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Recent advances in the genetics of systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the production of antinuclear autoantibodies and the inflammatory infiltration of many organ systems. SLE is a complex disorder in which multiple genetic variants, together with environmental and hormonal factors, contribute to disease risk. In this article, we summarize our current understanding of the genetic contribution to SLE in light of recent genome-wide association studies, which have brought the total number of confirmed SLE susceptibility loci to 29. In the second section, we explore the functional implications of these risk loci and, in particular, highlight the role that many of these genes play in the Toll-like receptor and type I interferon signaling pathways. Finally, we discuss the genetic overlap between SLE and other autoimmune and inflammatory conditions as several risk loci are shared among multiple disorders, suggesting common underlying pathogenic mechanisms.

Keywords

genome-wide association studies; pathogenesis; systemic lupus erythematosus; Toll-like receptor signaling; type I interferon signaling

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that predominantly affects women of childbearing age. The incidence of SLE in the general US population is approximately one in 2000, with a nine-to-one female gender bias and a two-to-fourfold greater prevalence in non-Caucasian compared with Caucasian populations [1]. In SLE, the tissue deposition of autoantibodies and immune complexes (ICs) leads to destructive inflammation in many organ systems, including the skin, blood elements, joints, kidneys, serosa, CNS and other tissues. The clinical manifestations of SLE are diverse, with renal inflammation (glomerulonephritis) being the most common cause of morbidity and mortality. A hallmark of SLE is the production of autoantibodies directed against intracellular antigens, many of which are associated with the nucleic acids DNA or RNA [2]. The cellular and

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molecular mechanisms governing inflammation in SLE remain uncertain; however, genetic, environmental and hormonal factors are all hypothesized to play a role.

Systemic lupus erythematosus has a significant genetic component, as familial aggregation studies have shown that siblings of SLE patients have a greater relative risk for the disease compared with the population as a whole. The sibling risk ratio (λ_s) has been estimated to be as high as 29 [3], and monozygotic twin pairs display a higher rate of concordance (34%) compared with dizygotic twin pairs (3%) [4,5]. Rare genetic mutations that cause SLE in a Mendelian fashion account for a small fraction of SLE cases; however, examples such as mutations that result in complete deficiencies of complement components provide insight into the critical pathways involved in SLE [6]. In particular, deficiencies in many of the early components of the classical complement pathway are associated with SLE (reviewed in [7]). In total, 41 cases of homozygous C1q deficiency have been reported and are associated with lupus in over 90% of known cases [8]. An absence of the C2 gene is relatively common in European populations, with an allele frequency of 1%. Approximately 33% of patients who are homozygous for this gene deletion develop SLE, and C2 deficiency is associated with autoantibodies against Ro [9]. Deficiency of any of the four alleles of the two C4 genes, C4A and C4B, is associated with SLE, and the rare complete absence of both genes is associated with the highest risk of disease [10]. The genes for the complement components C2 and C4 are in linkage disequilibrium with the major histocompatibility complex (MHC). C4A deficiency is linked to the HLA-B8-DR3 haplotype; however, it is hypothesized that the two polymorphisms contribute independently to the risk of SLE [11].

The majority of SLE cases involve a complex pattern of inheritance, where multiple genes and environmental triggers determine disease risk. Inherited genetic variation can be divided into three broad classes: common (>1%) single nucleotide polymorphisms (SNPs) and copy number variants (CNVs); rare (<1%) SNPs and CNVs; and epigenetic modifications. The association of SLE with rare coding variants in three prime repair exonuclease 1 (*TREX1*) [12], and CNVs in Fcγ receptor 3B (*FCGR3B*) [13], support a role for rare variants and CNVs in susceptibility to this disease. The ability of researchers to assess these sources of genetic variation in comprehensive and systematic studies depends on the available technology. Rare variation, CNV and epigenetic modification studies are on the horizon, owing to remarkable advances in second- and third-generation sequencing technology.

Our understanding of the role of common variants in complex human diseases and traits has exploded over the past 2 years owing to the development of genome-wide association study (GWAS) technology. GWAS involve the genotyping of hundreds of thousands of SNPs across the genome in large numbers of case and control samples and allow for the discovery of common variants that impact disease risk. To date, there have been four GWAS and a large-scale replication effort performed in European populations [14–18] and one GWAS in a Chinese Han population [19], which together have identified many new loci associated with SLE. Here, we will discuss progress in understanding the contribution of these common alleles to the risk of developing SLE and speculate on how many of them may function in the initiation or progression of disease. In the final section, we will focus on particular risk loci that are shared between SLE and other autoimmune diseases. The identification of such genes may offer insight into the basic mechanisms of tolerance and autoimmunity.

Confirmed SLE risk genes

Candidate gene studies, the GWAS described above and recent large-scale replication efforts have identified 29 loci that demonstrate ‘confirmed’ association with SLE, achieving genome-wide significance ($p < 5 \times 10^{-8}$) in at least one study. A list of these confirmed SLE risk loci is provided in Table 1 and will be discussed in more detail later. It is important to note that for

the vast majority of confirmed SLE risk loci, the causal variant(s) has not been identified. In those cases, the gene of interest listed in Table 1 therefore represents our ‘best guess’ based on the strength of the genetic signal, often taken together with inferred functional relevance. Deep resequencing and functional studies will be required to determine the true causal variants at each locus.

Linkage and case–control association studies have identified multiple SLE candidate risk genes (reviewed in [6,20,21]), with at least six loci demonstrating reproducible disease association, including HLA class II haplotypes [22–24], *FCGR2A* [25,26], protein tyrosine phosphatase, nonreceptor type 22 (*PTPN22*) [27,28], interferon regulatory factor 5 (*IRF5*) [29–31], signal transducer and activator of transcription 4 (*STAT4*) [32] and TNF ligand superfamily 4 (*TNFSF4*) [33]. The HLA region on the short arm of chromosome 6 (6p21.3) contains hundreds of genes, many of which function in the immune system, including the MHC class I (*HLA-A*, *-B* and *-C*) and class II (*HLA-DR*, *-DQ* and *-DP*) genes. This region is highly polymorphic and, not surprisingly, has been associated with most autoimmune, inflammatory and infectious diseases [34]. There is also a high degree of linkage disequilibrium across the region, making it difficult to localize the specific genetic signal as long stretches of DNA are inherited together as a set, or ‘haplotype’, of alleles. HLA class II haplotypes involving the *HLA-DRB1* and *HLA-DQB1* loci have been described for their association with SLE and, in particular, haplotypes bearing the *DRB1**1501/*DQB1**0602 (*DR2*) and *DRB1**0301/*DQB1**0201 (*DR3*) alleles have been associated with risk [35]. Interestingly, *DR2* haplotypes are associated with antibodies to the Sm autoantigen, whereas *DR3* haplotypes are associated with antibodies to Ro [36]. A high-density SNP screen across the MHC and the highly polymorphic *HLA-DRB1* locus revealed that the most strongly associated *DRB1* alleles were *0301, *1501 and *1401, and provided evidence for independent effects due to variation at the olfactory receptor family 2, subfamily H, member 2 (*OR2H2*), camp responsive element-binding protein-like 1 (*CREBL1*), *DQB2* and MHC class I polypeptide-related sequence B (*MICB*) loci [37].

The first three GWAS were published simultaneously in early 2008 and resulted in a dramatic leap forward in our understanding of the genetic basis of SLE [38]. In the Hom *et al.* study [16], more than 500,000 SNPs were genotyped in 1311 SLE cases and 3340 controls from Northern American individuals of European descent and top loci were replicated in 793 cases and 857 controls of Swedish descent. This study identified a SNP that mapped to the interval between B-lymphoid tyrosine kinase (*BLK*) and *C8orf13* as being associated with SLE. Gene expression datasets generated from Epstein–Barr virus-transformed B-cell lines revealed that the risk allele was associated with lower levels of *BLK* mRNA expression but higher levels of *C8orf13* expression [39]. This study also identified a SNP near the genes encoding integrin α M (*ITGAM*) and *ITGAX* as being associated with SLE. No difference in expression levels of either *ITGAM* or *ITGAX* were associated with this variant; however, this SNP correlated with two nonsynonymous variants of *ITGAM*.

