Understanding the genetics of systemic lupus erythematosus using Bayesian statistics and gene network analysis

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The publication of genetic epidemiology meta-analyses has increased rapidly, but it has been suggested that many of the statistically significant results are false positive. In addition, most such meta-analyses have been redundant, duplicate, and erroneous, leading to research waste. In addition, since most claimed candidate gene associations were false-positives, correctly interpreting the published results is important. In this review, we emphasize the importance of interpreting the results of genetic epidemiology meta-analyses using Bayesian statistics and gene network analysis, which could be applied in other diseases.

Key words: Systemic lupus erythematosus, False-positive report probability, Bayesian false-discovery probability, STRING database, Protein-protein interaction

Key message

- Bayesian false-discovery probability and false-positive report probability are the 2 major Bayesian methods used to evaluate noteworthiness of a genetic variant.
- Application of stricter P value is needed to confirm statistical significance in meta-analyses.
- Gene network analysis of noteworthy genetic variants shows a blueprint of the genetic background in complex diseases.

Introduction

Although the publication of meta-analyses has rapidly increased, researchers have started to determine that many of the statistically significant results are false-positive.1,2 Most such meta-analyses have redundant duplicate topics and many errors.1,3 Although there has been an impressive increase in meta-analyses from China, particularly those on genetic associations, most claimed candidate gene associations are likely false-positives, suggesting an urgent global need to incorporate genome-wide data and state-of-the-art statistical inferences to avoid a flood of false-positive genetic meta-analyses. In this review, we emphasize the importance of discerning meaningful studies and interpreting their results using Bayesian statistics and gene network analysis. For this purpose, we adopted and reanalyzed significant genes from our previously published systemic meta-analyses of genetic association studies of systemic lupus erythematosus (SLE) as an example.5

Current understanding of genetic associations with “noteworthiness”

The traditional interpretation of association studies was labeled as statistically significant by the chosen P value of less than 0.05.5 Over the past few decades, an unprecedented advance in genotyping technologies has led to a marked increase in the publication of genome-wide association studies (GWAS).6 GWAS results generally have much smaller P values than those of observational studies, which are expected to have higher numbers of false-positive noteworthy associations. However, in observational studies, the threshold P value is generally fixed at 0.05 and the small sample size of studies allows for a P value that is highly responsive to a change in the number of cases.5 In the case of GWAS, the genome-wide significance threshold should be \( P<5 \times 10^{-8} \).7 However, some uncertainty persists about the most appropriate genome-wide significance threshold. At the practical
level, some initial GWAS used a threshold of $P<1 \times 10^{-7}$. The general rule, however, is that associations with $P<5 \times 10^{-8}$ are considered replicable. And, associations with $P \geq 1 \times 10^{-7}$ are not accepted unless proven by more stringent replication.

**Discovering noteworthy variants**

The common misunderstanding of the $P$ value is that it is, in fact, not the probability of the null hypothesis being rejected by mistake but the probability that the null hypothesis is true. Therefore, the evaluation of the hypothesis requires a Bayesian approach that requires prior probability of the hypothesis and the data.

To date, 2 major Bayesian approaches in the assessment of false report probability were published, the false-positive report probability (FPRP) and the Bayesian false-discovery probability (BFDP). FPRP and BFDP have been used in various genetic studies and field synopses in cancer studies (i.e., lung, ovarian, colorectal, gastric, hematologic) to identify genuine noteworthy genetic variants. However, attempts to discover noteworthy variants in autoimmune diseases using FPRP and BFDP are scarce.

1. **False-positive report probability**

FPRP is defined as “the probability of no true association between a gene variant and disease (null hypothesis)” for a statistically significant finding now assumed as a $P<0.05$. Developed by Wacholder et al., FPRP is calculated with the observed $P$ value, statistical power of the test, and the prior probability that an association is true. The prior probabilities we assumed when calculating FPRP were $10^{-5}$ for a candidate gene variant and $10^{-6}$ for a random single nucleotide polymorphism (SNP) as suggested by Wacholder et al. In our previous field synopsis of SLE, we calculated FPRP at those 2 assumed prior probabilities. The statistical power to detect an odds ratio (OR) of 1.2 and 1.5 was used for FPRP at both prior probabilities. Statistical power based on the ability to detect an OR of 1.5 (or its reciprocal $1/1.5=0.67$ for an OR<1) was first proposed by Wacholder et al., which we thought might be too conservative. Thus, we advocate using statistical power to detect an OR of the median among the results of studies and 1.5. The FPRP can be obtained using the following equation:

$$\text{FPRP} = \frac{\alpha(1-\pi)}{\alpha(1-\pi)+ (1-\beta)\pi}$$

where $\pi$ is the prior probability, $\alpha$ is the lowest level of significance at which a test is noteworthy ($\alpha=0.05$), while $(1-\beta)$ is the statistical power obtained using the following equation:

$$1-\beta = \frac{[\log(\text{OR}v/\text{OR}o)]}{\sigma} - Z_{a/2}$$

where $\varphi$ is the cumulative distribution function of the standard normal distribution and $Z_{a/2}$ is the $a/2$ point of the standard cumulative normal distribution. For the actual computation of FPRP, $\sigma$ and $Z_{a/2}$ are replaced by the standard error of the log-OR estimates and the 2-sided $P$ value point of the standard normal distribution. All FPRP computations were performed using the Excel spreadsheet provided by Wacholder et al., and associations with FPRP <0.2 were considered noteworthy as recommended by the authors.

2. **Bayesian false-discovery probability**

BFDP values can be obtained using methods created by Wakefield. This provides information based on the cost of a false discovery and a false nondiscovery. Different from FPRP, BFDP is calculated using the following equation:

$$\text{BFDP} = \frac{\text{ABF} \times \text{PO}}{\text{ABF} \times \text{PO} + 1}$$

where $\text{PO}$ is the prior odds of the null hypothesis and is equal to $\pi/(1-\pi)$ wherein $\pi$ is the prior probability of the null hypothesis and $\text{ABF}$ is the approximate Bayesian factor computed using OR and standard error. Its approximation is based on a logistic regression model instead of a standard normal distribution. The noteworthiness is assessed with the cutoff value of 0.8 for BFDP, which means a false nondiscovery 4 times as costly as a false discovery.

BFDP seems more reasonable with sound methodological derivation than FPRP. While FPRP is stated as the lowest FPRP value at which a test would yield a noteworthy finding and assumes a specific point as a prior, BFDP uses average over all alternatives as a prior. In other words, FPRP produces posterior null estimates that are smaller than those produced by BFDP because FPRP is essentially the lower bound on the posterior probability corresponding to the observed estimates. All BFDP computations were performed using the Excel spreadsheet provided by Wakefield (http://faculty.washington.edu/JOINNO/cv.html).

3. **Tendencies of FPRP and BFDP with P values**

The main purpose of the methods we introduced in this review is to discover false-positive results, which already satisfy the current scientific statistical standards regarding a $P$ value indicating statistical significance. Therefore, with the published results of the SLE field synopsis and systematic review, we calculated the proportion of noteworthy variants relevant to the $P$ value. A conventional meta-analysis of observational studies defines its significance with a $P$ value of less than 0.05, whereas a meta-analysis of GWAS uses $5 \times 10^{-8}$ as a threshold. We excluded data with which the results of FPRP or BFDP were not mathematically calculable, expressed as “NA.”

The ratio for the noteworthy variants out of positive findings in the meta-analysis of observational studies decreased stifferly as the $P$ value exceeded 0.001 for both FPRP and BFDP (Fig. 1). In the same manner, the ratio of the noteworthy findings among the meta-analysis results of GWAS by FPRP computation decreased to 0.5 with a $P$ value $>10^{-5}$ (Fig. 2), while BFDP also showed a sudden decrease in the number of noteworthy variants at a
The difference between FPRP and BFDP is that more genetic variants located in the borderline \((5 \times 10^{-8} < P < 0.05)\) significance in GWAS meta-analyses were noteworthy in BFDP than in FPRP (Fig. 2).

The current cutoff for a \(P < 0.05\) might be too broad, as it would yield too many false-positive results, thus leading to the overinterpretation of the retrieved results. According to the findings of this review, the statistical significance in the meta-analysis of observational studies requires evaluation with a more stringent \(P\) value. Furthermore, GWAS meta-analysis results are highly reliable because all variants under a \(P\) value of \(5 \times 10^{-8}\) were noteworthy with FPRP and BFDP computations (Table 1).

