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Genetics of the type I interferon pathway in systemic lupus erythematosus

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Abstract

Genetic studies of systemic lupus erythematosus (SLE) have been successful, identifying numerous risk factors for human disease. While the list is not yet complete, it is clear that important immune system pathways are represented, one of which being type I interferon (IFN). Circulating type I IFN levels are high in SLE patients and this IFN pathway activation is heritable in families with SLE. We summarize our current understanding of the genetics of the type I IFN pathway in SLE, with an emphasis on studies that demonstrate an impact of the SLE-risk alleles upon type I IFN pathway activation in SLE patients. These studies illustrate that variations in type I IFN pathway genes represent a common genetic feature of SLE. By understanding the genetic regulation of type I IFN, we may be able to intervene in a more personalized fashion, based upon the molecular dysregulation present in a given individual.

Keywords

autoantibodies; autoimmune diseases; genetics; interferon; systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease involving multiple organs including the skin, musculoskeletal, renal and hematologic systems. SLE incidence is high in women compared with men (at a 9:1 ratio), particularly during reproductive years [1,2]. The production of circulating autoantibodies directed against dsDNA (anti-dsDNA) and small nuclear RNA-binding proteins (such as anti-Ro, anti-La, anti-Sm and anti-RNP) is a cardinal feature of SLE [3]. The pathogenesis of SLE is multifactorial and likely governed by a combination of genetic predispositions and environmental factors, resulting in an irreversible break in immunologic self-tolerance [4]. It is difficult to predict the spectrum of organ-system involvement and long-term outcomes in an individual patient, as the clinical manifestations of SLE are highly diverse.

Familial aggregation and monozygotic twin studies strongly support the idea that SLE has a genetic component. Familial aggregation studies demonstrated that siblings of SLE patients have greater relative risk for the disease, with a sibling risk ratio (λs) as high as 29 compared with the general population [5]. Similarly, a much higher concordance rate of SLE was observed among monozygotic twins (30%) compared with dizygotic twins (3%) [6,7]. In

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families with multiple affected members, the disease occurrence does not typically follow classical Mendelian inheritance. However, in a few cases, SLE is associated with highly penetrant rare mutations, resulting in complete deficiencies in classical complement components and/or defective DNA degradation. Relatively rare, but complete deficiency of the early complement pathway genes, such as *C1Q*, *C1R/S*, *C2*, *C4A* and *C4B* are associated with SLE [8–11]. Deficiencies of the classical complement component pathway are likely to affect SLE pathogenesis by reducing clearance of apoptotic cell debris and immune complexes (IC), resulting in increased self-antigen availability and increased IC-related Toll-like receptor (TLR) signaling [12]. The genes for complement components *C2* and *C4* are in linkage disequilibrium with MHC polymorphisms, and these genes are hypothesized to contribute independently to the risk of SLE [13]. Rare coding-change variants in *TREX1*, which encodes a DNA exonuclease, are also associated with SLE susceptibility [14], and a family has been described in which a recessive loss of *DNASE1L3* resulted in SLE [15].

Initial studies exploring SLE genetics included targeted and genome-wide linkage analysis in multiplex families, as well as candidate gene association studies. The drawbacks of these studies included bias in candidate gene selection, based on functional relevance to disease pathogenesis, lack of dense marker sets, and inability to map genetic variants of small phenotypic effect size [16]. Despite these limitations, some risk loci, such as *IRF5*, were identified in these early studies [17]. More recently, genetic studies of SLE based on high-density genome-wide association studies (GWAS) have been extremely successful. Since 2008, numerous GWAS have been performed in patients with SLE in various ethnic populations and currently more than 40 loci are definitively linked to SLE susceptibility in case–control genetic studies [18,19]. As predicted, the *HLA* locus consistently provides the strongest evidence for association among the common genetic variants linked to SLE. Many non-*HLA* loci are located within or near genes with functional relevance in the immune system, implicating the involvement of specific immune pathways. Case–control genetic studies in SLE have recently been reviewed [18,19], and a summary of SLE-associated loci and potential function of these genes is provided in Table 1. Remarkably, there is over-representation of a number of genes involved in type I interferon (IFN) signaling, production and response. In this review we will discuss recent advances in genetics of type I IFN in SLE pathogenesis.