The GWAS performed by the International SLE Genetics Consortium also identified SNPs near *ITGAM* as being associated with SLE, as well as variants near the phox homology (PX) domain containing serine/threonine kinase (*PXK*) and *KIAA1542*/PHD and ring finger domains 1 (*PHRF1*) [15]. This study genotyped SNPs from 729 SLE cases and 2337 controls and further examined the top loci in two independent replication cohorts. A SNP in *KIAA1542/PHRF1* had an r^2 value of 0.94 with a SNP in *IRF7*, a transcription factor critical for the induction of type I interferons (IFN-I). Given the known role of IFN-I in the pathogenesis of SLE (discussed later), *IRF7* is a very attractive candidate gene within this locus. A SNP in *PXK* also showed strong evidence for association with SLE. In addition, variants near pituitary tumor-transforming 1 (*PTTG1*), ubiquitin-conjugating enzyme E2L3 (*UBE2L3*), autophagy-specific gene 5 (*ATG5*), PR domain containing 1 (*PRDM1*) and v-yes-1 Yamaguchi sarcoma viral-related oncogene homolog (*LYN*) achieved a genome-wide significance cut-off of $p < 5 \times$

10^{-8} in this study. In a separate publication, a nonsynonymous SNP (rs1143679) in *ITGAM* that results in an arginine to histidine substitution at amino acid position 77 demonstrated the strongest association with SLE risk [40].

A genome scan published by Kozyrev *et al.* focused on non-synonymous SNPs in a cohort of 279 SLE cases and 515 controls in a Swedish population [17]. They identified a nonsynonymous substitution (R61H) and variants that affected regulatory sites in B-cell scaffold protein with ankyrin repeats 1 (*BANK1*) as being associated with SLE. A fourth GWAS was published in late 2008 and genotyped 431 cases and 2155 controls for a genome-wide set of SNPs [14]. This study identified multiple variants near TNF- α -induced protein 3 (*TNFAIP3*) as associated with SLE. Two independent signals were discovered, one of which has also been shown to be associated with RA [41,42]. *TNFAIP3* was also shown to be associated with SLE in an independent candidate gene study [43]. The genetics and biology of *TNFAIP3* in SLE and RA will be discussed in more detail later in this article.

While the first four GWAS were performed in populations of European descent, a GWAS was recently performed in a Chinese Han population [19]. This study genotyped 1047 SLE cases and 1205 controls and validated seven previously reported loci in this population: *BLK*, *IRF5*, *STAT4*, *TNFAIP3*, *TNFSF4*, the *PRDM1-ATG5* locus on 6q21 and the hypermethylated in cancer (*HIC*)2-*UBE2L3* locus on 22q11.21. Nine new SLE susceptibility loci were identified in this GWAS, including TNFAIP3-interacting protein 1 (*TNIP1*), RAS guanyl-releasing protein 3 (*RASGRP3*), Ikaros family zinc finger 1 (*IKZF1*), leucine-rich repeat-containing 18 (*LRRC18*), WD repeat and FYVE domain-containing family member 4 (*WDFY4*), DEAD (Asp-Glu-Ala-Asp)-box polypeptide 6 (*DDX6*), v-ets erythroblastosis virus E26 oncogene homolog 1 (*ETS1*), solute carrier family 15, member 4 (*SLC15A4*), and regions containing multiple genes on chromosomes 7q11.23 and 16p11.2.

A large-scale targeted replication study of the top SNPs from 2466 loci that demonstrated evidence of an association with SLE in a previous GWAS [16] was performed in order to identify additional risk loci [18]. These SNPs were genotyped in an independent cohort of 1953 cases and 4329 controls from the USA and Sweden. In addition to validating many of the loci described above, this study identified five new susceptibility alleles, including *TNIP1*, *PRDM1*, juxtaposed with another zinc finger gene 1 (*JAZF1*), ubiquitin-like containing PHD and RING finger domains-binding protein 1 (*UHRF1BP1*) and *IL10*. Candidate gene approaches in childhood-onset and adult SLE had suggested an association of IL-1 receptor-associated kinase 1 (*IRAK1*) [44,45] and later publications implicated the neighboring methyl CpG-binding protein 2 (*MECP2*) as a candidate gene in this locus [46,47]. The replication study confirmed an association with the *MECP2-IRAK1* locus; however, SNPs near *IRAK1* demonstrated the strongest evidence for association. Four previously implicated variants near *LYN*, signal peptide CUB domain EGF-like 1 (*SCUBE1*), Toll-like receptor 5 (*TLR5*) and lymphocyte antigen 9 (*LY9*) showed no evidence for association in this study.

Candidate genes

In addition to the confirmed genes listed in Table 1 and discussed previously, the GWAS have led to the discovery of a number of strong candidate genes for association in SLE that fell below the strict $p < 5 \times 10^{-8}$ cut-off of genome-wide significance, many of which probably represent true associations. A list of candidate genes that achieved a p-value cut-off of less than 5×10^{-7} in at least one study is provided in Table 2. The study by Harley *et al.* reported strong associations for nicotinamide nucleotide adenylyltransferase 2 (*NMNAT2*), islet cell autoantigen 1 (*ICAI*), *LYN* and *SCUBE1* [15]. A SNP in *IRF8* showed evidence of association in the Graham *et al.* study [14]. Case-control association studies identified a SNP in the NKX2.5 binding site of the inositol 1,4,5-triphosphate receptor 3 (*ITPR3*) promoter in a

Japanese population [48], and tyrosine kinase 2 (*TYK2*) in Swedish, Finnish and Icelandic patients [31]. Finally, the recent replication study identified four new candidate genes, including neutrophil cytosolic factor 2 (*NCF2*), armadillo repeat-containing 3 (*ARMC3*), IL-12 receptor β 2 (*IL12RB2*) and lysosomal trafficking regulator (*LYST*), and provided additional evidence for other candidate loci, including *NMNAT2*, *ICA1*, *TYK2* and *IRF8* [18].

Prior to the publication of the GWAS in 2008, there was convincing evidence to support the association of only six of the common alleles described above in SLE: HLA class II haplotypes, *FCGR2A*, *PTPN22*, *IRF5*, *STAT4* and *TNFSF4*. Since then, a total of 29 loci have achieved genome-wide significance for association with SLE and there is strong evidence to support a role for at least 11 other loci as contributing to risk. Despite this tremendous leap forward in the identification of associated genes, much work remains to be done if the critical questions of how these variants function in SLE biology are to be answered. Several recent reviews have applied pathway analysis tools to the genetics of common diseases as an unbiased approach to discover the involvement of known and potentially novel pathways in disease pathogenesis [49,50]. In other words, what can the susceptibility loci tell us about the biology of the disease? Here, we take the opposite (and, admittedly, much more biased) approach and instead focus on what the biology of SLE can tell us about potentially novel functions of the newly discovered SLE risk loci. In particular, we focus on evidence for the involvement of many of these genes in two pathways known to be central to the pathogenesis of this autoimmune disease: TLR/IFN-I signaling and lymphocyte development and signaling.