### Noteworthy genetic variants in SLE and their functions

Our previous systematic review of SLE calculated noteworthyness of published significant genetic variants using FPRP and BFDP. Table 1 summarizes the proportion of noteworthy gene variants in each type of GWAS according to the different statistical approaches and significance thresholds. Seventy-five distinct genes with 133 genotype comparisons from observational studies were identified as significant. Of the 133 genotype comparisons, 23 (17%) and 11 (8%) were verified as noteworthy (<0.2) using FPRP estimation at a prior probability of \(10^{-3}\) and \(10^{-6}\) with statistical power to detect an OR of 1.2. In addition, 34 (26%) and 18 (14%) showed a noteworthyness at a prior probability of \(10^{-3}\) and \(10^{-6}\) with a statistical power to detect an OR of 1.5. In terms of BFDP, 50 (38%) and 29 (22%) comparisons had noteworthy findings (<0.8) at a prior probability of \(10^{-3}\) and \(10^{-6}\). Seventy genes with 89 genotype comparisons extracted from GWAS were reportedly significant with a \(P\) value < \(5 \times 10^{-8}\). On FPRP, 64 comparisons were noteworthy (<0.2) at both prior probabilities of \(10^{-3}\) and \(10^{-6}\) with a statistical power to detect an OR of 1.2 and 1.5. The noteworthiness of 25 comparisons was not available for the same reason as mentioned above. With respect to BFDP estimations, all of the calculated values at both prior probabilities of \(10^{-3}\) and \(10^{-6}\) were <0.8, indicating noteworthiness. As a result, all of the statistically significant results of the meta-analyses of GWAS were assessed to be definitely noteworthy under FPRP and BFDP. A total of 25 genes with 27 genotype comparisons were organized, which had a borderline statistical significance (\(P\) value of 0.05 to
Table 1. Proportion of noteworthy gene variants by statistical approach and significance threshold

| Meta-analyses | No. of SNP studies | P<0.05 | FPRP values at prior probability |
|---------------|-------------------|--------|---------------------------------|
|               |                   |        | OR 1.2                          |
|               |                   |        | 0.001                           |
|               |                   |        | 0.000001                        |
|               |                   |        | OR 1.5                          |
|               |                   |        | 0.001                           |
|               |                   |        | 0.000001                        |
| Observational studies | 133 | 133 (100) | 23 (17) | 11 (8) | 34 (26) | 16 (14) | 50 (38) | 29 (22) |
| GWAS (P<5×10^{-6})a | 89 | 89 (100) | 64 (100) | 64 (100) | 64 (100) | 64 (100) | 89 (100) | 89 (100) |
| GWAS (5×10^{-6}<P<0.05) | 27 | 27 (100) | 13 (48) | 2 (7) | 13 (48) | 2 (7) | 15 (56) | 1 (4) |

Values are presented as number (%). SNP, single nucleotide polymorphism; FPRP, false-positive report probability; OR, odds ratio; BFDP, Bayesian false-discovery probability; GWAS, genome-wide association studies.

The noteworthiness of 25 comparisons was not available for FPRP among 89 genotype comparisons extracted from meta-analyses of GWAS with a P<5×10^{-6}.

5×10^{-6}). Under FPRP estimation, 13 (48%) and 2 (7%) were assessed to be noteworthy at a prior probability of 10^{-3} and 10^{-6} with a statistical power to detect an OR of 1.2. Moreover, 13 (48%) and 2 (7%) were identified as noteworthy at a prior probability of 10^{-3} and 10^{-6} with a statistical power to detect an OR of 1.5. In terms of BFDP, 15 (56%) and 1 (4%) comparisons were found noteworthy at a prior probability of 10^{-3} and 10^{-6}.

We found that the GWAS meta-analysis results were highly reliable because all variants under a P value of 5×10^{-6} were evaluated as noteworthy with FPRP and BFDP computations. The GWAS results with P<5×10^{-8} could be identically replicated in observational studies. In addition, of the 27 genotype comparisons that had borderline statistical significance, 13 (48%) were noteworthy under both Bayesian methods, suggesting that results with a P value of 0.05 to 5×10^{-8} may be genuine associations. To verify the results obtained from genetic analyses, both Bayesian approaches may have advantages, especially for the interpretation of results obtained from observational studies. When determining the results of GWAS with P values ranging between 0.05 and 5×10^{-8}, statistical approaches other than single standard significance may be beneficial, and we were able to confirm significance in almost half of the genetic variants within this borderline significance range. Therefore, it is attractive to speculate that genetic variants with borderline significance require further analysis for a genuine association.

Noteworthy genetic variants in SLE and their functions are summarized in Table 2. Investigation of the sorted list of significant genes identified a prominent representation of genes that have a role in interferon (IFN) signaling, which was in line with previous reports. These genes were IFIH1, IRF5, IRF8, and STAT4 from the observational studies and IFIH1, IRF5, IRF7, IRF8, PRDM1-ATG5, STAT4, ad TYK2 from GWAS. IFN-α, a type I IFN, is traditionally known to be concerned with a defense against viruses and its involvement in breaking self-tolerance via the activation of antigen-presenting cells after absorbing self-materials, which explains some essential parts of the current understanding of SLE. In addition, the proportion of genes whose function is related to nuclear factor kappa B (NF-κB) signaling was also outstanding. NF-κB plays a critical role in proinflammatory processes through regulating the expression of tumor necrosis factor-α (TNF-α), toll-like receptors, and interleukin 1 receptor. These were MECP2 and TNFAIP3 from observational studies and IKBKE, IRAK1, MECP2, SLC15A4, TNFAIP3, TNIP1, and UBE2L3 from GWAS. Other genes with relevance to the immune system such as complement activation, apoptosis, and neutrophil, monocyte, NK cell, and B- and T-cell signaling were significantly related to the genetic susceptibility loci for SLE.

Gene network analysis

As the bioinformatic open resources are overwhelming, we thought that using noteworthy genetic variants for gene network analyses with open source methods should derive a genuine etiopathology of the respective disease. Several databases have compiled data from experimental and computational sources, integrating extensive protein-protein interactions (PPIs) or gene-gene interactions. STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) and GeneMANIA are representative freely available databases that were constructed from various biological and literature sources. The utilization of these interactions among genes aids the understanding of the underlying biological mechanisms as well as the hidden pathology of human disease associated with the genes. Since different databases are constructed based on different biological evidence, the utilization of the appropriate network database is very critical for identifying meaningful interaction information. A recent interesting benchmarking study comparing the performance of different network databases in the context of virus-host interactions and STRING databases revealed overall good performance for detecting known host factors for various human genes. In this review, we introduced the process of sorting out noteworthy variants from the known statistically significant variants; furthermore, we applied the 2 representative databases STRING and GeneMANIA and genetic variants associated with SLE in our previous field synopsis to the STRING database to construct a PPI network.

1. GeneMANIA

The GeneMANIA database includes 1,800 networks covering 500 million gene-gene interactions and PPI from 9 organisms...
### Table 2. Noteworthy genetic variants and their functions