Role of type I IFN in SLE

The biological role of type I IFN in the pathogenesis of human SLE has been an area of considerable interest [20–23]. High levels of type I IFN have been observed in serum of SLE patients [24]. Consistent with this observation, gene expression studies have shown that there is a dominant pattern of IFN-inducible gene expression signatures in peripheral blood mononuclear cells from patients with SLE [25,26]. The genes that are overexpressed in the peripheral blood cells of SLE patients are not necessarily the same genes that are implicated as genetic risk factors. Instead, the pattern of IFN-induced gene expression in peripheral blood strongly supports the idea that the type I IFN receptor is being ligated in these cells. Type I IFNs include IFN-α and IFN-β; both of these cytokines signal through the same type I IFN receptor and play a vital role in viral defense. IFN-α signaling results in wide range of effects on the immune system, including the activation of dendritic cells and other antigen-presenting cells, as well as increased expression of MHC class I and II molecules, leading to increased antigen presentation [27]. Thus, IFN-α is a critical mediator which bridges the innate and adaptive immune systems, supporting its importance in setting thresholds for self-reactivity and autoimmunity. Serum IFN-α is elevated in many SLE patients and elevations frequently correlate with disease activity [24,25,28–30]. A subset of patients administered recombinant IFN-α as a therapy for chronic viral hepatitis and malignancy, developed a lupus-like syndrome that was reversible when IFN-α therapy is discontinued [31,32]. This

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experience provides some proof of principle that IFN-α can break tolerance in humans, and highlights its causative role in SLE etiology and pathogenesis [33]. Additionally, the effect of age and sex on serum IFN-α activity has been evaluated in families with lupus [34]. It was observed that serum IFN-α activity is higher in younger individuals in the SLE family cohorts, and this trend is accentuated in affected individuals, suggesting that the age-related pattern of IFN-α activity may contribute to the increased incidence of SLE in early adulthood. Interestingly, each gender had similar age-related patterns of IFN-α activity [34].

High serum IFN-α: a heritable risk factor for SLE

Abnormally high levels of IFN-α are present in 20% of healthy first-degree relatives of SLE patients as compared with 5% of healthy unrelated subjects [35], suggesting that high serum IFN-α is an inherited risk factor for SLE. Twins tended to be concordant for high or low IFN-α. Spouses of SLE patients did not have high serum IFN-α, supporting the concept that genetic, and not environmental factors, are driving familial clustering [36]. A number of genetic variants have now been associated with increased IFN-α in SLE [20–22], highlighting some of the genetic architecture of this SLE-associated trait and supporting the concept of heritability. The high IFN-α trait is shared across SLE patients of all ancestral backgrounds [37], although the particular genetic variants responsible for this SLE-associated trait sometimes differ between ancestral backgrounds [36,38–41].

Genetic variants in IFN & IFN-related pathways are associated with SLE risk

Over the past 5 years, there has been significant progress in the identification of type I IFN pathway genes that associate with SLE. IFN-related genetic variants playing an important role in SLE pathogenesis are discussed in detail below.