Functional implications of SLE susceptibility genes

TLR & IFN-I in the pathogenesis of SLE

The biological role of IFN-I in the pathogenesis of SLE in humans has been studied extensively (reviewed most recently in [51]). An increase in circulating IFN- α in the serum of lupus patients was first noted by Hooks *et al.* in 1979 and levels were later shown to correlate with disease activity [52–54]. Peripheral blood mononuclear cells (PBMCs) from SLE patients display an IFN-I-inducible gene signature ([55–58] and reviewed in [59]) and increased levels of IFN-I-inducible chemokines in SLE sera are biomarkers for active disease [60,61]. This interferon (IFN)-inducible gene-expression signature defines a subgroup of patients with severe SLE characterized by renal disease, complement activation and autoantibody production to RNA-associated autoantigens [62]. A subset of patients treated with recombinant IFN- α for nonautoimmune disorders such as hepatitis develop a lupus-like syndrome that is reversible when IFN- α therapy is discontinued (reviewed in [63]), suggesting that IFN-I play a causative role in SLE pathogenesis.

As described previously, over the years many groups have noted hyperactivation of the IFN-I pathway in SLE patients, however, it was the relatively recent characterization of the nucleic acid-sensing TLRs that has provided insight into the elusive mechanism of activation of this pathway in SLE. TLRs are a family of pattern-recognition receptors that are activated by conserved molecular patterns present on microbes, such as bacterial and viral nucleic acids. The endosomal location of the nucleic acid-sensing TLRs (TLR3, TLR7, TLR8 and TLR9) is critical for the prevention of recognition of self-derived nucleic acids [64]. A serum factor in SLE patients that induced IFN-I production in normal PBMCs was identified in the form of circulating ICs that contain nucleic acids [65–71]. The induction of IFN-I in plasmacytoid dendritic cells (pDCs) by SLE-ICs requires FCGR2A, which delivers ICs to endosomes, and either the dsDNA receptor, TLR9, in the case of DNA-associated autoantigens [72], or the ssRNA receptor, TLR7, in the case of RNA-associated autoantigens [73,74]. An autoreactive B cell can also become activated by these autoantigens by dual engagement of the B-cell receptor (BCR), which internalizes bound antigen into endosomes, and TLR7 or TLR9 [75, 76]. Interestingly, duplication of the *TLR7* gene is sufficient for the induction of autoantibodies

against RNA-containing autoantigens and the dysregulation of myeloid cells in mice carrying the Y chromosome-linked modifier *Yaa* [77–79]; however, some studies suggest that other genes at this locus may also contribute to inflammation in this model [80,81]. In addition, IFN-I itself is critical for the upregulation of TLRs in B cells and their subsequent maturation into IgG-secreting plasma cells [82–86]. Taken together, these studies highlight the critical role that TLRs play in the induction of IFN-I in pDCs and in the activation of autoreactive B cells by nucleic acid-containing auto-antigens and may explain how this subset of molecules becomes the target of autoantibodies in SLE.

SLE risk genes in TLR signaling

Given the known role of TLRs and IFN-Is in SLE pathogenesis, it is hypothesized that mutations resulting in the hyperactivation of these pathways may predispose individuals to the development of SLE. Figure 1 is a simplified diagram of the TLR and IFN signaling pathways, highlighting the roles that a number of the confirmed and candidate SLE risk genes may play. Briefly, TLR7/8 and TLR9 signal through the adaptor protein myeloid differentiation primary response gene 88 (MyD88), the kinases IRAK1 and IRAK4, and the E3 ubiquitin ligase TNF receptor-associated factor 6 (TRAF6). Stimulation of TLRs by nucleic acids activates two main families of transcription factors; namely, NF- κ B, which results in the induction of proinflammatory cytokines such as IL-1, IL-6, IL-12 and TNF- α , and IRF, which results in the induction of IFN-I. The proteins of the IFN-I family, which include many subtypes of IFN- α and the single IFN- β protein, bind to and signal through the IFN-I receptor (IFNAR), resulting in activation of the Janus kinases (JAK), JAK1 and TYK2, and the STAT transcription factors, STAT1, STAT2 and STAT4. Polymorphisms in many of these well-characterized TLR and IFN signaling intermediates have been shown to be associated with SLE, including *IRF5*, a variant near *IRF7* (*PHRF1*), *IRAK1*, *TYK2* and *STAT4*. In addition, there is evidence for the involvement of many other SLE risk loci in these pathways, including *IRF8*, *TNFAIP3*, *TNIP1*, *UBE2L3*, *ATG5*, *FCGR2A*, *LYN*, *TNFSF4*, *IL10*, *NCF2*, *IL12RB2*, *ITGAM*, *IKZF1*, *PRDM1* and *ETS1*.

Interferon regulatory factors are a family of transcription factors that play important roles in the induction of IFN-I and downstream IFN-inducible genes (reviewed in [87]). IRF7 is essential for TLR-induced MyD88-dependent IFN-I production by pDCs [88], which are the major producers of IFN-I (reviewed in [89]). Importantly, both IRF5 and IRF7 are critical for the induction of IFN-I in pDCs by RNA-containing ICs [90]. The production of many proinflammatory cytokines, including IL-1, IL-12, TNF- α and IL-6, is also impaired in conventional DCs, pDCs, macrophages and B cells from *Irf5*^{-/-} mice following TLR stimulation [91]. Mice genetically deficient for *Irf8* completely lack pDCs, indicating the importance of this transcription factor for the development of this IFN-producing DC subset [92–94]. There is also evidence that IRF8 participates directly in TLR signaling as it interacts with TRAF6 [95] and *Irf8*^{-/-} conventional DCs fail to produce proinflammatory cytokines upon TLR9 stimulation but are responsive to TLR4 stimulation [96].

The IRAK family members, which include IRAK1, IRAK2, IRAKM and IRAK4, are serine/threonine protein kinases that play critical roles in signaling through TLRs and the IL-1 receptor family members IL-1R, IL-18R and IL-33R (reviewed in [97]). IRAK1 recruits key components of the TLR signaling complex, including MyD88, IRAK4 and TRAF6 [98,99]. Macrophages from *Irak1*-deficient mice only have partial defects in NF- κ B activation following TLR or IL-1 stimulation [100,101], and it has been suggested that IRAK1 and IRAK2 function redundantly in TLR-induced NF- κ B signaling downstream of IRAK4 [102]. Interestingly, despite only minor defects in proinflammatory cytokine induction, IFN- α production is completely abrogated in *Irak1*^{-/-} mice following TLR7 and TLR9 stimulation

in vitro and upon intravenous injection of a TLR7 agonist, indicating a specific requirement for IRAK1 in IFN-I production *in vivo* [100].

The ubiquitination of signaling molecules is an integral component of TLR signaling (reviewed in [103]), and several SLE risk genes play key roles in this process. TRAF6 is an E3 ubiquitin ligase and catalyzes the addition of activating K63-linked polyubiquitin chains onto target proteins. TNFAIP3 is a critical negative regulator of TLR signaling through its ability to deubiquitinate TRAF6 (discussed in greater detail later). TNIP1 (also called ABIN1) was first identified as a TNFAIP3-interacting protein and promotes the inhibition of TNF-induced NF- κ B activation and apoptosis [104–106]. However, whether TNIP1 has a role in TLR-induced NF- κ B activation or IFN-I production has not yet been examined. UBE2L3 is an E2 ubiquitin-conjugating enzyme. Although UBE2N (UBC13) is considered to be the canonical E2 involved in TRAF6-mediated NF- κ B induction [107], at least one study has demonstrated a role for UBE2L3 in the activity of TRAF6-mediated K63-linked polyubiquitination [108]. As the ubiquitination of IRF5 and IRF7 by TRAF6 appears to be key to their activity [109,110], it is possible that UBE2L3 plays a role in the induction of IFN-I.

Studies using *Atg5*^{-/-} pDCs have revealed a surprising requirement for autophagy in IFN-I production by pDCs in response to viral infection [111]. The authors hypothesize that ATG5 may be involved in sorting TLRs to the particular endocytic compartment in which TLR signaling leads to IFN-I production. As spatiotemporal regulation of MyD88-dependent TLR signaling is crucial for IFN production by pDCs [112], functional variants of *ATG5* could potentially alter the threshold for IFN-I induction by self-nucleic acids by retaining nucleic acid-sensing TLRs in endocytic vesicles.