| Study                  | Gene       | Variant (RS number) | Ethnicity, study No. (types of study) | Comparison | OR (95% CI)   | P value | Function of genes                                                                 |
|------------------------|------------|---------------------|--------------------------------------|------------|---------------|---------|----------------------------------------------------------------------------------|
| Bentham et al., 2015   | ABHD6-PXK  | rs9311676           | European 2 (MG)                      | C>T        | 1.17 (1.13-1.22) | 3.06x10^-14 | ABHD6 gene codes for the abhydrolase domain-containing protein 6. ABHD6 catalyzes the hydrolysis of 2-arachidonoylglycerol and takes part in the endocannabinoid signaling regulation. PXK gene encodes a phosphoxyn (PX) domain-containing protein which may be involved in synaptic transmission and the ligand-induced internalization and degradation of epidermal growth factors. PXK also operates on the B-cell antigen receptor (BCR) and influences the rate of BCR internalization. |
| Lessard et al., 2016   | ANKST1     | rs1048257           | Chinese 2 (MG)                       | T>C        | 0.82 (0.76-0.89) | 8.66x10^-7   | ANKST1 gene encodes a large nucleoprotein that may play a role in calcium signaling by associating with calcium channel proteins. |
| Zhang et al., 2016     | ALOX5AP    | rs12876893          | Asian 5 (MG)                         | G>A        | 1.12 (1.06-1.180) | 6.20x10^-5   | ALOX5AP gene encodes a protein which is required for leukotriene synthesis. ALOX5AP is expressed in airway leukocytes in response to stimuli implicated in various inflammatory responses including asthma, arthritis and psoriasis. |
| Molineros et al., 2017 | ANKST1     | rs2762340           | Overall 9 (MG)                       | G>A        | 0.87 (0.84-0.90) | 4.93x10^-15 | ANKST1, also known as ODIN, a Src kinase that negatively regulates growth factor receptor signaling pathways. ANKST1 interacts with and is phosphorylated by Lck (lymphocyte-specific protein tyrosine kinase), a critical component of T-cell activation. |
| Bentham et al., 2015   | ARI0268    | rs4948496           | European 2 (MG)                      | C>T        | 1.14 (1.10-1.19) | 1.04x10^-10 | The encoded protein forms a histone H3K9Me2 demethylase complex with PHD finger protein 2 and regulates the transcription of target genes involved in adipogenesis and liver development. This gene also plays a role in cell growth and differentiation of B-lymphocyte progenitors. |
| Molineros et al., 2017 | ATG16L2    | rs11235604          | Asian 8 (MG)                         | T>C        | 0.78 (0.71-0.85) | 8.87x10^-12 | An autophagy-related gene associated with systemic lupus erythematosus (SLE), multiple sclerosis, and Crohn disease. ATG16L2 is involved in apoptosis and physically interacts with SLE locus ATG5. |
| Morris et al., 2016    | ATXN1      | rs17603856          | Overall 3 (MG)                       | T>G        | 0.88 (0.85-0.91) | 3.27x10^-12 | ATXN1 binds RNA and several transcription factors, and is involved in transcriptional regulation. The diseased allele of ATXN1 with the expansion of CAG repeats is associated with spinocerebellar ataxia type 1. |
| Morris et al., 2016    | BACH2      | rs597325            | Overall 3 (MG)                       | G>A        | 0.89 (0.86-0.92) | 4.03x10^-12 | A transcription regulator protein. BACH2 is expressed in primary B cells. BACH2 protein play important role as transcriptional activators or repressors. The superenhancer associated genes critical for T-cell biology are repressed by BACH2. |
| Bentham et al., 2015   | BANK1      | rs10028805          | European 2 (MG)                      | G>A        | 1.20 (1.15-1.25) | 4.31x10^-17 | BANK1 encodes a protein adaptor that is predominately expressed in B cells. It promotes LYN-mediated tyrosine phosphorylation of inositol 1,4,5-trisphosphates. |
| Lee et al., 2012       | BLK        | rs13277113          | European 2 (MG)                      | A>G        | 1.39 (1.256-1.540) | 2.28x10^-10 | BLK gene encodes a nonreceptor tyrosine kinase of the Src family of proto-oncogenes that are typically involved in cell proliferation and differentiation. The protein has a role in B-cell receptor signaling and B-cell development. |
| Bentham et al., 2015   | BLK        | rs2736340           | European 2 (MG)                      | T>C        | 1.29 (1.22-1.37) | 6.28x10^-10 | The superdenamer associated genes including lymphocyte activation, recirculation and homing, hematopoiesis, and tumor metastasis. |
| Molineros et al., 2017 | CCL22      | rs223881            | Overall 9 (MG)                       | C>T        | 0.87 (0.84-0.90) | 5.87x10^-16 | CCL22 is a Cys-Cys (CC) cytokine gene. The encoded cytokine displays chemotactic activity for monocytes, dendritic cells (DCs), natural killer cells, and chronically activated T lymphocytes. It binds to chemokine receptor CCR6. |
| Lee et al., 2015       | CD40       | rs4810485           | European 2 (MO)                      | TT vs. TG+GG | 0.339 (0.205-0.508) | 1.74x10^-4 | The encoded protein of CD40 gene is a receptor on antigen-presenting cells of the immune system and is essential for mediating a broad variety of immune responses including T-cell-dependent immunoglobulin class switching, memory B-cell development, and germinal center formation. |
| Lessard et al., 2011   | CD44       | rs387619            | European (MG)                        | C>T        | 0.82 (0.76-0.88) | 1.46x10^-8 | The protein encoded by the CD44 gene is a cell-surface glycoprotein involved in cell-cell interactions, cell adhesion and migration. This protein participates in a wide variety of cellular functions including lymphocyte activation, recirculation and homing, hematopoiesis, and tumor metastasis. |
| Sheng et al., 2015     | CD44       | rs2732547           | Chinese 3 (MG)                       | G>A        | 0.82 (0.77-0.87) | 1.55x10^-11 | The encoded protein of CD80 gene is a membrane receptor that is activated by the binding of CD28 or CTLA-4. The activated protein induces T-cell proliferation and cytokine production. |
| Bentham et al., 2015   | CD44       | rs2732549           | European 2 (MG)                      | T>C        | 1.24 (1.19-1.29) | 1.20x10^-29 | The superdenamer associated genes including lymphocyte activation, recirculation and homing, hematopoiesis, and tumor metastasis. |
| Lessard et al., 2011   | CD44       | rs2732552           | European (MG)                        | C>T        | 0.82 (0.76-0.88) | 1.82x10^-9  | The encoded protein of CD80 gene is a membrane receptor that is activated by the binding of CD28 or CTLA-4. The activated protein induces T-cell proliferation and cytokine production. |
| Zhang et al., 2016     | CD80       | rs2222631           | Asian 5 (MG)                         | A>G        | 0.86 (0.81-0.91) | 4.50x10^-8  | The encoded protein of CD80 gene is a membrane receptor that is activated by the binding of CD28 or CTLA-4. The activated protein induces T-cell proliferation and cytokine production. |
| Sheng et al., 2015     | CD80       | rs6804441           | Chinese 3 (MG)                       | G>A        | 0.86 (0.82-0.91) | 5.90x10^-4  | The encoded protein of CD80 gene is a membrane receptor that is activated by the binding of CD28 or CTLA-4. The activated protein induces T-cell proliferation and cytokine production. |
Table 2. Noteworthy genetic variants and their functions (Continued)

