 (31.21%)       | 82 (22%)           |
| Arthritis                      | 133 (29.23%)       | 148 (39.89%)       |
| Renal disorders                | 284 (62.42%)       | 149 (40.16%)       |
| ANA                            | 350 (76.92%)       | 214 (57.68%)       |

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### Table 2 List of significant variants at individual locus from the meta-analysis

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The percentages of unknown clinical data (n/a) in the observatory dataset are listed here.

- **Sex = 0.88%**, Hematologic disorder = 1.76%, Neurological disorder = 2.20%, Ulcer = 4.18%, Discoid rash = 3.96%, Malar rash = 5.71%, Arthritis = 4.18%, Renal disorders = 1.76%, and ANA = 9.89%

The percentages of unknown clinical data (n/a) in the replication dataset are listed here.

- **Sex = 0.00%**, Hematologic disorder = 36.93%, Neurological disorder = 37.2%, Ulcer = 37.4%, Discoid rash = 37.2%, Malar rash = 37.47%, Arthritis = 37.2%, Renal disorders = 37.74%, and ANA = 36.93%
| HAP  | dbSNP     | CHR | BP   | RA  | MAP affected | MAP unaffected | Locus upstream | Locus downstream | Discovery dataset | Replication dataset | Meta-analysis | \( P_{het} \) |
|------|------------|-----|------|-----|-------------|---------------|----------------|-----------------|-------------------|--------------------|---------------|-----------|
| q32.3| rs7574965  | 2   | 191099907 | A   | 0.47 | 0.36        | STAT4         | 1.54 (1.33-1.79) | 1.45E-08 | 1.61 (1.37-1.89) | 7.45E-09 | 1.57       | 8.21E-16 |
| q23.3| rs74989671 | 5   | 128396268 | G   | 0.16 | 0.11        | FBN2          | 1.52 (1.24-1.86) | 4.31E-05 | 1.58 (1.26-1.98) | 7.61E-05 | 1.54       | 1.61E-08 |
| p21.32| rs9270970 | 6   | 32605797  | G   | 0.42 | 0.30        | HLA-DRB1, HLA-DQA1 | 2.02 (1.73-2.35) | 8.71E-20 | 1.63 (1.39-1.93) | 4.15E-09 | 1.83       | 3.61E-07 |
| q11.23| rs73666469 | 7   | 74619286  | G   | 0.14 | 0.09        | RP5-1186P10.2, GTF2I | 1.8 (1.45-2.24) | 1.09E-07 | 1.65 (1.3-2.1)   | 2.84E-05 | 1.73       | 2.42E-11 |
| p23.1 | rs13277113 | 8   | 11491677  | G   | 0.26 | 0.32        | FAM167A, BLK   | 0.64 (0.54-0.76) | 2.16E-07 | 0.74 (0.61-0.88) | 8.76E-04 | 0.68       | 1.58E-09 |
| q24.33| rs1385374  | 12  | 128816149 | A   | 0.20 | 0.15        | SLC15A4       | 1.54 (1.28-1.85) | 5.76E-06 | 1.37 (1.12-1.69) | 2.36E-03 | 1.46       | 7.62E-08 |
| p11.2  | rs1143679 | 16  | 31265490  | A   | 0.07 | 0.03        | ITGAM         | 1.67 (1.21-2.28) | 1.39E-03 | 2.27 (1.6-3.23) | 2.55E-06 | 1.91       | 5.81E-08 |

Footnote:  
A Haplotype,  
B dbSNP from single nucleotides polymorphisms database (NCBI),  
C chromosome,  
D position,  
E risk alleles,  
F \( p \) value of heterogeneity