One study has demonstrated that the crosslinking of blood DC antigen 2 (BDCA2) on the surface of pDCs leads to the induction of IFN-I through a mechanism involving a ‘BCR-like signalosome’ including the SLE risk gene *LYN* [113]. It is therefore possible that a functional allele of *LYN* could promote both increased BCR activation and also production of IFN-I. Finally, although FCGR2A is not normally thought to play a direct role in TLR signaling, several studies have shown that FCGR2A expression on pDCs is critical for the induction of IFN-I by SLE autoantibodies owing to its ability to bind and internalize circulating ICs and deliver associated nucleic acids to endosomal TLRs [66,72].

SLE risk genes in IFN-I signaling

Several genes that function downstream of the IFN-I receptor are also associated with SLE. As described above, binding of IFN-I to the receptor triggers a JAK/STAT signaling cascade through TYK2 and STAT4. SLE patients that carry the *STAT4* risk variant have increased expression of downstream IFN-I-regulated genes *in vivo* compared with patients who do not carry the allele [114]. IKZF1 (also called Ikaros) is a transcription factor involved in the development of cells of the lymphoid lineages [115] and has also been shown to play a role in transcriptional regulation of STAT4 [116]. PRDM1 (also known as B-lymphocyte-induced maturation protein [BLIMP]1) is a transcriptional repressor that binds to the positive regulatory domain (PRD) I of the IFN- β promoter and acts as a negative regulator of IFN- β gene transcription [117–119]. PRDM1 is also essential for the differentiation of B cells into antibody-secreting plasma cells (reviewed in [120]). ETS1 has been shown to bind to IFN-stimulated response elements (ISRE) and may function as a negative regulator of IFN-I-induced transcription [121]. ETS1 is also involved in the development and differentiation of many different cells of the immune system, including T cells, B cells, plasma cells, natural killer cells and natural killer T cells [122].

Given the pleiotropic immunomodulatory effects of IFN-Is, it is not surprising that many SLE risk genes involved in other aspects of the innate or adaptive immune system are themselves

IFN-I-inducible. IFN-I upregulates the expression of many of the components of TLR and IFN signaling listed above as part of a positive feedback loop. IFN-I signaling can also promote the upregulation of MHC class II (HLA-DRB1), costimulatory molecules (TNFSF4), other cytokines and cytokine receptors (IL-10 and IL-12RB2), and adhesion molecules (ITGAM [123]), as well as promoting the maturation of monocytes into mature DCs, T cells into Th1 cells and B cells into antibody-secreting plasma cells. Dysregulation of the TLR or IFN-I pathways could therefore have broad effects on the immune response and hence contribute to the risk of developing autoimmunity.

SLE risk genes in lymphocyte development & signaling

Signaling through the antigen receptors on the surface of B and T cells promotes the development, differentiation and activation of these critical mediators of the adaptive immune response. The signaling pathways downstream of the BCR or T-cell receptor (TCR) are extremely complex and thus many layers of regulation exist in order to prevent their inadvertent activation by self-antigens. It is therefore hypothesized that alterations in the strength of signal during development may alter the BCR and TCR repertoires, or alternatively may lower thresholds for activation by self in the periphery, leading to breaks in tolerance to self antigens.

One of the strongest genetic signals in the susceptibility to all autoimmune diseases is the HLA locus. MHC class II mediates the presentation of antigen to CD4⁺ T cells and the MHC genotype therefore drives the spectrum of peptides presented and, ultimately, the ability of T cells to respond to particular antigens. It is hypothesized that different MHC alleles will have differing abilities to bind and present self-peptides, and therefore offer either susceptibility to, or protection from, autoimmune disease. The MHC genotype may contribute to the breaking of tolerance in at least two ways: first, a particular allelic variant could present an autoantigenic peptide to an autoreactive T cell and promote its activation in the periphery. Second, the presentation of self-peptides by specific MHC alleles in the thymus could either promote the positive selection of self-reactive T cells or fail to negatively select autoreactive T cells. The highly polymorphic MHC alleles therefore play critical roles in both shaping the T-cell repertoire during development in the thymus and in promoting their activation in the periphery. ATG5 is also likely to participate in antigen presentation to CD4⁺ T cells owing to its known role in autophagy, a cellular process by which proteins in the cytosol are delivered to the lysosomes for degradation. In antigen-presenting cells (APCs) such as DCs, autophagy allows for the cross-presentation of cytosol-derived peptides on MHC class II (reviewed in [124]).

Several SLE risk genes are thought to function downstream of antigen receptors, including *BLK*, *PTPN22*, *RASGRP3*, *BANK1*, *LYN*, *ITPR3* and *TNFSF4*. The function of *BLK* and *PTPN22* are discussed later in this article as variants in these genes have been implicated in multiple autoimmune diseases. Ras signaling plays an important role in both BCR and TCR signaling, and *RASGRP3* links BCR signaling to the phospholipase C (PLC) γ 2-diacylglycerol (DAG) pathway [125]. Activation through the BCR leads to phosphorylation of the scaffold protein *BANK1*, which in turn promotes *LYN*-mediated phosphorylation of *ITPR3*, ultimately resulting in calcium mobilization [126]. *TNFSF4* (also called OX40L) is a costimulatory molecule on the surface of APCs that has been shown to both promote the activation of conventional T cells and suppress the function of T-regulatory cells (reviewed in [127]). Taken together, the association of multiple genes in lymphocyte signaling pathways with risk of SLE suggests that altering signaling thresholds of lymphocytes is an important mechanism in the breakdown of tolerance in this disease.

SLE risk genes with unknown functions

Although many SLE susceptibility genes have been implicated in innate and adaptive immunity as previously outlined, many have no known function or have functions that are not easily

extrapolated to the immune system. For instance, *JAZF1* is a transcriptional repressor that has no known immune function to date [128]. The variant identified as being associated with SLE in this locus has also been implicated in the risk of Type 2 diabetes [129] and in height variation [130], complex traits that are not typically thought to result from variation in immune-related genes. The association of *JAZF1* and other risk alleles with SLE implies that they may have important roles in the function of the immune system. A clear understanding of the biology of the disease being studied may also lead to the discovery of novel functions for already well-characterized genes. For example, mutations that lead to a complete deficiency of the protein encoded by the *LYST* gene result in the disorder Chediak–Higashi syndrome (reviewed in [131]). Studies in this disease have revealed that *LYST* functions in lysosomal trafficking in many immune cells, a process that is also crucial in the activation of TLRs by self-nucleic acids in SLE [64]. However, much work remains to be done in order to fully understand how each variant functions in the pathogenesis of SLE.