| Study | Gene | Variant (RS number) | Ethnicity, study No. (types of study) | Comparison | OR (95% CI) | P value | Function of genes |
|-------|------|---------------------|---------------------------------------|------------|-------------|---------|------------------|
| Bentham et al. 2015[38] | CFB | rs1270942 | European 2 (MG) | G<A | 2.28 (2.15-2.42) | 2.25×10^-16 | CFB gene encodes complement factor B, a component of the alternative pathway of complement activation. [29] |
| Bentham et al. 2015[38] | CIITA-SOCS7 | rs9652601 | European 2 (MG) | A<G | 1.21 (1.15-1.26) | 7.42×10^-17 | CIITA gene encodes a protein with an acidic transcriptional activation domain, 4 LRRs (leucine-rich repeats) and a guanosine triphosphate binding domain. The protein acts as a positive regulator of class II major histocompatibility complex gene transcription. SOCS7 gene encodes a member of the signal transducer and activator of transcription (STAT)-induced STAT inhibitor (SSI) family, also known as suppressor of cytokine signaling. It takes part in a negative feedback loop to attenuate cytokine signaling. [29] |
| Bentham et al. 2015[38] | CSK | rs2289583 | European 2 (MG) | A<C | 1.19 (1.14-1.24) | 6.22×10^-15 | The protein encoded by the CSK gene is involved in multiple pathways, including the regulation of Src family kinases. It plays an important role in T-cell activation through its association with the protein encoded by the protein tyrosine phosphatase, nonreceptor type 22 (PTP1B-22) gene. An intrinsic polymorphism (rs34933034) in this gene has been found to affect B-cell activation and is associated with SLE. [29] |
| Shojaa et al. 2014[38] | CTLA-4 | rs733618 | Overall 8 (MO) | TT vs. CC | 2.32 (1.62-3.32) | <0.001 | CTLA-4 gene is a member of the immunoglobulin superfamily and encodes a protein which transmits an inhibitory signal to T cells. [29] |
| Zhang et al. 2014[38] | CXCR5 | rs10892301 | Asian 3 (MG) | A<G | 0.85 (0.80-0.90) | 2.51×10^-06 | CXCR5 gene encodes a multipass membrane protein that belongs to the CXC chemokine receptor family. This cytokine receptor is involved in B-cell migration into B-cell follicles of spleen and Peyer patches. [29] |
| Bentham et al. 2015[38] | Cxcr2 | rs887369 | European 2 (MG) | A<C | 1.15 (1.10-1.21) | 5.26×10^-10 | A protein coding gene of unknown function. [29] |
| Lessard et al. 2016[38] | DCK1 | rs10901656 | Asian 2 (MG) | T<C | 1.21 (1.12-1.32) | 9.56×10^-06 | DCK1 gene encodes a member of the dck-kinase protein family. Dector of cytokines protein regulates the small GTPase Rac, thereby influencing several biological processes, including phagocytosis and cell migration. [29] |
| Wang et al. 2013[38] | ETS1 | rs6590330 | Caucasian 3 (MG) | A<G | 1.22 (1.10-1.34) | 9.8×10^-5 | ETS1 gene encodes for a transcription factor containing an ETS DNA-binding domain. [29] |
| Bentham et al. 2015[38] | ETS1-FLJ1 | rs7941765 | European 2 (MG) | T<C | 1.14 (1.10-1.19) | 1.35×10^-10 | FLJ1 gene encodes a transcription factor containing an ETS DNA-binding domain. [29] |
| Lee et al. 2012[38] | FAM167A | rs12680762 | European 2 (MG) | A<G | 1.335 (1.208-1.475) | 1.45×10^-06 | FAM167A gene is a ubiquitously expressed gene of unknown function. [29] |
| Bentahm et al. 2015[38] | FCGR2A | rs1801274 | European 2 (MG) | C<T | 1.16 (1.11-1.21) | 1.04×10^-12 | FCGR2A gene encodes a cell-surface receptor found on phagocytic cells such as macrophages and neutrophils, and is involved in the process of phagocytosis and clearing of immune complexes. [29] |
| Zhu et al. 2016[38] | FGFR2B | rs1050501 | Overall 12 (MO) | CC vs. CT+TT | 1.754 (1.422-2.165) | 1.61×10^-7 | FGFR2B is an immunoreceptor tyrosine-based inhibitory motif (ITIM)-containing receptor and it mediates both endocytic and apoptotic signaling on B cells and myelomonocytic cells. [29] |
| Zhu et al. 2016[38] | FGFR3A | rs396991 | Overall 26 (MO) | TT vs. TG+GG | 1.263 (1.123-1.421) | 9.62×10^-5 | FGFR3A gene is involved in the removal of antigen-antibody complexes from the circulation, as well as other antibody-dependent responses. The encoded receptor is expressed on natural killer (NK) cells. [29] |
| Lessard et al. 2016[38] | FCHSD2-P2RY2 | rs11235667 | Asian 2 (MG) | G<A | 0.63 (0.55-0.72) | 6.67×10^-11 | FCHSD2 gene has been described as regulator of F-actin assembly through interactions with WAS (also known as WASP) and WASL (also known as N-WASP). WAS plays an important role in the migration of T cells through reorganization of the actin cytoskeleton subsequent to interactions with dendritic or B cells. P2RY2 is a receptor for adenosine triphosphate (ATP) and uridine triphosphate (UTP) that acts as a sensor for the release of nucleotides by apoptotic cells. It is also known to induce CCL2 secretion in macrophages. [29] |
| Sheng et al. 2015[38] | FLJ25996 | rs9866504 | Chinese 3 (MG) | G<A | 0.85 (0.79-0.92) | 6.44×10^-2 | No information |
| Sheng et al. 2015[38] | GPM6A | rs997779 | Chinese 3 (MG) | G<A | 1.17 (1.08-1.26) | 4.48×10^-2 | GPM6A gene is abundant in all rat hippocampal subregions, and it localized to membrane protrusions (filopodia/spines) of primary hippocampal neurons. This gene has a role in neurite/filopodium outgrowth and synapse formation. [29] |
| Lessard et al. 2016[38] | GTF2RD1 | rs2267828 | Asian 2 (MG) | G<A | 0.81 (0.76-0.88) | 6.46×10^-5 | The protein encoded by this gene contains 5 GTF2D-like repeats and each repeat possesses a potential helix-loop-helix (HLH) motif. It may interact with other HLH-proteins and function as a transcription factor or as a positive transcriptional regulator under the control of Retinoblastoma protein. This gene plays a role in craniofacial and cognitive development. [29] |
Interleukin (IL)-10 is produced primarily by monocytes and macrophages, natural killer cells, B cells and cytotoxic T cells. 

This gene encodes a phosphoprotein containing 6 characteristic repeat motifs. The encoded protein binds to the initiator element (Inr) and E-box element in promoters and functions as a regulator of transcription. 

This gene is a member of the host cell factor family and encodes a protein with 5 Kelch repeats, a fibronectin-like motif, and 6 HCF repeats, each of which contains a highly specific cleavage signal. It is involved in control of the cell cycle and transcriptional regulation during herpes simplex virus infection. 

Major histocompatibility complex, class II, DR beta 1 (HLA-DRB1) gene.

The HLA-DRB1 locus is ubiquitous and encodes a very large number of functionally variable gene products (HLA-DR1 to HLA-DR17). HLA-DRB1 belongs to the HLA class II beta chain paralogs. It plays a central role in the immune system by presenting peptides derived from extracellular proteins. Class II molecules are expressed in antigen-presenting cells (APC: B lymphocytes, DCs, macrophages).

Table 2. Noteworthy genetic variants and their functions (Continued)