IRF5

Certain lupus-associated genetic variations have been shown to increase IFN-α levels or response to IFN-α signaling. *IRF5* is one of a family of nine IFN regulatory factors, three of which have been genetically associated with SLE [42]. *IRF5* is particularly relevant when considering the genetic architecture of type I IFN production in SLE because it can induce transcription of IFN-α mRNA [43]. *IRF5* itself is activated by IFN-α signaling, producing a potential positive feedback loop. In addition to type I IFN [44], *IRF5* plays a role in upregulating expression of IL-6, IL-12b, IL-17, IL-23, TNF-α, IFN-β-IP-10, MCP1 and RANTES [45,46] and hence has been called the ‘master regulator of proinflammatory cytokines’ [42,47]. *IRF5* has been confirmed as a risk locus for SLE in several different ancestral backgrounds [48–52], and a number of functional genetic variants have been identified. One well-studied single nucleotide polymorphism (SNP), rs2004640, creates an alternate splice site (exon 1B) in the untranslated first exon [53], and this locus has subsequently been replicated in individuals of European, African and Asian ancestry [30,49,50,53–58]. Other functional elements include a 30-bp insertion/deletion sequence in exon 6 [31], a five base pair insertion-deletion proximal to the 5′ UTR [59] and rs10954213, which creates an alternate polyadenylation site, resulting in shorter and more stable mRNA [54]. Haplotypes generated from combination of these variants are associated with varying degrees of SLE risk, although linkage disequilibrium makes it difficult to unravel the functional impact of specific variants. Since *IRF5* activates IFN-α production, presumably the SLE-risk associated variants may result in excess IFN-α production. Niewold *et al.* [30,58] studied this question in SLE patients, and found that the risk haplo-type of *IRF5* predisposes to greater serum IFN-α, supporting the idea that the risk haplotype is a gain-of-function variant. It was observed that the effect of *IRF5* genotype on serum IFN-α levels was driven by the presence of anti-dsDNA and anti-RNA-binding protein autoantibodies, supporting a ‘gene plus autoantibody equals high IFN-α’ pattern of association [58]. This

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suggests that these autoantibodies may provide chronic stimulation of the endosomal TLR pathway of IFN-α generation, and that this chronic stimulation combined with gain-of-function polymorphisms in *IRF5* results in dysregulation of the pathway SLE patients *in vivo* [21].

It is possible that *IRF5* haplotypes are associated with autoantibodies only because these antibodies stimulate the TLR receptors and activate the particular *IRF5* variants to result in type I IFN generation, which then predisposes to lupus. It is also possible that *IRF5* variants could directly predispose the autoantibody formation, potentially via a role for IRF5 in TLR signaling in B cells, and these human cross-sectional analyses do not rule out this possibility. In fact, in a murine SLE model, knockout of *IRF5* results in a significant decrease in autoantibody formation [60]. Cherian *et al.* [61] studied *IRF5* polymorphisms in a unique population of autoantibody-positive asymptomatic individuals to address this question directly – does *IRF5* influence the formation of these autoantibodies in humans outside the context of SLE? They found that *IRF5* haplotypes were strongly associated with anti-Ro antibody formation, supporting the idea of a feed–forward loop, in which *IRF5* facilitates autoantibody formation, and then the autoantibodies trigger increased type I IFN production in the setting of the same gain-of-function variations [42].

IRF7

IRF7 can also stimulate induction of IFN-α RNA [62].

IRF7 is a transcription factor found in plasmacytoid dendritic cells (pDCs), which is critical for TLR signaling leading to type I IFN production [63]. It interacts with the TLR adaptors MyD88 and TRIF, and heterodimerizes with IRF5 [64]. *IRF7* has been highlighted by the association of the *IRF7*/*KIAA1542* locus with lupus in recent studies [65,66]. The top risk variant in this region is the intronic rs4963128*C SNP located in *PHRF1*, a gene directly upstream of *IRF7*; the risk haplotype includes the entire *IRF7* gene [65]. It has been observed that a nonsynonymous SNP, rs1131665 (412Q) in *IRF7*, confers elevated activation of IRF7 and predisposes to the development of SLE in multiple ethnic groups [67]. Salloum *et al.* [40] examined the relationship between *IRF7/PHRF1* locus, presence of autoantibodies and presence of serum IFN-α. Their findings indicated that *IRF7* variants in combination with SLE-associated autoantibodies result in higher serum levels of IFN-α. *IRF5* and *IRF7* are activated by signaling through the endosomal TLRs 7, 8 and 9. Interestingly, when *IRF5* and *IRF7* risk genotypes were examined together, an additive effect was observed on serum IFN-α.