Overlap of SLE with other autoimmune & inflammatory disorders

Shared autoimmune loci

The immune system is in a constant struggle to maintain a balance between immunity (the elimination of foreign pathogens) and tolerance (the lack of response to self-tissue). When the mechanisms regulating the immune response fail, the inflammatory destruction of self-tissues can occur. Recent studies have suggested that many chronic autoimmune and inflammatory disorders may stem from common pathogenic mechanisms that result from variation in shared genetic pathways (reviewed in [132,133]). Interestingly, many immune-related disorders demonstrate co-occurrence within both individuals and families. For example, asthma, Type 1 diabetes (T1D) and autoimmune thyroid disease (AIT) have been shown to co-occur in individuals with rheumatoid arthritis (RA), and AIT, T1D, SLE and multiple sclerosis (MS) all demonstrate familial clustering with RA [134–136]. Recent evidence supports the idea that some genetic variants are associated with multiple autoimmune diseases, whereas others are specific for particular disorders. For example, a functional SNP in *PTPN22* is associated with risk of T1D, RA, SLE and Hashimoto's thyroiditis, but not MS, in a collection of families with a history of multiple auto-immune diseases, suggesting a common underlying etiology for some, but not all, autoimmune disorders [137]. Here, we discuss the genetic evidence for overlap between SLE and other autoimmune and inflammatory disorders. Table 3 contains a list of genes that have demonstrated an association with SLE and at least one other autoimmune disease. Putative functions of each gene are given and are classified below into a few broad categories for the purpose of this discussion: lymphocyte signaling (*PTPN22*, SH2B adaptor protein 3 [*SH2B3*], *BLK* and *PRDM1*), Th1 development (*STAT4*, *IL12B* and *IL10*) and innate immunity (*TNIP1*, *IRF8*, *TYK2*, *TNFAIP3*, IFN induced with helicase C domain 1 [*IFIH1*], complement factor B [*CFB*], *FCGR2A* and macrophage migration inhibitory factor [*MIF*]). In addition, SNPs near *CLEC16A*, a C-type lectin domain family member with no known function, have been associated with SLE [18], MS [138], T1D [138,139] and Addison's disease [140]; SNPs near the predicted gene, *C10orf67*, are associated with SLE [18] and Crohn's disease (CD) [141].

Lymphocyte signaling genes as shared autoimmune loci

Protein tyrosine phosphatase, nonreceptor type 22 is a protein tyrosine phosphatase that functions as a negative regulator of T- and B-cell responses through its ability to dephosphorylate key downstream signaling molecules, including lymphocyte-specific protein tyrosine kinase (LCK), protein-tyrosine kinase fyn (FYN) and ζ -chain (TCR)-associated protein kinase 70 kDa (ZAP70) [142]. A missense mutation results in a change from an arginine to a tryptophan at position 620 within a proline-rich region. The functional consequences of this substitution appear to be a decreased ability to bind C-terminal Src tyrosine kinase, an

important negative regulator of lymphocyte-specific protein tyrosine kinase [143,144]. The consequences of the substitution are controversial, with decreased activation through both the BCR and TCR reported by some [145–147] and conversely, increased TCR signaling reporter by others [148]. The 620W allele has been associated with risk for SLE, T1D [143], RA [144] and Graves' disease [149], but interestingly is associated with protection against CD [150]. In addition, there is evidence that this allele is not associated with other autoimmune diseases, such as celiac disease [151] and MS [137]. Recently, a rare missense substitution (R263Q) in *PTPN22* was shown to reduce phosphatase activity and was associated with protection from SLE [152].

SH2B adaptor protein 3 (also called LNK) is an SH2-domain containing protein that functions as an adaptor protein in TCR, BCR, growth factor and cytokine receptor signaling pathways and therefore plays an important role in hematopoietic homeostasis [153–155]. Mice genetically deficient for SH2B3 are hypersensitive to stimulation with multiple cytokines [153]. SH2B3 also functions as a regulator of T-cell signaling as overexpression of SH2B3 inhibits the activation of nuclear factor of activated T cells (NFAT) following TCR stimulation *in vitro* [156]. Variants that affect *SH2B3* function could therefore alter the signaling thresholds through many different receptors on cells of both the lymphoid and myeloid lineage. A nonsynonymous SNP that leads to a R262W substitution in *SH2B3* is associated with SLE, T1D [157] and celiac disease [158], and occurs in the pleckstrin homology domain, which is known to be important for targeting to the plasma membrane [157,159,160].

B-lymphoid tyrosine kinase is a Src family kinase that is hypothesized to transduce signals downstream of the BCR. The expression of BLK is highly restricted to the B-cell lineage [161] and the risk allele is associated with reduced expression of BLK in transformed B-cell lines [16]. This SNP has demonstrated association with SLE, RA [162] and antiphospholipid syndrome [163]. However, exactly how decreased expression of BLK may predispose an individual to the development of autoimmunity is unknown, as mice genetically deficient for *Blk* display no obvious phenotypes in B-cell development or function [164].

Th1 cells in the predisposition to autoimmunity

The contribution of different subsets of T-helper cells to the pathogenesis of inflammatory diseases has been the subject of much research over the years and, more recently, much debate [165]. The Th1–Th2 model was first proposed by Coffman and Mosmann in 1986 and postulates that CD4⁺ Th1 cells drive the cell-mediated immune responses that lead to tissue damage and the particular IgG responses thought to play a role in many inflammatory diseases, whereas CD4⁺ Th2 cells drive the production of certain antibodies (IgE) that predominantly underlie allergic responses ([166,167] and reviewed in [168]). In recent years, the characterization of novel subsets of T helper cells, most notably Treg and Th17 cells, has led to a major paradigm shift in T-cell biology.

Although Th17 cells have been shown to be central to the pathogenesis of many autoimmune diseases, including MS, RA, inflammatory bowel disease, asthma and psoriasis, the data supporting a role for this population in SLE are not as clear. Accordingly, while there is a clustering of variants in Th17 pathway genes in the aforementioned diseases, these loci do not appear to predispose to risk of SLE, with the possible exception of *IL12B* as described below [169,170]. However, variants in genes known to contribute to the development of Th1 cells have been shown to be associated with SLE and other autoimmune diseases, including *STAT4* [32], *IL12B* [171,172] and *IL10* [173,174]. IL-12 and IL-23 are cytokines that share the subunit (p40) encoded by *IL12B*. When IL-12B dimerizes with the p35 subunit (IL-12A), signaling through the receptor induces Th1 differentiation, which requires STAT4. However, when IL-12B dimerizes with the p19 subunit (IL-23A), signaling through the IL-23 receptor and STAT3 promotes Th17 differentiation and survival, which requires STAT3. IL-10 is a

broad immunosuppressive cytokine and, in particular, regulates the development of Th1 cells [175].

Innate immunity genes in autoimmune disease

Several shared autoimmune loci function in innate immunity and putative functions for *TNIP1* (also associated with psoriasis [172]), *IRF8* (also associated with MS [176]), *TYK2* (also associated with MS [177]) and *TNFAIP3* are discussed elsewhere in this review. A missense allele of *IFIH1* is associated with risk for T1D [178], Graves' disease [179] and SLE [18]. *IFIH1* (also called MDA5) is a cytoplasmic RNA sensor that promotes IFN-I production when activated by viruses [180]. As the innate immune response to viral infection is hypothesized to play a role in the pathogenesis of multiple autoimmune diseases, the inappropriate activation of nucleic acid sensors such as TLRs and *IFIH1* may contribute to a general predisposition towards autoimmunity [181]. A missense allele (*R32Q*) of *CFB*, an activator of the alternative complement pathway, is associated with protection from age-related macular degeneration (AMD) and SLE, and has reduced hemolytic activity [182,183]. Defects in complement components have been associated with both SLE and AMD and, interestingly, the incidence of SLE is increased in AMD patients relative to matched controls, suggesting a common pathogenic mechanism between these two diseases [184]. *MIF* is an immunoregulatory cytokine that functions in both innate and adaptive immunity and is expressed by many immune cells such as monocytes, macrophages, and T and B lymphocytes. Polymorphisms in the *MIF* gene have been associated with multiple autoimmune and inflammatory diseases (reviewed in [185]), including SLE [186], RA [187], CD [188], psoriasis [189] and celiac disease [190].