| Study                | Gene                  | Variant (RS number) | Ethnicity, study No. (types of study) | Comparison | OR (95% CI) | P-value | Function of genes                                                                 |
|----------------------|-----------------------|---------------------|--------------------------------------|------------|-------------|---------|-----------------------------------------------------------------------------------|
| Morris et al., 2016(61) | GTF2IRD1- GTF2I       | rs73135369          | Overall 3 (MG)                        | C>T        | 1.32        | (1.23-1.42) | 8.77×10^{-14} | This gene encodes a phosphoprotein containing 6 characteristic repeat motifs. The encoded protein binds to the initiator element (Inr) and E-box element in promoters and functions as a regulator of transcription. |
| Zhang et al., 2015(57,58) | IKZF3                | rs17422             | Asian 2 (MG)                          | T>C        | 0.75        | (0.71-0.80) | 1.47×10^{-15} | This gene is a member of the host cell factor family and encodes a protein with 5 Kelch repeats, a fibronectin-like motif, and 6 HCF repeats, each of which contains a highly specific cleavage signal. It is involved in control of the cell cycle and transcriptional regulation during herpes simplex virus infection. |
| Niu et al., 2015(60)    | HLA-DR3              |                      | Overall 17 (MO)                       | DR3        | 1.88        | (1.58-2.23) | <0.0001 | Major histocompatibility complex, class II, DR beta 1 (HLA-DRB1) gene. The HLA-DRB1 locus is ubiquitous and encodes a very large number of functionally variable gene products (HLA-DR1 to HLA-DR17). HLA-DRB1 belongs to the HLA class II beta chain paralogs. It plays a central role in the immune system by presenting peptides derived from extracellular proteins. Class II molecules are expressed in antigen-presenting cells (APC: B lymphocytes, DCs, macrophages). |
| Niu et al., 2015(60)    | HLA-DR11             |                      | Overall 15 (MO)                       | DR11       | 0.72        | (0.60-0.85) | <0.0001 | Nonclassic HLA-G class I molecules inhibit natural killer cell function. |
| Castaño-Rodriguez et al., 2008(54) | HLA-DR2         | rs1063320           | Latin American 9 (MG)                 |            |             |         | HLA-G belongs to the HLA class I heavy chain paralogs. Nonclassic HLA-G class I molecules inhibit natural killer cell function. (67) |
| Lee et al., 2015(58)    | HLA-G                | rs1034430           | Overall 4 (MO)                        | G vs. C    | 1.367       | (1.158-1.613) | 2.2×10^{-5} | ICAM1 gene encodes a cell-surface glycoprotein which is mainly expressed in the vascular endothelium, macrophages and lymphocytes, and plays a role in immunological events including extravasation and T-cell-mediated responses. ICAM4 gene encodes the Landsteiner-Wiener blood group antigen(s) that belongs to the immunoglobulin (Ig) superfamily. It contains 2 Ig-like C2-type domains and binds to the leukocyte adhesion LFA-1 protein. ICAM5 is preferentially expressed in brain. |
| Kim et al., 2015(58)    | ICAM1+ICAM4+ICAM5    | rs3093030           | Overall 4 (MO)                        | A vs. G    | 1.16        | (1.11-1.22) | 4.88×10^{-10} | ICAM1 gene encodes a cell-surface glycoprotein which is mainly expressed in the vascular endothelium, macrophages and lymphocytes, and plays a role in immunological events including extravasation and T-cell-mediated responses. ICAM4 gene encodes the Landsteiner-Wiener blood group antigen(s) that belongs to the immunoglobulin (Ig) superfamily. It contains 2 Ig-like C2-type domains and binds to the leukocyte adhesion LFA-1 protein. ICAM5 is preferentially expressed in brain. |
| Bentham et al., 2015(58) | IRF1                 | rs2111485           | European 2 (MG)                       | C>G        | 1.15        | (1.11-1.20) | 1.27×10^{-11} | IRF1 gene encodes a DEAD box protein that is upregulated in response to treatment with beta-interferon and a protein kinase C-activating compound, mezerein. The encoded protein participates in the activation of apoptosis in viral dsRNA infected cells, modulating type 1 interferon (IFN) response, production of proinflammatory cytokines and apoptotic processes. |
| Morris et al., 2016(59) | KBKE                 | rs2297550           | Overall 3 (MG)                        | G<C        | 1.16        | (1.11-1.21) | 1.31×10^{-11} | KBKE is a noncanonical I-kappa-B kinase that is essential for regulating antiviral signaling pathways. |
| Bentham et al., 2015(58) | IKZF1               | rs4917014           | European 2 (MG)                       | G<T        | 1.18        | (1.13-1.24) | 6.39×10^{-14} | IKZF1 gene encodes a transcription factor associated with chromatin remodeling. It functions as a regulator of lymphocyte differentiation. |
| Bentham et al., 2015(58) | IKZF2               | rs3788792           | European 2 (MG)                       | G<A        | 1.24        | (1.17-1.31) | 1.21×10^{-12} | IKZF2 gene encodes a member of the Ikaros family of zinc-finger proteins that is involved in the regulation of lymphocyte development. |
| Bentham et al., 2015(58) | IKZF3               | rs2941509           | European 2 (MG)                       | T>C        | 1.35        | (1.22-1.49) | 7.98×10^{-9} | IKZF3 gene encodes a member of the Ikaros family of zinc-finger proteins. This gene product is a transcription factor that is important in the regulation of B-lymphocyte proliferation and differentiation. |
| Bentham et al., 2015(58) | IL-10                | rs3024505           | European 2 (MG)                       | A>G        | 1.17        | (1.11-1.24) | 4.64×10^{-9} | Interleukin (IL)-10 is produced primarily by monocytes and to a lesser extent by lymphocytes, It down-regulates the expression of Th1 cytokines, major histocompatibility complex (MHC) class II Ags, and costimulatory molecules on macrophages. It enhances B-cell survival, proliferation, and antibody production. It can block NF-kappa B activity, and is involved in the regulation of the Janus kinase (JAK)-STAT signaling pathway. |
| Bentham et al., 2015(58) | IL-12A               | rs564799            | European 2 (MG)                       | C>T        | 1.14        | (1.09-1.18) | 1.54×10^{-9} | IL-12A acts on T and natural killer cells. It is required for the T-cell-independent induction of IFN-gamma, and is important for the differentiation of both Th1 and Th2 cells. |
| Qi et al., 2015(59)     | IL-21                | rs907715            | Overall 7 (MO)                        | GG+GA vs. AA | 1.20 | (1.09-1.31) | 0 | IL-21 plays a role in both the innate and adaptive immune responses by inducing the differentiation, proliferation and activity of multiple target cells including macrophages, natural killer cells, B cells and cytotoxic T cells. |
| Webb et al., 2009(59)   | IL-21R               | rs3093301           | Overall 2 (MO)                        | A vs. G    | 1.16        | (1.08-1.25) | 1.0×10^{-4} | IL-21R gene encodes a cytokine receptor for IL-21. It transduces the growth promoting signal of IL-21, and is important for the proliferation and differentiation of T cells, B cells, and NK cells. |
| Study                          | Gene    | Variant (RS number) | Ethnicity, study No. (types of study) | Comparison | OR (95% CI) | P value | Function of genes                                                                 |
|-------------------------------|---------|---------------------|--------------------------------------|------------|-------------|---------|-----------------------------------------------------------------------------------|
| Katmak et al. 2017[35]        | IL-6    | rs1800797           | Overall 13 (MO)                      | G vs. C    | 1.36        | 0.00    | IL-6 functions in inflammation and the maturation of B cells. In addition, it has been shown to be an endogenous pyrogen capable of inducing fever in people with autoimmune diseases or infections. |
| Zhang et al. 2015[36]         | IRAK1   | rs1059702           | Asian 2 (MG)                         | C>T        | 0.83        | 0.00    | IRAK1 gene encodes the interleukin-1 receptor-associated kinase 1. It is partially responsible for IL1-induced upregulation of the transcription factor NF-kappa B. |
| Bentham et al. 2015[37]       | IRFS    | rs1048631           | European 2 (MG)                      | C>T        | 0.83        | 0.00    | Proteins of the interferon regulatory factor (IRF) family bind to                 |
|                               |         |                     |                                      |            |             |         | JAK2 encodes a tyrosine kinase involved in a specific subset of                    |
|                               |         |                     |                                      |            |             |         | IFN-stimulated response element and regulate expression of                      |
|                               |         |                     |                                      |            |             |         | genes stimulated by type I IFNs, namely IFN-alpha and IFN-beta. IRF family proteins also control expression of IFN-alpha and IFN-beta-regulated genes that are induced by viral infection. |
| Lee et al. 2012[38]           | IRFS    | rs729302            | European 2 (MG)                      | C>A        | 1.26        | 0.00    | MYNN encodes the zinc-finger transcription factor myo-neurin, which regulates neuromuscular junctions and telomere length. |
| Bentham et al. 2015[39]       | IRAF    | rs1280220           | European 2 (MG)                      | A>C        | 1.25        | 0.00    | JAK2 encodes a tyrosine kinase involved in a specific subset of                    |
| Bentham et al. 2015[39]       | IRF8    | rs1164403           | European 2 (MG)                      | A>G        | 0.83        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Sheng et al. 2015[39]         | IRF8    | rs2934498           | Chinese 2 (MG)                       | G>A        | 1.25        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Bentham et al. 2015[39]       | ITGAM   | rs34572943          | European 2 (MG)                      | A>G        | 1.25        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Morris et al. 2016[40]        | JAK2    | rs1887428           | Overall 3 (MG)                       | G>C        | 1.25        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Bentham et al. 2015[40]       | JAZF1   | rs849142            | European 2 (MG)                      | C>T        | 0.87        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Zhang et al. 2015[40]         | L1CAM   | rs4898457           | Asian 2 (MG)                         | G>A        | 1.25        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Morris et al. 2016[41]        | LBH     | rs17321999          | Overall 3 (MG)                       | A>C        | 0.83        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Morris et al. 2016[41]        | LBH     | rs7579944           | Overall 3 (MG)                       | C>T        | 0.90        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Morris et al. 2016[41]        | LPP-TRG1-AS1 | rs6762714       | Overall 3 (MG)                       | C>T        | 1.16        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Wang et al. 2013[42]          | LRR1C18-WDFY44 | rs1913517      | Caucasian 3 (MG)                     | A>G        | 1.16        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Bentham et al. 2015[43]       | LYST    | rs9782955           | European 2 (GWAS)                    | T>C        | 1.16        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Lee et al. 2012[44]           | MBL2    | rs1800450           | Overall 21 (MO)                      | B vs. A    | 1.298       | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Bentham et al. 2015[45]       | MECP2   | rs1734787           | European 2 (MG)                      | C>A        | 1.31        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Zhang et al. 2015[46]         | MECP2   | rs2734647           | Asian 2 (MG)                         | C>T        | 0.72        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Bentham et al. 2015[47]       | miR-146a| rs2431697           | European 2 (MG)                      | C>T        | 1.26        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Molineros et al. 2017[48]     | MYNN    | rs10936599          | Overall 9 (MG)                       | C>T        | 1.14        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Zhang et al. 2015[49]         | NAA10   | rs1557501           | Asian 2 (MG)                         | C>T        | 0.83        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |
| Zhang et al. 2015[50]         | NAA10   | rs2071128           | Asian 2 (MG)                         | G>A        | 0.81        | 0.00    | proteins of the interferon regulatory factor (IRF) family bind to                 |

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35) LTP-TRG1-AS1 is a long non-coding RNA gene that encodes a protein that regulates intracellular protein trafficking in endosomes, and may be involved in the activation of TLRs by self-nucleic acids in SLE.