IRF8

A third member of the IFN regulatory factor family, *IRF8*, was reported as an associated risk factor for SLE in a recent large-scale multiracial GWAS replication [68]. Additionally, it has been demonstrated that a functional polymorphism in the 3′ UTR of *SPI1*, is known to regulate expression of *IRF2*, *IRF4* and *IRF8* [69–71]. Also within the *IRF8* locus, a different variant has been associated with risk of multiple sclerosis (MS) [72], underscoring the significance of this region to autoimmune disease susceptibility. It is remarkable that different genetic variations in the same *IRF* gene are associated with two autoimmune syndromes that demonstrate an opposite relationship with type I IFN (causal in SLE, and therapeutic in MS). To explore this relationship of *IRF8* with type I IFN in SLE and MS, Chrabot *et al*. [73] investigated the association of *IRF8* alleles with type I IFN levels and serologic profiles in SLE and MS. The study reported that the MS-associated rs17445836G allele was associated with antidsDNA autoantibodies in SLE patients. This allele was also associated with increased *IRF8* expression in SLE patient B cells, supporting its role in humoral tolerance. The same allele was associated with decreased serum IFN activity and

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decreased type I IFN-induced gene expression in SLE patients. In secondary progressive MS patients, rs17445836G was also associated with decreased serum type I IFN. Thus, carriage of the *IRF8* rs17445836G in human autoimmune disease patients is characterized by low-type I IFN levels and autoantibody formation. These data may be relevant to pharmacogenetics as type I IFN is modulated in SLE and MS. The discovery of genetic associations between *IRF8* variants in both SLE and multiple sclerosis are recent, and further fine-mapping and sequencing of this region will likely be required to understand the functional genetic variations underlying these associations.

STAT4

STAT4 encodes the STAT4 and represents one of six primary members of the STAT family, all of which play important roles in cytokine signaling. It is involved in proliferation, differentiation and apoptosis. The *STAT4* gene can be activated and phosphorylated upon ligation of the type I IFN receptor by IFN-α [74], and subsequently induce downstream transcription of IFN-α-induced genes. The minor T allele of rs7574865, in the third intron of *STAT4* has been associated with risk of SLE in individuals of European ancestry [75], and this SNP has been associated with risk of rheumatoid arthritis in individuals of European and Asian ancestry [75,76]. Kariuki *et al.* [77] demonstrated that the risk variant of *STAT4* (T allele; rs7574865) was associated with increased sensitivity to IFN-α signaling. This *STAT4*–SLE association was further replicated in multiple GWAS in European or Asian ancestry [65,78–80]. The SNP rs7574865 is also associated with a more severe SLE phenotype, which is characterized by disease onset at a younger age (<30 years), a high frequency of nephritis and the presence of anti-dsDNA antibodies [81–83]. An association between rs7574865 and anti-dsDNA-positive autoantibody production in SLE ($p = 2 \times 10^{-20}$) has been confirmed in a GWAS by Chung *et al*. [84]. A recent meta-analysis also supports the association between the *STAT4* rs7574865 polymorphism with SLE and the presence of anti-dsDNA antibodies in SLE patients [85].