Overlap of SLE with RA

Systemic lupus erythematosus and RA in particular share many clinical, serological and phenotypic features, and studies have demonstrated familial aggregation of RA with SLE [3]. A recent population-based study demonstrated that by 25 years after RA incidence, four or more SLE features were observed in 15.5% of RA patients, highlighting the substantial overlap between these two diseases [191]. It is therefore believed that common pathogenic mechanisms underlie the susceptibility to, and progression of, these two diseases. Genetic data support this model as several loci have been identified that are associated with the risk of both SLE and RA, including HLA haplotypes, *BLK* [162], *PTPN22* [144], *STAT4* [32], *FCGR2A* [192], *PRDM1* [192] and *TNFAIP3*. *IRF5* has also been shown to be associated with RA in some studies [193,194], however, others have failed to demonstrate an association [195,196]. Although these two diseases do share some overlapping phenotypes, many key features are distinct and, consistent with this, many loci appear to be associated exclusively with one disease and not the other [197]. The genes implicated in susceptibility to SLE and RA are known to play a role in pathways critical to the induction and maintenance of tolerance, including lymphocyte selection (*HLA*), activation (*BLK*, *PTPN22*) and differentiation (*PRDM1*, *STAT4*). As detailed descriptions of the putative functions of many of these genes and speculations on how they may predispose to autoimmunity have been discussed in detail elsewhere in this review, next we focus on the genetics and biology of *TNFAIP3* in RA and SLE.

TNFAIP3 in the susceptibility to SLE & RA

As described above, *TNFAIP3* is a negative regulator of NF- κ B, a key transcription factor in the inflammatory response. Variants near *TNFAIP3* have been associated with risk for multiple auto-immune diseases, including RA [41], SLE [14,43], T1D [198], psoriasis [172], celiac disease [199] and CD [200]. *TNFAIP3* is also frequently inactivated in human B-cell lymphomas and, therefore, contributes to the persistent NF- κ B activation known to play a role

in the development and progression of cancer [201,202]. Regulation of NF- κ B by TNFAIP3 is therefore central to the pathogenesis of a spectrum of human diseases where inflammation is known to play a role (reviewed in [203]).

NF- κ B is a transcription factor that is activated by many different stimuli, including TLR agonists, TNF and IL-1. A crucial mechanism in the regulation of this pathway is the ubiquitination of key signaling components by both K48-linked polyubiquitin chains, which target a protein for degradation, and K63-linked polyubiquitin chains, which are associated with protein activation. A20, the protein encoded by *TNFAIP3*, is a ubiquitin-editing enzyme, as it contains an N-terminal ovarian tumor domain that functions as a deubiquitinase by removing K63-linked ubiquitin chains, and a C-terminal zinc finger domain that functions as an E3 ubiquitin ligase by catalyzing the addition of K48-linked ubiquitin chains to target proteins. These seemingly opposing functions promote the inactivation and subsequent degradation of key NF- κ B signaling components, including receptor-interacting protein 1 (RIP1), which mediates signaling downstream of TNFR [204], and TRAF6, which has been seen to mediate signaling downstream of TLRs and IL-1R [205,206]. A20 also plays an important role in TNF-induced apoptosis [207]: *A20*^{-/-} mice develop severe inflammation in multiple organs and are hypersensitive to sublethal doses of the TLR4 agonist lipopolysaccharide and TNF, demonstrating the crucial role of this gene in the regulation of inflammation *in vivo* [208].

A GWAS in RA and data from the Wellcome Trust Case Control Consortium of seven common inflammatory diseases identified two independent variants at 6q23 that fell further than 150 kb from the nearest genes, *TNFAIP3* and oligodendrocyte transcription factor 3 [41,42,200]. Given that inhibition of TNF- α is an effective therapy for severe RA [209], *TNFAIP3* emerged as a strong candidate gene in this region. A 'protective' haplotype tagged by rs10499194 and a 'risk' haplotype tagged by rs6920220 were defined for RA. *TNFAIP3* was subsequently identified as being associated with SLE in two studies [14,43]. Taken together with data for RA, the results suggest a genetic model of three alleles with independent effects at the *TNFAIP3* locus: a risk allele defined by rs6920220 for both RA and SLE, a protective allele defined by rs10499194 in RA that was not present in SLE, and an SLE-specific risk haplotype defined by the minor alleles rs10499197 and rs77949323. The genetics of this locus are therefore very complex and suggest that, while variants near *TNFAIP3* are associated with a generalized susceptibility to multiple inflammatory conditions, disease-specific polymorphisms may influence the development or progression of particular autoimmune phenotypes. A nonsynonymous SNP that results in a phenylalanine to cysteine substitution at amino acid 127 in the ovarian tumor domain was associated with risk for SLE and decreased the ability of the A20 protein to inhibit TNF-induced NF- κ B activity in an *in vitro* system [43]. A hypomorphic allele of *TNFAIP3* that results in decreased expression or activity could lead to dysregulation of both TNF and TLR-induced NF- κ B signaling, as well as TNF-induced apoptosis and TLR-induced IFN production, resulting in a generalized susceptibility to inflammation.

Expert commentary

In this review, we have outlined and reviewed the identification of over 40 loci implicated in the risk for SLE and other auto-immune and inflammatory diseases. We have also speculated about how candidate genes within these loci may function in the development and progression of autoimmunity, with the goal of identifying testable hypotheses for future experiments.

The rapidly growing catalog of loci associated with auto-immunity represents a key early step in our understanding of these diseases, however, the vast majority of the genetic burden of this disease has yet to be discovered. In a recent large SLE genetic study, it was estimated that the

26 confirmed SLE loci accounted for only 8% of the total genetic susceptibility to SLE [18]. There is much debate in the field regarding the potential sources of this ‘missing heritability’ in complex human diseases and traits [210], which might include the presence of a large number of variants with small effects, rare variants with larger effects, structural variants such as CNVs that are not captured on current platforms, epigenetic modifications, the inability to detect gene–gene interactions, imprecise phenotyping and disease heterogeneity, and the presence of suppressor alleles in control populations.

Identifying the causal variant at each locus and understanding the biology of how the variant alters the risk of developing disease will provide a major advance in our ability to translate genetic associations into new therapeutic targets and diagnostic applications. Of the 29 known SLE loci, few causal variants have been identified [26,29,30,40] and detailed biological mechanisms for how the causal variants alter disease risk are understood for even fewer of the loci. The identification of causal variants will be greatly enhanced by emerging ‘next-generation’ sequencing technologies [211] and public efforts such as the ‘1000 Genomes Project’ [301]. However, proving the biological mechanism of candidate causal variants will be arduous. Among the challenges are the expected modest effect that common variants may have on protein function or expression, with some effects visible only under particular environmental conditions or perturbations, certain genetic backgrounds, developmental stages or cell types. One success story that illustrates these challenges is the identification of cell-type-specific phenotypes in the surface expression of IL-2A based on the genotype at the IL-2A locus, which has been shown to be associated with T1D and MS [212]. This study relied on access to a large collection of approximately 5000 normal volunteers who were recalled on the basis of risk and protective haplotypes to donate fresh blood samples as the phenotype of interest was not present in cryopreserved samples from the same donors. In addition, the IL-2A genotype accounted for only 18% of the variation in the level of surface expression observed, suggesting a crucial role for confounding genetic and environmental factors.

Five-year view

In the next 5 years, we expect progress to be made in identifying additional risk loci, both by larger genome-wide and targeted association studies, and by examining other sources of genetic variation, including rare variants, CNVs and epigenetics. In addition, causal variant identification will be greatly enhanced by near-complete catalogs of human variation and next-generation sequencing technologies, and better understanding the biological mechanism of causal variants by the establishment of large ‘bio-banks’ of normal individuals. These will be important incremental efforts in our quest to fully understand the underlying genetic and environmental causes of lupus, and to apply this knowledge to the development of new therapies and preventive measures.