36) LYM7 encodes a protein that regulates intracellular protein trafficking in endosomes, and may be involved in the activation of TLRs by self-nucleic acids in SLE.

37) MBL22 gene encodes the soluble mannose-binding lectin or protein. It recognizes mannose and N-acetylgalactosamine on many microorganisms, and is capable of activating the classical complement pathway.

38) MBL2 encodes the soluble mannose-binding lectin or protein. It recognizes mannose and N-acetylgalactosamine on many microorganisms, and is capable of activating the classical complement pathway.

39) MECP2 encodes a dichotomy transcriptional regulator that either activates or represses gene expression.

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Table 2. Noteworthy genetic variants and their functions (Continued)

| Study               | Gene         | Variant (RS number) | Ethnicity, study No. (types of study) | Comparison | OR (95% CI) | P value | Function of genes                                                                 |
|---------------------|--------------|---------------------|---------------------------------------|------------|-------------|---------|-----------------------------------------------------------------------------------|
| Bentham et al. 2015 | RAD51B       | rs6658431           | European 2 (MG)                       | T>C        | 1.21        | 5.04×10^-14 | PRDM1 encodes a protein that acts as a repressor of beta-interferon gene expression. The encoded protein by ATG5 gene is involved in several cellular processes, including autophagic vesicle formation, mitochondrial quality control after oxidative damage, negative regulation of the innate antiviral immune response, lymphocyte development and proliferation, MHC II antigen presentation, adipocyte differentiation, and apoptosis. |
| Zhang et al. 2015   | PHLD81       | rs2238672           | European 2 (MG)                       | T>C        | 1.25        | 2.93×10^-9  | The protein encoded by this gene catalyzes the hydrolysis of phosphatidylincholine to phosphatic acid and choline. This protein localizes to the peripheral membrane and may be involved in cytoskeletal organization, cell cycle control, transcriptional regulation, and/or regulated secretion. |
| Lee et al. 2017     | OPN          | rs11229919          | Asian 2 (MO)                           | C vs. T    | 2.070       | 2.5×10^-7   | The protein encoded by this gene is involved in the attachment of osteoclasts to the mineralized bone matrix. It is also a cytokine that upregulates expression of interferon-gamma and interleukin-12. |
| Sheng et al. 2015   | ARXN1        | rs2048979           | Chinese 3 (MG)                         | G/A        | 0.87        | 1.35×10^-3  | Neurexins are cell-surface receptors that bind neuroligins to form Cal(2+)-dependent neuropilin-complexes at synapses in the central nervous system. This complex is required for efficient neurotransmission and is involved in the formation of synaptic contacts. |
| Zhang et al. 2014   | PHLDB1       | rs11603023          | Asian 3 (MG)                           | T>C        | 1.20        | 1.25×10^-6  | PHLDB1 is an insulin responsive protein that enhances AKT activation. AKT signaling pathway plays an important role in cellular proliferation and growth signaling. Abnormal activation of the AKT signaling pathway was found in peripheral blood T cells from individuals with SLE. |
| Bentham et al. 2015 | PLD2         | rs2238672           | European 2 (MG)                       | T>C        | 1.25        | 2.93×10^-9  | The protein encoded by this gene catalyzes the hydrolysis of phosphatidylincholine to phosphatic acid and choline. This protein localizes to the peripheral membrane and may be involved in cytoskeletal organization, cell cycle control, transcriptional regulation, and/or regulated secretion. |
| Tan et al. 2011     | PPP2CA       | rs10491322          | Overall 4 (MO)                         | G vs. A    | 1.2         | 3.8×10^-4   | PPP2CA gene encodes the phosphatase 2A catalytic subunit. Protein phosphatase 2A is implicated in the negative control of cell growth and division. |
| Tan et al. 2011     | PPP2CA       | rs7704116           | Overall 4 (MO)                         | A vs. G    | 1.3         | 3.8×10^-7   | |
| Bentham et al. 2015 | PRDM1-ATG5   | rs6556431           | European 2 (MG)                       | A>C        | 1.21        | 5.04×10^-14 | PRDM1 encodes a protein that acts as a repressor of beta-interferon gene expression. The encoded protein by ATG5 gene is involved in several cellular processes, including autophagic vesicle formation, mitochondrial quality control after oxidative damage, negative regulation of the innate antiviral immune response, lymphocyte development and proliferation, MHC II antigen presentation, adipocyte differentiation, and apoptosis. |
| Bentham et al. 2015 | PTPN22       | rs2476601           | European 2 (MG)                       | T>C        | 1.43        | 1.10×10^-6  | PTPN22 gene encodes a lymphoid-specific intracellular phosphatase that associates with the molecular adapter protein CBL and may be involved in regulating CBL function in the T-cell receptor signaling pathway. |
| Morris et al. 2016  | PTPRC        | rs34889541          | Overall 3 (MG)                         | A>G        | 0.81        | 2.44×10^-12 | The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitosis, and oncogenic transformation. PTP is also an essential regulator of T- and B-cell receptor signaling. |
| Ramos et al. 2011   | PXK          | rs6445975           | Overall 4 (MG)                         | G>T        | 1.20        | 5.27×10^-9  | This gene encodes a phox (PX) domain-containing protein which may be involved in synaptic transmission and the ligand-induced internalization and degradation of epidermal growth factors. |
| Bentham et al. 2015 | RAD51B       | rs4902562           | European 2 (MG)                       | A>G        | 1.14        | 6.15×10^-10 | RAD51 family members are evolutionarily conserved proteins essential for DNA repair by homologous recombination. Overexpression of this gene was found to cause cell cycle G1 delay and cell apoptosis, which suggested a role of this protein in sensing DNA damage. |
| Molineros et al. 2014 | RNAASEH2C   | rs1308020           | Overall 9 (MG)                        | T>C        | 0.84        | 2.96×10^-19 | RNAASEH2C encodes subunit C of the human ribonuclease H2 enzyme complex that trims RNA-DNA duplexes. |
| Tang et al. 2015    | SHC2B3       | rs10774625          | European 2 (MG)                       | A>G        | 1.13        | 4.09×10^-9  | The protein encoded by this gene encodes a lymphoid-specific intracellular phosphatase that associates with the molecular adapter protein CBL and may be involved in regulating CBL function in the T-cell receptor signaling pathway. |
| Bentham et al. 2015 | SLC15A4      | rs1059312           | European 2 (MG)                       | G>A        | 1.17        | 1.48×10^-13 | SLC15A4 belongs to a superfamily of proton-coupled oligopeptide transporters. Kobayashi et al. (2014) found that B-cell-derived Scl15a4 was crucial for Tfr7 (300365)-triggered type I interferon (e.g., IFNA) and autoantibody production in a mouse model of lupus (SLE). |
| Study                     | Gene    | Variant (RS number) | Ethnicity, study No. (types of study) | Comparison | OR (95% CI) | P value     | Function of genes                                                                 |
|--------------------------|---------|---------------------|--------------------------------------|------------|-------------|-------------|-----------------------------------------------------------------------------------|
| Bentham et al, 2015[95]  | TNPO3   | rs17849501          | European 2 (MG)                      | T>C        | 2.10        | 3.45×10^-6  | SMG7 gene encodes a protein that is essential for nonsense-mediated mRNA decay; a process whereby transcripts with premature termination codons are targeted for rapid degradation by a mRNA decay complex. NC2 gene encodes neutral cystolic factor 2, the cytosolic subunit of the multiprotein nicotinamide adenine dinucleotide phosphate oxidase complex found in neurons. It produces a burst of superoxide which is delivered to the lumen of the neutral phagosome.[89] |
| Lee et al, 2012[10]      | STAT4   | rs10931481          | European 2 (MG)                      | A>G        | 1.312       | 1.74×10^-9  | STAT4 encodes a member of the STAT family of transcription factors. In response to cytokines and growth factors, it acts as transcription activator. This protein is essential for mediating responses to IL-12 in lymphocytes, and regulating the differentiation of T helper cells.[68] |
| Bentham et al, 2015[95]  | STAT4   | rs1189341           | European 2 (MG)                      | T>C        | 1.73        | 5.59×10^-12 | TCF7 is a T-cell-specific transcription factor that regulates the expression of CD3, plays a critical role in natural killer cell and innate lymphoid cell development.[86] |
| Lee et al, 2012[10]      | TCF7    | rs7726414           | European 2 (MG)                      | T<G        | 1.477       | 4.06×10^-14 | The protein encoded by this gene is a member of the Toll-like receptor family which plays a fundamental role in pathogen recognition and activation of innate immunity.[70] |
| Bentham et al, 2015[95]  | TCF7    | rs3853839           | Asian 3 (MO)                         | allele 2 vs. allele 1 | 0.773 | <1.0×10^-9 | This gene consists of 2 exons and encodes a multipass membrane protein. An alternatively spliced transcript variant encoding the same protein has been found, but its biological validity is not determined.[81] |
| Zhang et al, 2015[95]    | TMEM187 | rs2266888           | Asian 2 (MG)                         | G>A        | 0.76        | 8.2×10^-15  | This gene consists of 2 exons and encodes a multipass membrane protein. An alternatively spliced transcript variant encoding the same protein has been found, but its biological validity is not determined.[81] |
| Zhang et al, 2015[95]    | TMEM187 | rs6571303           | Asian 2 (MG)                         | C>T        | 0.80        | 3.06×10^-13 | The gene encodes a cytokine of the TNF ligand family. The encoded protein functions in T-cell APC interactions and mediates adhesion of activated T cells to endothelial cells.[81] |
| Sheng et al, 2015[95]    | TMEM39A | rs12494314          | Chinese 3 (MG)                       | C>T        | 0.84        | 1.01×10^-9  | The gene encodes a cytokine of the TNF ligand family. The encoded protein functions in T-cell APC interactions and mediates adhesion of activated T cells to endothelial cells.[81] |
| Bates et al, 2009[95]    | TNFAIP3 | rs5029939           | Caucasian 2 (MG)                     | G>T        | 2.09        | 1.67×10^-14 | The gene encodes a cytokine of the TNF ligand family. The encoded protein functions in T-cell APC interactions and mediates adhesion of activated T cells to endothelial cells.[81] |
| Bentham et al, 2015[95]  | TNFAIP3 | rs6932056           | European 2 (MG)                      | C>T        | 1.83        | 1.97×10^-31 | The gene encodes a cytokine of the TNF ligand family. The encoded protein functions in T-cell APC interactions and mediates adhesion of activated T cells to endothelial cells.[81] |
| Ramos et al, 2011[95]    | TNFSF4  | rs10798269          | Overall 4 (MG)                       | A>G        | 0.83        | 4.04×10^-10 | The gene encodes a cytokine of the TNF ligand family. The encoded protein functions in T-cell APC interactions and mediates adhesion of activated T cells to endothelial cells.[81] |
| Sheng et al, 2015[95]    | TNFSF4  | rs1418190           | Chinese 2 (MG)                       | C>T        | 0.81        | 1.08×10^-6  | The gene encodes a cytokine of the TNF ligand family. The encoded protein functions in T-cell APC interactions and mediates adhesion of activated T cells to endothelial cells.[81] |
| Sheng et al, 2015[95]    | TNFSF4  | rs4916219           | Chinese 2 (MG)                       | A>G        | 0.80        | 7.77×10^-9  | The gene encodes a cytokine of the TNF ligand family. The encoded protein functions in T-cell APC interactions and mediates adhesion of activated T cells to endothelial cells.[81] |
| Bentham et al, 2015[95]  | TNFSF4  | rs704840            | European 2 (MG)                      | G>T        | 1.22        | 3.12×10^-9  | The gene encodes a cytokine of the TNF ligand family. The encoded protein functions in T-cell APC interactions and mediates adhesion of activated T cells to endothelial cells.[81] |
| Yang et al, 2017[95]     | TNF-α   | rs1800629           | Overall 41 (MO)                      | A vs. G    | 1.70        | <0.001      | TNF is a pleiotropic cytokine that produces different stimuli in various physiological and pathological conditions. TNF contributes importantly to the development of T cells, B cells, and DCs.[81] |
| Bentham et al, 2015[95]  | TNIP1   | rs10036748          | European 2 (MG)                      | C<T        | 1.38        | 1.27×10^-15 | TNIP1 gene encodes an A20-binding protein which plays a role in autoimmunity and tissue homeostasis through the regulation of nuclear factor kappa B activation.[81] |
| Wang et al, 2013[95]     | TNIP1   | rs7703892           | Caucasian 3 (MG)                     | C>G        | 1.29        | 1.2×10^-6   | TNIP1 gene encodes an A20-binding protein which plays a role in autoimmunity and tissue homeostasis through the regulation of nuclear factor kappa B activation.[81] |
| Lee et al, 2012[95]      | TNPO3   | rs12531711          | European 2 (MG)                      | G<A        | 1.93        | 6.4×10^-13  | TNPO3 is a nuclear import receptor for serine/arginine-rich (SR) proteins, which are essential precursor-mRNA splicing factors.[81] |
| Kurreeman et al, 2010[95]| TRAF1-C5| rs10818488          | Overall 3 (MG)                       | A          | 1.22        | 1.02×10^-6  | TRAF1 is involved in the negative regulation of T-cell proliferation and serves as an essential effector of the TNF signaling cascade. It is known to be a factor in the complement cascade and may increase susceptibility to autoimmune and inflammatory disease.[81] |
Table 2. Noteworthy genetic variants and their functions (Continued)