PTPN22

PTPN22 encodes PTPN22, a lymphoid-specific phosphatase known to inhibit T-cell activation [86]. A nonsynonymous SNP rs2476601 (Arg-620Trp) C1858T in *PTPN22* results in decreased T- and B-cell responsiveness, as well as deregulated cytokine production in lymphocytes *in vitro* [87,88]. This SNP has been associated with risk of SLE, as well as multiple other autoimmune diseases including autoimmune thyroid disease, juvenile idiopathic arthritis, rheumatoid arthritis, and Type I diabetes [89]. Interestingly, *PTPN22* risk alleles are not a common feature of all autoimmune diseases and, in fact, the 1858T multiple autoimmune disease risk allele is actually associated with protection against Crohn's disease [90]. GWAS of SLE have confirmed the association between rs2476601 and SLE in European populations [65,78] but a similar association has not been observed in the Asian GWAS studies done to date [79,91]. This difference may be due to the decreased frequency of the risk allele in non-European ancestry populations. There is even a large northern versus southern Europe allelic gradient, and a two- to three-fold decrease in the allele frequency in southern Europe has impeded statistical power in this population [92] A recent meta-analysis demonstrated that the rs2476601 SNP was associated with SLE susceptibility in different ancestral groups, and that its prevalence varies widely by ancestry [93]. *PTPN22* has also been associated with anti-dsDNA autoantibody production in SLE [84].

Studies have shown that the Arg620Trp change increases the intrinsic lymphoid-specific phosphatase activity of *PTPN22*, by reducing the threshold for T-cell receptor signaling and promoting autoimmunity [94]. Supporting this idea, a *PTPN22* variant that reduces the phosphatase activity of *PTPN22* (Arg263Gln in the catalytic domain) and thus increases the

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threshold for T-cell receptor signaling has been associated with protection against SLE in European populations [95]. It has also been suggested that the *PTPN22* allele associated with autoimmune disease impairs the removal of autoreactive B cells, supporting both T and B cell effects of this allele [96]. A relationship between *PTPN22* and the type I IFN pathway has been proposed on the basis of elevated serum IFN-α and decreased TNF-α levels in SLE patients carrying the rs2476601 risk allele [97,98].

OPN

OPN or SPP1 is a secreted extracellular matrix cell adhesion glycoprotein expressed in bone, damaged renal tissues and T cells. OPN has been implicated in the development of murine lupus and is overexpressed in humans with SLE [99,100]. OPN has diverse immunological functions such as macrophage chemotaxis, T-helper type 1 polarization and B-cell activation, supporting its role in SLE pathogenesis [101]. OPN interacts with the MyD88 adaptor protein downstream of TLR ligation, and is a key molecule for IFN-α production in pDCs [102]. High levels of OPN have been documented in biopsies of inflamed tissues in SLE and other autoimmune diseases [103,104]. In addition, studies have shown that an increased plasma OPN level is correlated with increased disease activity and organ damage in SLE patients [105,106].

Genetic variants of the *OPN* gene have been associated with SLE susceptibility [100,107,108]. Presence of the lupus risk allele (rs9138C) was associated with high IFN levels in males and young-onset female lupus patients [109]. Additionally, a number of studies have linked *OPN* alleles to clinical manifestations in SLE. A study of European–American ancestry patients demonstrated an association between lymphadenopathy and rs7687316 in the promoter region [108]. Another study of 81 SLE patients of European–American ancestry demonstrated an association between a synonymous change in exon 7 with avascular necrosis and renal insufficiency [100]. A third study examining clinical subphenotypes of SLE in relation to SLE risk alleles of the *OPN* gene in multiethnic cohort revealed that the risk allele rs9138C in the 3′ UTR was associated with photosensitivity in lupus patients across all ancestral backgrounds. Additionally, the promoter variant rs11730582C demonstrated suggestive evidence for association with two hematologic traits: thrombocytopenia and hemolytic anemia [110]. These clinical associations with SNPs in the promoter and 3′ UTRs are in accordance with previously reported SLE-susceptibility SNPs in *OPN*, and suggest potential roles for these variants in antibody-mediated cytopenias and skin inflammation in SLE.