Table 3 List of known SLE susceptible SNPs in Thai SLE patients
| rs     | CHR | BP       | RA  | Locus     | Annotation      | MAF affected | MAF unaffected | OR | SE | P    |
|--------|-----|----------|-----|-----------|-----------------|--------------|---------------|----|----|------|
| rs5426045 | 1   | 161648724 | A   | FCGR2B    | intergenic      | 0.80         | 0.75          | 1.38 | 0.09 | 1.83E-04 |
| rs1234315 | 1   | 173203324 | A   | TNFSF4    | intergenic      | 0.53         | 0.46          | 1.27 | 0.07 | 1.02E-06 |
| rs205980 | 1    | 173191475 | T   | TNFSF4    | intergenic      | 0.27         | 0.22          | 1.26 | 0.08 | 2.37E-03 |
| rs46895541 | 1   | 196851932 | A   | ATP6V1G3  | intergenic      | 0.10         | 0.13          | 0.75 | 0.11 | 7.66E-03 |
| rs1416190 | 1   | 173616979 | T   | LOC100506023 | ncRNA_intronic | 0.59         | 0.56          | 1.18 | 0.07 | 1.55E-02 |
| rs13365775 | 1   | 183563302 | A   | NCF2      | nonsynonymous   | 0.11         | 0.08          | 1.48 | 0.09 | 1.73E-02 |
| rs13385731 | 2   | 33701890  | C   | RASGRP3   | intronic        | 0.13         | 0.17          | 0.70 | 0.09 | 1.71E-05 |
| rs6705628 | 2    | 74208362  | T   | DGUOK:AS1 | ncRNA_exonic    | 0.11         | 0.13          | 0.79 | 0.10 | 1.83E-02 |
| rs1990760 | 2    | 163124051 | I   | IFIH1     | missense       | 0.23         | 0.21          | 1.17 | 0.08 | 4.93E-02 |
| rs10936599 | 3   | 169492101 | T   | MYNN      | synonymous SNV  | 0.52         | 0.56          | 0.84 | 0.07 | 6.95E-03 |
| rs564799 | 3   | 159728987 | T   | IL12A     | ncRNA_intronic | 0.12         | 0.14          | 0.80 | 0.10 | 1.97E-02 |
| rs10028805 | 4  | 102737250 | A   | BANK1     | intronic       | 0.45         | 0.49          | 0.87 | 0.07 | 4.08E-02 |
| rs7726159 | 5   | 1282319   | A   | TERT      | intron         | 0.43         | 0.40          | 1.25 | 0.07 | 5.00E-05 |
| rs2736100 | 5   | 1286401   | C   | TERT      | intron         | 0.51         | 0.43          | 1.25 | 0.07 | 4.67E-05 |
| rs10036748 | 5  | 150458146 | T   | TNIP1     | intergenic     | 0.66         | 0.61          | 1.16 | 0.07 | 3.04E-02 |
| rs5431697 | 5   | 15879978  | C   | PTTG1: MIR146A | intergenic    | 0.07         | 0.09          | 0.77 | 0.13 | 3.36E-02 |
| rs546234 | 6   | 10658034  | T   | PRDM1: ATG5 | intergenic     | 0.67         | 0.72          | 0.81 | 0.07 | 2.21E-03 |
| rs220926 | 6   | 138166066 | G   | TNFAIP3  | missense       | 0.04         | 0.03          | 1.49 | 0.18 | 2.92E-02 |
| rs5748266 | 6   | 34823187  | C   | UHRF1BP1 | intronic       | 0.21         | 0.19          | 1.18 | 0.08 | 4.68E-02 |
| rs4726142 | 7   | 128573967 | A   | KCP: IRF5 | intergenic     | 0.19         | 0.13          | 1.61 | 0.09 | 1.34E-07 |
| rs729302 | 7   | 128568960 | C   | KCP: IRF5 | intergenic     | 0.25         | 0.30          | 0.77 | 0.07 | 3.32E-04 |
| rs12531718 | 7  | 128617466 | G   | IRF5: TNPO3 | interon       | 0.03         | 0.01          | 2.03 | 0.25 | 4.27E-03 |
| rs4917014 | 7   | 50305863  | G   | C7orf72: IKZF1 | intergenic    | 0.15         | 0.17          | 0.81 | 0.09 | 1.84E-02 |
| rs7097397 | 10  | 50025396 | A   | WDFY4    | missense       | 0.59         | 0.64          | 0.78 | 0.07 | 3.84E-04 |
| rs4948496 | 10  | 63805617  | C   | ARID5B   | intronic       | 0.66         | 0.62          | 1.17 | 0.07 | 2.19E-02 |
| rs1128334 | 11  | 128328959 | T   | ETS1     | UTR3           | 0.35         | 0.28          | 1.36 | 0.07 | 1.50E-05 |
| rs2732552 | 11  | 35084592 | C   | PDHX     | intergenic     | 0.78         | 0.75          | 1.18 | 0.08 | 3.04E-02 |
| rs11235604 | 11  | 72533536 | T   | ATG16L2  | missense       | 0.04         | 0.05          | 0.70 | 0.17 | 3.93E-02 |
| rs1385374 | 12  | 129300694 | T   | SLC15A4  | intronic       | 0.21         | 0.15          | 1.46 | 0.09 | 7.62E-08 |
| rs10845606 | 12  | 12834819  | A   | GPR19    | interonic      | 0.32         | 0.37          | 0.75 | 0.07 | 3.19E-06 |
| rs2612280 | 14  | 10539556  | C   | PLD4     | nonsynonymous  | 0.52         | 0.45          | 1.01 | 0.07 | 5.81E-08 |
| rs1143679 | 16  | 31276811 | A   | ITGAM    | missense       | 0.07         | 0.04          | 1.71 | 0.14 | 6.18E-08 |
| rs11860650 | 16  | 31315385 | A   | ITGAM    | intronic       | 0.09         | 0.07          | 1.74 | 0.10 | 4.64E-03 |
| rs1170426 | 16  | 68603798 | T   | ZFP90    | intronic       | 0.69         | 0.73          | 0.82 | 0.07 | 5.91E-03 |
| rs74644 | 22   | 21976393 | C   | UBE2L3   | UTR3           | 0.64         | 0.60          | 1.17 | 0.07 | 1.81E-02 |
| rs463426 | 22   | 21809185 | C   | HIC2: TMEM191C | intergenic    | 0.38         | 0.40          | 0.85 | 0.08 | 4.50E-02 |