| Study            | Gene     | Variant (RS number) | Ethnicity, study No. (types of study) | Comparison | OR (95% CI) | P value | Function of genes                        |
|------------------|----------|---------------------|--------------------------------------|------------|-------------|---------|-----------------------------------------|
| Namjou et al.    | TRAF6    | rs4755453           | Overall 4 (MO)                       | C vs. G    | 0.88        | 4.73×10^{-5} | TRAF6 encodes an adaptor molecule that has a central role in the nuclear factor NF-κB activation pathway, it regulates inflammation, DC development, thymic selection and regulatory T-cell production as well as osteoclast formation. |
| Namjou et al.    | TRAF6    | rs5030437           | Overall 4 (MO)                       | A vs. G    | 0.88        | 7.65×10^{-5} |                                             |
| Namjou et al.    | TRAF6    | rs5030445           | Overall 4 (MO)                       | A vs. G    | 0.88        | 1.31×10^{-4} |                                             |
| Namjou et al.    | TRAF6    | rs5030472           | Overall 4 (MO)                       | A vs. G    | 0.85        | 4.75×10^{-4} |                                             |
| Bentham et al.   | TYK2     | rs2304256           | European 2 (MG)                      | A>C        | 1.24        | 3.50×10^{-13} | TYK2 gene encodes a member of the tyrosine kinase and, more specifically, the JakS protein families. This protein associates with the cytoplasmic domain of type I and type II cytokine receptors and promulgate cytokine signals by phosphorylating receptor subunits. It is also component of both the type I and type III interferon signaling pathways. |
| Diaz-Gallo et al.| UBAH3a   | rs9976767           | Overall 2 (MO)                       | G vs. A    | 1.23        | 2.4×10^{-4}  | UBAH3a gene encodes one of 2 family members belonging to the T-cell ubiquitin ligand family. Both family members can negatively regulate T-cell signaling. |
| Ramos et al.     | UBE2L3   | rs181359            | Overall 4 (MG)                       | T>C        | 1.23        | 1.15×10^{-9} | The modification of proteins with ubiquitin is an important cellular mechanism for targeting abnormal or short-lived proteins for degradation. This gene encodes a member of the E2 ubiquitin-conjugating enzyme family. It participates in the ubiquitination of p53, c-Fos, and the NF-κB-KB precursor p105 in vitro. UBE2L3 participates in ubiquitylation and has a key role in the regulation of innate and adaptive immune systems. |
| Bentham et al.   | UBE2L3   | rs7444              | European 2 (MG)                      | T>C        | 1.27        | 1.84×10^{-2} |                                             |
| Bentham et al.   | UHRF1BP1 | rs9462027           | European 2 (MG)                      | A>G        | 1.14        | 7.55×10^{-7} | UHRF1 binding protein 1                     |
| Sheng et al.     | ULK3     | rs881536            | Chinese 2 (MG)                       | A/C        | 1.16        | 5.78×10^{-3} | The kinase domain of ULK3 was required for reporter activation. ULK3 showed autophosphorylation activity, and it showed serine/threonine kinase activity toward GLU2, with lower kinase activity toward GLU1 and GLU3. |
| Zhou et al.      | VDRr     | rs2228570           | Overall 6 (MO)                       | F vs. F    | 0.75        | <0.0001    | VDRr gene encodes vitamin D3 receptor, which is a member of the nuclear hormone receptor superfamily of ligand-inducible transcription factors. Downstream targets of vitamin D3 receptor are principally involved in mineral metabolism, though this receptor regulates a variety of other metabolic pathways, such as those involved in immune response and cancer. |
| Bentham et al.   | WDFY4    | rs2663052           | European 2 (MG)                      | G>A        | 1.16        | 5.25×10^{-9} | WDFY4 is a huge protein with unknown function but is predominantly expressed in primary and secondary immune tissues. |
| Zhang et al.     | YDJC     | rs2298428           | Overall 3 (MG)                       | T>C        | 1.23        | 1.31×10^{-11} | The role of the YDJC gene is currently largely unknown. |
| Morris et al.    | ZFP90    | rs1170426           | Overall 3 (MG)                       | C          | 1.12        | 2.24×10^{-8} | ZFP90 gene encodes a member of the zinc-finger protein family that modulates gene expression. The encoded protein derepresses the transcription of certain fetal cardiac genes and may contribute to the genetic reprogramming that occurs during the development of heart failure. |