Key issues

- Recent genome-wide association studies in systemic lupus erythematosus (SLE) have brought the current total of confirmed susceptibility alleles achieving genome-wide significance ($p < 5 \times 10^{-8}$) in this disease to 29.
- An additional 11 candidate loci have demonstrated strong evidence of association with SLE ($p < 5 \times 10^{-7}$), probably representing true genetic signals.
- The induction of type I IFN following stimulation of Toll-like receptors by nucleic acid-associated autoantigens is critical to the pathogenesis of SLE. It is hypothesized that genetic variation resulting in hyperactivation of this pathway predisposes individuals to SLE. Accordingly, there is evidence to support a role for several SLE risk genes in this pathway.

- SLE shares many susceptibility alleles with other autoimmune and inflammatory conditions. The identification and functional characterization of shared autoimmune loci may provide insight into the common pathogenic mechanisms that promote the breakdown of immunological tolerance.
- Many challenges remain in identifying the causal variant(s) at each locus in SLE and other complex diseases. Furthermore, as the effect size of each common genetic variant is small and confounded by other genetic and environmental factors, translating a genotype into a measurable phenotype is an extremely complex problem.
- Deep resequencing efforts using emerging 'next-generation' sequencing technologies have the potential to allow the detection of rare genetic variants that demonstrate association with disease, as well as assisting in the identification of causal alleles.

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Website

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Figure 1. Many SLE risk loci function in the Toll-like receptor/IFN-I signaling pathway

Nucleic acid-sensing TLRs, which include TLR-3, -7, -8 and -9, are localized to endosomal compartments. SLE immune complexes that contain nucleic acids are bound by FCGR2A on the surface of dendritic cells and are subsequently internalized where they gain access to the endosome and activate TLRs. TLR7, TLR8 and TLR9 signal through the adaptor protein MyD88, the kinases IRAK1 and IRAK4, and the E3 ubiquitin ligase TRAF6. Upon stimulation, the IRF family members IRF5 and IRF7 are phosphorylated, dimerize and translocate to the nucleus where they induce transcription of IFN-I. IRF5 is also critical for the induction of proinflammatory cytokines in response to TLR stimulation. TLR signaling activates the NF-κB transcription factor, which promotes the induction of many proinflammatory cytokines and other inflammatory genes. TNFAIP3 is a negative regulator of TRAF6 and inhibits the activation of NFκB. IFN-Is, which include many subtypes of IFN-α and a single subtype of IFN-β, bind to their receptor, which is composed of two chains, IFNAR1 and IFNAR2. Signaling through the receptor results in the activation of receptor-associated Janus kinases, JAK1 and TYK2, which in turn promote the phosphorylation of the STAT family members STAT1, STAT2 and STAT4. Upon activation, STAT proteins dimerize, translocate to the nucleus and induce the expression of IFN-I-inducible genes. In many cases, the evidence supporting certain functions is preliminary or inconclusive, as indicated by the ‘?’ and as described in the main text.

ATG: Autophagy-specific gene; BDCA: Blood dendritic cell antigen; ETS1: v-ets erythroblastosis virus E26 oncogene homolog 1; FCGR2A: Fc fragment of IgG receptor IIa; IFN-I: Type I interferon; IFNAR: IFN (α and β) receptor; IKZF1: Ikaros family zinc finger 1; IRAK: IL-1 receptor-associated kinase; IRF: Interferon regulatory factor; ITGAM: Integrin α M; JAK: Janus kinase; LYN: v-yes-1 Yamaguchi sarcoma viral-related oncogene homolog; MyD88: Myeloid differentiation primary response gene 88; NCF2: Neutrophil cytosolic factor

2; PRDM1: PR domain containing 1; STAT: Signal transducer and activator of transcription; TLR: Toll-like receptor; TNFAIP: TNF- α -induced protein; TNFSF4: TNF ligand superfamily 4; TRAF6: TNF receptor-associated factor 6; TYK2: Tyrosine kinase 2; UBE2L3: Ubiquitin-conjugating enzyme E2L3.

Table 1

Confirmed systemic lupus erythematosus risk loci based on the presence of at least one report with $p \leq 5 \times 10^{-8}$.

Putative function(s)	Gene of interest	Full name	Common aliases	Chromosome	SNP	Ref.
TLR/IFN signaling	<i>IRF5[†]</i>	Interferon regulatory factor 5		7q32.1	rs2070197	[15,16,18,19,29-31]
	<i>PHRF1/IRF7</i>	PHD and ring finger domains 1/interferon regulatory factor 7	<i>KIAA1542</i>	11p15.5	rs4963128	[15,18]
	<i>IRAK1/MECP2</i>	IL-1 receptor-associated kinase 1/methyl CpG-binding protein 2	<i>IRAK, pelle/RS</i>	Xq28	rs2269368	[18,44,47]
	<i>TNFAIP3[†]</i>	TNF- α -induced protein 3	<i>A20</i>	6q23.3	rs6920220	[14,16,19,43]
	<i>TNIP1</i>	TNFAIP3 interacting protein 1	<i>ABIN1, NAF1</i>	5q33.1	rs7708392	[18,19]
	<i>UBE2L3</i>	Ubiquitin-conjugating enzyme E2L 3	<i>UBCH7</i>	22q11.2	rs5754217	[15,18,19]
	<i>FCGR2A</i>	Fc fragment of IgG, low-affinity IIa, receptor	<i>CD32</i>	1q23.3	rs1801274	[15,18,25,26]
	<i>STAT4</i>	Signal transducer and activator of transcription 4		2q32.2	rs7574865	[15,16,18,19,32]
	<i>IKZF1</i>	IKAROS family zinc finger 1	<i>IKAROS</i>	7p12.2	rs4917014	[18,19]
	<i>ITGAM</i>	Integrin, α M	<i>CD11B, CR3A, MAC1</i>	16p11.2	rs1143679	[15,16,18,40]
TLR/IFN and lymphocyte signaling	<i>ATG5</i>	Autophagy-related 5 homolog		6q21	rs2245124	[15,18,19]
	<i>PRDM1</i>	PR domain containing 1, with ZNF domain	<i>BLIMP1</i>	6q21	rs6568431	[15,18,19]
	<i>ETS1</i>	v-ets erythroblastosis virus E26 oncogene homolog 1		11q24.3	rs6590330	[19]
Lymphocyte development and signaling	<i>HLA-DRB1</i>	MHC, class II, DR β 1		6p21.32	rs3135394	[15,16,18,22-24]
	<i>HLA-DRB1</i>	MHC, class II, DR β 1		6p21.32	rs9271366	[15,16,18,22-24]
	<i>BLK</i>	B-lymphoid tyrosine kinase		8p23.1	rs2736340	[15,16,18,19]
	<i>PTPN22</i>	Protein tyrosine phosphatase, non-receptor type 22	<i>LYP, PEP, PTPN8</i>	1p13.2	rs2476601	[15,16,18,27,28]
	<i>RASGRP3</i>	RAS guanyl-releasing protein 3		2p22.3	rs13385731	[18]
	<i>BANK1</i>	B-cell scaffold protein with ankyrin repeats 1		4q24	rs10516487	[17,18]
	<i>TNFSF4</i>	TNF superfamily, member 4	<i>OX40L, CD252</i>	1q25.1	rs2205960	[18,19,33]
	<i>IL10</i>	IL-10		1q31.1	rs3024505	[18]
Other/no known immune function	<i>JAZF1</i>	Juxtaposed with another zinc finger gene 1	<i>TIP27</i>	7p15.1	rs849142	[18]
	<i>PXK</i>	PX domain containing serine/threonine kinase		3p14.3	rs2176082	[15,18]
	<i>PTTG1</i>	Pituitary tumor-transforming 1	<i>EAP1, TUTRI</i>	5q33.3	rs2431099	[15,18]
	<i>LRRC18-WDFY4</i>	Leucine-rich repeat-containing 18/WDFY family member 4		10q11.22	rs1913517	[19]

Putative function(s)	Gene of interest	Full name	Common aliases	Chromosome	SNP	Ref.
	<i>DDX6</i>	DEAD box polypeptide 6	<i>HLR2</i> , <i>P54</i> , <i>RCK</i>	11q23.3	rs503425	[18,19]
	<i>SLC15A4</i>	Solute carrier family 15, member 4	<i>PTR4</i>	12q24.32	rs1385374	[18,19]
	<i>UHRF1BP1</i>	UHRF1-binding protein 1	<i>ICBP90BP1</i>	6p21.31	rs11755393	[18]

[†] Multiple independent alleles are associated with risk at these loci.