Footnote: A dbSNP from single nucleotides polymorphisms database (NCBI), B chromosome, C position, D alleles

Table 4: Analyses based on different inheritance models on the P2N2 locus
| Locus  | Model     | Genotypes or Alleles | SLE n | Control n | OR    | 95% CI       | P     |
|--------|-----------|----------------------|-------|-----------|-------|--------------|-------|
| FBN2   | Codominant| GG                   | 21    | 26        | 1.75  | 0.93-3.27    | 7.96E-02 |
|        |           | AG                   | 235   | 334       | 1.53  | 1.25-1.86    | 2.38E-05 |
|        |           | AA                   | 562   | 1219      | ref   | ref          | ref   |
|        | Dominant  | AG+GG                | 256   | 360       | 1.54  | 1.27-1.87    | 8.83E-06 |
|        |           | AA                   | 562   | 1219      | ref   | ref          | ref   |
|        | Recessive | GG                   | 21    | 26        | 1.57  | 0.84-2.93    | 0.161 |
|        | Allelic   | AG + AA              | 797   | 1553      | ref   | ref          | ref   |
|        | Allelic   | A                    | 277   | 386       | ref   | ref          | ref   |
|        | Allelic   | G                    | 1359  | 2772      | 1.38  | 1.17-1.64    | 1.31E-04 |
| FBN2   | Codominant| GG                   | 655   | 1366      | 0.72  | 0.23-2.47    | 5.80E-01 |
|        |           | AG                   | 162   | 212       | 1.15  | 0.36-4.36    | 1.00  |
|        |           | AA                   | 6     | 9         | ref   | ref          | ref   |
|        | Dominant  | GG+GA                | 817   | 1578      | 0.78  | 0.25-2.66    | 0.60  |
|        |           | AA                   | 6     | 9         | ref   | ref          | ref   |
|        | Recessive | GG                   | 655   | 1366      | 0.63  | 0.38-0.97    | 5.43E-05 |
|        | Allelic   | AA+GA                | 168   | 221       | ref   | ref          | ref   |
|        | Allelic   | A                    | 174   | 230       | ref   | ref          | ref   |
|        | Allelic   | G                    | 1472  | 2944      | 12.34 | 10.6-14.4    | 2.20E-16 |

**Figures**
Figure 1

Quality control and datasets preparation flow diagram of both discovery and validation dataset. The flow diagram was modified from PRISMA Flow Diagram [68] (A). Manhattan plot on the meta-analysis result of the two SLE GWAS datasets in the Thai population using R-Bioconductor package qqman (B).
Figure 2

Regional plot of novel SLE susceptible variants on FBN2 locus with their relative variants around FBN2 locus (A). Haplotype block of significant variants on FBN2 locus with their correlation to show linkage disequilibrium between SNPs (B). Picture illustrated histone markers overlapped with FBN2 SNPs site (C).

Figure 3

Diagram plot showed enrichment pathway from functional annotation analysis of significant variants (p-value < 5E-05) using SNPnexus.

Figure 4

The graph shows the polygenic risk scored calculation and the mean difference between SLE and healthy controls (A). The circular plot showed loci which identified in this study at individual chromosomes using package Rcircos [69] (B).

Supplementary Files

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