OR, odds ratio; CI, confidence interval; MG, meta-analysis of genome-wide association studies; MO, meta-analysis of observation studies.

(Arabidopsis thaliana, Caenorhabditis elegans, Danio rerio, Drosophila melanogaster, Escherichia coli, Homo sapiens, Mus musculus, Rattus norvegicus, and Saccharomyces cerevisiae). It provides a comprehensive compiled network from hundreds of different sources such as coexpression, genetic interactions, colocalization information, and shared protein domains. GeneMANIA utilizes linear regression models to combine different functional association networks from multiple data sources and Gaussian field label propagation methods are applied to predict the gene function based on composite functional networks. The combined edge scores are calculated as the weighted sum of scores by emphasizing the directly connected genes.

2. STRING database

The STRING 9.1 network database is one of the largest databases of direct (physical) PPI and indirect (functional) interactions constructed from various data sources. The STRING database covers 9.6 million proteins from 2,031 different organisms and incorporates PPI information from a number of known databases, such as Reactome, KEGG pathways, HPRD, BioGrid, and MINT as well as automated text mining including PubMed abstracts and OMIM database. It also includes com-
putationally predicted PPI by utilizing ortholog information between different species. The STRING database provides the PPI score using a naïve Bayesian algorithm to combine different scores from different biological evidence with a correction for random observation probability of interactions. Thus, the combined STRING edge score is used to indicate strong confidence for such PPI.

3. Construction of PPI networks using the STRING database

In our study, we used the STRING database to identify the PPI associated with gene mapping to genetic variants of SLE. First, our gene lists represented by gene symbol were converted to Ensembl protein identifiers using mapping information from the NCBI ftp server. Some of the gene symbols were preprocessed for conversion to official gene symbols before Ensembl ID mapping due to their ambiguity. Based on given Ensembl protein identifiers and the minimum PPI score, each PPI is extracted from the STRING databases. Depending on interests, we also extracted the closely associated genes with current gene lists using the Random Walk with Restart Algorithm, where functional closeness of 2 gene lists is represented by an XD score using the STRING database. We applied our in-house program written with Perl and C. Once the functionally related genes are selected, Cytoscape, which is a free software package for visualizing, modeling, and analyzing molecular and genetic interaction networks, is used for network visualization. To import the PPI file into Cytoscape, users must prepare the network input file constructed from at least 3 columns: source node, interaction type, and target node. Edge attributes such as interaction score can also be imported into the network. The node property file can be prepared to indicate any property of each gene/proteins such as name, function, and node type (i.e., node data source). These 2 files (i.e., network file, node property file) were imported into Cytoscape for the visualization.

4. PPI network for SLE

Here we constructed the PPI network with genes mapping to the compiled reported genetic variants of SLE. Fig. 3A represents the PPI networks with genes having genetic variants with statistical significance from observational studies. Among the 135 genetic variants mapping to 79 genes, 54 genes revealed 846 interactions between them and IL-6, TP53, IL-10, ITGAM, and NFKB1 were identified as strong hub nodes. In addition, TRAF6, IRF5, ITGAM, TNFAIP3, and BLK were identified as critical genes having more than 4 reported genetic variants in SLE, which shows a strong association of such genes with SLE. Fig. 3B and 3C also show the PPI networks with statistically significant and borderline genes from GWAS studies (i.e., $P < 5 \times 10^{-8}$, $5 \times 10^{-8} < P < 0.05$), respectively. TNFSF4, CD44, STAT4, and TNFAIP2 also showed a strong association with SLE from GWAS studies. Moreover, PTPRC, STAT4, and IL-10 also revealed strong hubness in the PPI network.

Next, we integrated these PPI networks with the genes mapping to overall genetic variants of SLE from 3 criteria. As shown in Fig. 4, genes from observational studies, GWAS with 2 different $P$ values, are closely connected within the PPI network. Many genes have genetic variants identified from at least 2 studies (i.e., orange, green, and purple nodes). Among the 148 genes, 97 revealed 1,554 PPI. Interestingly, TP53, PTPRC, NFKB1, IL-6, IL-10, and STAT4 have more than 60 interactions in the PPI network and IL-10, STAT4, ITGAM, FCGR2A, and PTPN22 are also identified as genes having genetic variants in SLE from both observational and GWAS.

Discussion

In this review, we provided general concepts for applying Bayesian methods and gene network analyses to interpret genetic

![Fig. 3. PPI network with genes mapping to the statistically significant genetic variants. (A) Statistically significant genes from observational studies ($T1: P<0.05$), (B) statistically significant genes ($T2: P<5\times10^{-8}$) from GWAS, (C) statistically significant genes at the borderline ($T3: 5\times10^{-8}<P<0.05$) from GWAS. Node size represents the number of interactions, while edge width represents the PPI score from the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) databases. The width of interactions shows the strength of the interactions mapping to the STRING score. PPI, protein-protein interactions; GWAS, gene-wide association studies.](https://doi.org/10.3345/2020.00633)
epidemiology results. The Bayesian approach is unfamiliar in genetics and the need for filtering true-positive or “noteworthy” genetic variants is unavoidable due to the enlarging amount of research data. Although a meta-analysis provides one of the highest levels of evidence within research in the medical field, different meta-analyses from different groups must be integrated and rehighlighted. We refined scattered positive data of meta-analyses in SLE with discovering false-positive results using Bayesian approaches, FPRP and BFDP, consequently suggesting a comprehensive PPI for the disease.

The Bayesian approach and its value depend on the prior probabilities, the calculation of power (1-β), and the probability of type I error (α). FPRP has been criticized for its heuristic derivation of α and 1-β as P0(t) and P(t), for which P0(t) is the probability of observing a value greater than |t| or less than -|t| under the null hypothesis, versus P(t) under the alternative; in other words, α and 1-β are pre-study quantities as properties of a test, while P0(t) and P(t) are post-study parameters.22 In fact, not related to the test genuine parameters. Also, FPRP calculates its likelihood with its tail-area; thus, information is lost compared to BFDP, in which the exact ratio of the probability densities in the indicated point is calculated. Still, both assessments are recommended in a study to determine the true impact of the discovery.

Our gene network construction with genes having noteworthy genetic variants found sound PPI in SLE. The hub genes with more than 50 interactions were PTTPRC, TP53, NFKB1, IL6, STAT4, IL10, ITGAM, TLR7, IFNG, IL1B, FCGR2A, JAK2, CD40, FCGR3A, PTPN22, RANTES, ICAM1, IRAK1, FCGR2B, CD80, IL18, and TNFAIP3.

The PPI construction using the STRING database provides insight for further wet lab-based research. On the other hand, although observational studies or GWAS elicited statistically significant genetic variations, they might not reveal the actual biological mechanism until epigenetic or molecular changes are proven. To overcome this hurdle, a combination analysis of gene expression and the matching SNP profile may be the way forward for discovering the disease etiology.

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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