IFIH1

IFIH1 (also known as *MDA5*) is a DEAD-box helicase that recognizes viral RNA and mediates transcription of type I IFN and IFN-induced genes when activated [111]. IFIH1 is localized in the cytoplasm, and shares significant similarities with *RIG-I*, another cytoplasmic RNA sensor [111]. Genetic variants of *IFIH1* have been associated with Type I diabetes [112], autoimmune thyroid disease [113], psoriasis [114] and, more recently, with SLE [65,78,115]. A common coding-change variant in *IFIH1* (rs1990760, A946T) has been associated with these autoimmune conditions. This coding-change variant is not predicted to induce a damaging change to local protein folding by informatics algorithms, but instead has been associated with increased IFIH1 expression. Thus, the A946T variant is likely to be a gain-of-function in nature [116], although this finding has not been uniformly replicated [117]. Additionally, rare loss-of-function variations in *IFIH1* (nonsense mutations, among others) have been shown to be protective against Type I diabetes [118]. Taken together, these data propose that increased expression or gain-of-function in IFIH1 predisposes to human autoimmunity.

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Based on the importance of this protein in type I IFN responses and the pathogenic importance of IFN-α in human SLE, Robinson *et al.* investigated the impact of the *IFIH1* rs1990760 polymorphism on the IFN-α pathway in SLE patients *in vivo*. They reported the risk allele was associated with dsDNA, and modulated IFN-α-induced gene expression in peripheral blood cells in anti-dsDNA positive SLE patients [119]. A study in transgenic murine models revealed that IFIH1 overexpression, when combined with a SLE-susceptible genetic background (*FCGR2B* deficiency), led to chronic type I IFN pathway activation that triggered autoimmunity manifested by accelerated production of switched autoantibodies, increased glomerulonephritis and early lethality [120].

TYK2

TYK2 is a member of the JAK family of nonreceptor tyrosine kinases that play a vital role in initiating signaling cascades of a large number of cytokine receptors [121]. In the type I IFN pathway, TYK2 is stably associated to the IFN-α receptor (IFNAR1/2) complex, along with JAK1. TYK2 is phosphorylated following receptor ligation, and initiates a JAK/STAT signaling cascade leading to the transcription of IFN-induced genes [122–124]. Along with the type I IFN pathway, TYK2 is also important in the response to IL-12 and IL-23, as well as several members of the IL-6 and IL-10 receptor families [125].

The SNPs in *TYK2* loci have been associated with SLE [17,66,126–129]. In a Scandinavian study, a strong association signal was observed for rs2304256 in all patients and for rs12720356 in the Swedish patients only [17]. The rs2304256 SNP is located in exon 8 results in Val362Phe substitution in the JH4 region of *TYK2*. This region is essential for the interaction of TYK2 with IFNAR1 [124]. There is another common missense variant in *TYK2* (rs12720356, Ile-684Ser), located in the pseudo kinase region JH2 [17]. When studied in isolation neither of these SNP showed an association in the UK study; however, rs2304256 was reported to lie within an identified core associated region of 2.8 kb [126]. In the UK data, rs12720270 showed the strongest association, with the G allele being over transmitted in SLE families. This variant is located close to an intron/exon boundary, suggesting a potential role for this allele in aberrant splicing events [126]. Hellquist *et al.* replicated the association between the C allele of rs2304256 and risk for SLE [127]; however, the International Consortium on the Genetics of Systemic Lupus Erythematosus GWAS failed to replicate this association [65]. Hellquist *et al.* also reported that the G allele of rs12720270 was found significantly more often in SLE cases than in controls. The rs12720356 SNP failed to show association to SLE in the Finnish population when analyzed individually; however, in agreement with the UK study, two *TYK2* haplotypes (includes all three markers) showed evidence for association with SLE [127]. It is possible that future fine-mapping and replication studies will clarify the association between *TYK2* and SLE.

Conclusion

This review summarizes important recent advances in our understanding of the genetics of the type I IFN pathway in human SLE. SLE is highly heritable, polygenic in nature and likely results from the synergistic effect of different genetic loci that are impacting upon different immune system phenotypes in concert. Advances in genotyping technology and the assembly of large patient sample collections have helped us to explore common gene variants in SLE pathogenesis, and current studies are aggressively validating these associations across different ancestral backgrounds. With the increased use of next generation sequencing, we are also identifying additional rare variations that are associated with SLE. Our next major frontier is in understanding the molecular and immunologic significance of the genetic variations that are associated with SLE. This review outlines

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some very promising work that has transpired in the field of type I IFN pathway genetic variants and, of course, there are still many open questions.