ABIN1: A20 binding and inhibitor of NF-κB 1; BLIMP1: B-lymphocyte-induced maturation protein 1; CR3A: Complement component receptor 3A; DEAD: Asp-Glu-Ala-Asp; EAP1: ESP1-associated protein 1; HLR2: Helicase RNA nuclear 2; ICPB90BP1: Inverted CAAT box-binding protein of 90-kDA binding protein 1; IRAK: IL-1 receptor-associated kinase; LYP: Lymphoid-specific protein tyrosine phosphatase; NAF1: Nef-associated factor 1; OX40L: OX40 ligand; PEP: PEST-domain phosphatase; PTPN8: Protein tyrosine phosphatase, nonreceptor type 8; PTR4: Peptide-histidine transporter 4; PX: Phox homology; RCK: Oncogene RCK; RS: Rett syndrome; SNP: Single nucleotide polymorphism; TIP27: TAK1-interacting protein 27; TLR: Toll-like receptor; TUTR1: Tumor-transforming protein 1; UBCH7: Ubiquitin-conjugating enzyme H7; UHRF: Ubiquitin-like with plant homeodomain and ring finger domains; WDFY: WD repeat and FYVE domain-containing.

Table 2
Candidate systemic lupus erythematosus risk loci based on the presence of at least one report with $p \leq 5 \times 10^{-7}$.

Putative function(s)	Gene of interest	Full name	Common aliases	Chromosome	SNP	Ref.
TLR/IFN signaling	<i>IRF8</i>	Interferon regulatory factor 8	<i>ICSBP1</i>	16p24.1	rs12444486	[14,18]
	<i>TYK2</i>	Tyrosine kinase 2		19p13.2	rs280519	[18,31]
	<i>IL12RB2</i>	IL-12 receptor, $\beta 2$		1p31.3-p31.2	rs1874791	[18]
Lymphocyte development and signaling	<i>LYN</i>	v-yes-1 Yamaguchi sarcoma viral- related oncogene homolog		8q12.1	rs7829816	[15]
	<i>ITPR3</i>	Inositol 1,4,5-triphosphate receptor, type 3	<i>IP-3R</i>	6p21.31	rs3748079	[48]
Other/no known immune function	<i>LYST</i>	Lysosomal trafficking regulator	<i>CHS1</i> , <i>Beige</i>	1q42.1-q42.2	rs9782955	[18]
	<i>NMNAT2</i>	Nicotinamide nucleotide adenyltransferase 2	<i>PNAT2</i>	1q25.3	rs2022013	[15,18]
	<i>ICAI</i>	Islet cell autoantigen 1	<i>ICA69</i>	7p21.3	rs10156091	[15,18]
	<i>SCUBE1</i>	Signal peptide, CUB domain, EGF-like 1		22q13.2	rs2071725	[15]
	<i>NGF2</i>	Neutrophil cytosolic factor 2	<i>NOXA2</i>	1q25	rs10911363	[18]
	<i>ARMC3</i>	Armadillo repeat-containing 3	<i>CT81</i>	10p12.31	rs11013210	[18]

CHS1: Chediak-Higashi syndrome 1; CT81: Cancer/testis antigen 81; CUB: Complement C1r/C1s, embryonic sea urchin protein, bone morphogenetic protein 1; ICA69: Islet cell autoantigen, 69 kDa; ICSBP1: Interferon consensus sequencing binding protein 1; IFN: Interferon; ITP3R: Inositol trisphosphate receptor; NOXA2: NADPH oxidase activator 2; PNAT2: Pyridine nucleotide adenyltransferase 2; SNP: Single nucleotide polymorphism; TLR: Toll-like receptor.

Table 3
Shared non-human leukocyte antigen autoimmune loci with evidence of association with systemic lupus erythematosus.

Putative function(s)	Gene of Interest	Full name	Common aliases	Phenotype	Same allele? [†]	Ref.
Lymphocyte signaling	<i>PTPN22</i>	Protein tyrosine phosphatase, non-receptor type 22	<i>LYP, PEP, PTPN8</i>	CD ⁺ , RA, T1D, Graves' disease, Hashimoto's thyroiditis	Yes	[15,16,18,27,28,137,143,144,149,150]
	<i>SH2B3</i>	SH2B adaptor protein 3	<i>LNK</i>	T1D, celiac disease	Yes	[18,157,158]
	<i>BLK</i>	B-lymphoid tyrosine kinase		RA, APS	Yes	[15,16,18,19,162,163]
	<i>PRDM1</i>	PR domain containing 1, with ZNF domain	<i>BLIMP1</i>	RA, CD	Unknown	[15,150,192]
Th1 development	<i>STAT4</i>	Signal transducer and activator of transcription 4		RA	Yes	[15,16,18,19,31]
	<i>IL12B</i>	IL-12B		CD, psoriasis	Yes	[18,172,173]
	<i>IL10</i>	IL-10		UC, T1D	Yes	[18,173,174]
Innate immunity	<i>TNIP1</i>	TNFAIP3 interacting protein 1	<i>ABIN1, NAF1</i>	Psoriasis	No	[18,172]
	<i>IRF8</i>	Interferon regulatory factor 8	<i>ICSBP1</i>	MS	No	[14,18,175]
	<i>TYK2</i>	Tyrosine kinase 2		MS	No	[18,31,177]
	<i>TNFAIP3</i>	TNF- α -induced protein 3	<i>A20</i>	RA, T1D, psoriasis, celiac disease, CD	Yes and no [§]	[14,41,43,172,198–200]
	<i>IFIH1</i>	Interferon induced with helicase C domain 1	<i>MDA5</i>	T1D, Graves' disease	Yes	[18,178,179]
	<i>CFB</i>	Complement factor B		AMD	Yes	[18,183]
	<i>FCGR2A</i>	Fc fragment of IgG, low affinity IIa, receptor	<i>CD32</i>	RA	Unknown	[15,18,25,26,192]
	<i>MIF</i>	Macrophage migration inhibitory factor	<i>GIF</i>	RA, CD, psoriasis, celiac disease	Yes and no	[186–190]
Unknown	<i>CLEC16A</i>	C-type lectin domain family 16, member A		T1D, Addison's disease, MS	Yes	[18,138–140]
	<i>C10orf67</i>	Chromosome 10 open-reading frame 67		CD	No	[18,141]

[†] $r^2 > 0.4$ with systemic lupus erythematosus single nucleotide polymorphism.

[‡] Same SNP but opposite direction: PTPN22 allele is protective in CD, but is a risk in systemic lupus erythematosus, RA, T1D and Graves' disease.

[§] For these genes, there are multiple alleles with independent effects.

ABIN1: A20 binding and inhibitor of NF- κ B 1; AMD: Age-related macular degeneration; APS: Antiphospholipid syndrome; BLIMP1: B-lymphocyte-induced maturation protein 1; CD: Crohn's disease; GIF: Glycosylation-inhibiting factor; ICSPB1: IFN consensus sequence-binding protein 1; LYP: Lymphoid-specific protein tyrosine phosphatase; MDA5: Melanoma differentiation-associated protein 5; MS: Multiple sclerosis; NAF1: Nef-associated factor 1; PEP: PEST-domain phosphatase; RA: Rheumatoid arthritis; T1D: Type 1 diabetes; UC: Ulcerative colitis.