Future perspective

In next 5–10 years, remarkable advances in next-generation sequencing technologies and bioinformatics will continue to aid us in identifying additional risk loci, novel rare variants, copy number variations and functional variants in multiple ancestral backgrounds that might account for more of the inherited liability of SLE. In addition, epigenetic studies will also help to show us how expression of the genetic sequence is modified in different situations and different cell types. We feel that functional studies of causal allelic variants will provide key advances in our ability to translate genetic associations into new diagnostic applications and therapeutic targets for SLE. Ideally, the field is working toward understanding the genetic regulation of immune system pathways that will allow prediction of disease onset, disease manifestations and severity, and also response/nonresponse to therapeutic intervention. In particular, studies such as those addressing type I IFN may be important to therapeutics, as targeting cytokines has been a successful approach in many autoimmune diseases, and type I IFN inhibitors are currently in clinical trials in SLE.

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Executive summary

- Many genetic risk factors for systemic lupus erythematosus (SLE) have been identified.
- Type I interferon (IFN) levels are high in SLE patients, and are a heritable risk factor for disease.
- A number of the genetic risk factors for SLE function within the type I IFN pathway.
- Studies of these genetic variations support the idea that they are gain-of-function, increasing the output of the type I IFN pathway.
- By mapping the genetics of the type I IFN pathway, we will greatly increase our understanding of SLE pathogenesis and improve diagnostic and therapeutic protocols.

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Table 1

Summary of systemic lupus erythematosus-associated loci and potential function of these genes.

Associated pathway	Reported locus/gene	Reported odds ratio	Population	Comments/potential function	Ref.
TLR and type I IFN signaling	*IRF5/TNPO3*†	1.3–2.0	Asian, European	Transcription of IFN-α and IFN-α-induced genes	[65,79,84,130,131]
	PHRF1 (*KIAA1542*)/*IRF7*†	1.3	European, African–American	Associated variant in linkage with *IRF7*, which is involved in production of IFN-α	[65,84]
	IRF8	1.2	European, African–American	Downstream non-MyD88 dependent signals from TLRs	[68,73]
	TYK2‡	1.1	European	Initiates signaling cascades of a large number of cytokine receptors	[17,126–127]
	IFIH1	1.2	European, African–American	Sensing of intracellular nucleic acid, induces IFN-α and IFN-α-induced genes	[119,120]
	TREX1‡	Rare, high penetrance	European, African–American	DNA degradation as a 3′–5′ exonuclease, high IFN observed in the monogenic syndrome	[132]
	SPP1 (*OPN*)	1.3	European, African–American	Gene encoding the cytokine OPN, interacts with IFN-α pathway	[100,108,110]
NF-κB signaling	*TNIP1*†	1.3	Asian, European	Interacts with *TNFAIP3* and can act as a negative regulator of the NF-κB pathway downstream of TNF-α, has a key role in modulating cell activation, cytokine signaling and apoptosis	[78,79,131]
	TNFAIP3†	1.7–2.7	Asian, European	Termination of immune responses by protein ubiquitination	[79,80,131]
	HIC2/UBE2L3‡	1.4	Asian, European	Ubiquitination of NF-κB precursor p105	[79,84,131]
	SLC15A4‡	1.4	Asian	Involved in Nod1-dependent NF-κB signaling, with potential participation in the antigen presentation in immune response	[79,131]
TLR/type I IFN, NF-κB and T-cell signaling	*IRAK1*‡	1.2	European	Critical for TLR-7 and -9 signaling	[133,134]
	STAT4†	1.5–1.8	Asian, European, African–American	Downstream responses to IFN-α and other cytokine signals	[65,78–80,130,131]
T-cell function and signaling	*PTPN22*†	1.3	European	Modulation of lymphocyte activation and cytokine profile	[65,78] [65,79,131]
	TNFSF4†	1.4–1.5	Asian, European	Involved in T-cell/antigen-presenting cell interactions	

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Associated pathway	Reported locus/gene	Reported odds ratio	Population	Comments/potential function	Ref.
	CD80†§	1.3	Asian	T-cell proliferation and cytokine production	[131]
	CDKN1B†§	1.2	Asian	Inhibition of T-lymphocytes cell cycle progression	[131]
	PDCD1	1.2	European	Involved in lymphocyte signaling	[135]
B-cell function and signaling	*BLK/FAM167A/XKR6*†	1.3–1.5	Asian, European, African–American	Modulation of B-cell activation	[65,79,80,130,131]
	BANK1†	1.4	Asian, European	Modulation of B-cell activation	[131,136]
	PRDM1†	1.3	Asian, European	Repressor of IFN-β gene expression; lymphocyte signaling	[78,79]
	ETS1†	1.3–1.5	Asian	Regulate the development, senescence and death of many immune cells and that play a role in innate and adaptive immune response	[79,91,131]
	IKZF1†	1.2–1.4	Asian	Regulates lymphocyte differentiation and proliferation, as well as self-tolerance through regulation of B-cell receptor signaling	[79]
	RASGRP3‡	1.4	Asian	Responsible for Ras-ERK signaling mediated by B-cell receptor ligation and might be involved in immunoglobulin production and B-cell proliferation	[79,131]
	ARID5B†§	1.2	Asian	Growth and differentiation of B-lymphocyte progenitors and other lymphocytes	[131]
T- and B-cell function and signaling	*HLA* region†	1.4–2.4	Asian, European,	Multiple immune system genes contained within this locus	[65,79,84,130,131]
	HLA-DQA1,*HLA-DQA2*,		African–American		
	HLA-DR3 and *HLA-DRB1*				
	AFF1†§	1.2	Asian	Important role in helper T cells and B cells, essential for normal lymphocyte development	[137]
Immune complex processing and hagocytosis	Early complement proteins (C1Q, C2, C4A and C4B)	All >2		Rare variants of these genes show high penetrance for systemic lupus erythematosus	[9–12]
	FcGR2A†	1.4	European, African–American	Clearance of immune complexes	[65,138]
	FcGR3A	1.6	European	Clearance of immune complexes	[138]
	CRP	1.3	European	Clearance of immune complexes	

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Associated pathway	Reported locus/gene	Reported odds ratio	Population	Comments/potential function	Ref.
Cellular adhesion; neutrophil, monocyte function and signaling	*ITGAM/ITGAX*[†]	1.3–1.9	Asian, European, African–American	Facilitates leukocyte adhesion to endothelial cells	[65,78,80,130,131]
Apoptosis	*ATG5*[†]	1.3	Asian, European	Required for autophagy	[65,78,79,131]
	DRAM1[†]	1.2	Asian	Induction of autophagy and apoptosis and target of TP53	[131]
DNA methylation	*MECP2*	1.2	European	Found on X chromosome, involved in DNA methylation	[134,139,140]
	TET3, DGUOK[†]	1.3	Asian	Important in DNA demethylation	[131]
Other/unknown immune function	*PXK*[†]	1.3	European		[65]
	WDFY4/LRRC18[†]	1.2–1.5	Asian, European		[79,80,91,131]
	UHRF1BP1[†]	1.6	European		[78]
	JAZF1[†§]	1.2	European	Unknown function currently	[78]
	TREH–DDX6[†§]	1.3	Asian		[79,131]
	GPR19[†]	1.3	Asian		[130]

[†]Confirmed association with $p < 10^{-7}$.

[‡]Confirmed association with $p < 10^{-5}$.

[§]Have not been replicated independently.

IFN: Interferon; TLR: Toll-like receptor.