

REVIEW

# The genetics of lupus: a functional perspective

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## Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease with a strong genetic component and is characterized by chronic inflammation and the production of anti-nuclear auto-antibodies. In the era of genome-wide association studies (GWASs), elucidating the genetic factors present in SLE has been a very successful endeavor; 28 confirmed disease susceptibility loci have been mapped. In this review, we summarize the current understanding of the genetics of lupus and focus on the strongest associated risk loci found to date ( $P < 1.0 \times 10^{-8}$ ). Although these loci account for less than 10% of the genetic heritability and therefore do not account for the bulk of the disease heritability, they do implicate important pathways, which contribute to SLE pathogenesis. Consequently, the main focus of the review is to outline the genetic variants in the known associated loci and then to explore the potential functional consequences of the associated variants. We also highlight the genetic overlap of these loci with other autoimmune diseases, which indicates common pathogenic mechanisms. The importance of developing functional assays will be discussed and each of them will be instrumental in furthering our understanding of these associated variants and loci. Finally, we indicate that performing a larger SLE GWAS and applying a more targeted set of methods, such as the ImmunoChip and next-generation sequencing methodology, are important for identifying additional loci and enhancing our understanding of the pathogenesis of SLE.

## Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease characterized by hyperactive T and B cells, auto-antibody production, and immune complex

(IC) deposition [1]. SLE has a prevalence of approximately 1 in 2,500 in European populations [2] and is more frequent in those of non-European ancestry. SLE affects predominantly women (the female-to-male ratio is 9:1) of child-bearing age and is characterized by variable clinical features, including malar rash, glomerulonephritis, arthritis, and neuropsychiatric disease [3]. Although the exact etiology of lupus is not fully understood, a strong genetic link has been identified through the use of association and family studies. The heritability of SLE is approximately 66%; the rates of concordance are 24% to 56% in monozygotic twins and 2% to 4% in dizygotic twins [4,5].

To date, genome-wide association studies (GWASs) have identified more than 30 associated loci. In Table 1, we show the variants that have reached genome-wide significance ( $1.0 \times 10^{-8}$ ) in one or more GWASs, a meta-analysis, or replication studies. We have also included the Fcy locus, because it contains multiple associated variants, including a confirmed copy number variation (CNV) in SLE. However, these loci account for less than 10% of the genetic heritability [6].

GWASs in SLE have been useful tools for expanding the genetic understanding of SLE by identifying new loci and replicating previously associated loci. In this review, we categorize these risk loci into a number of pathways on the basis of the current understanding of the potential role for the locus in SLE. We note that the clinical heterogeneity of SLE is mirrored by the diversity of the pathways reported to contain the associated loci from the genetic studies, apoptosis, innate immune response, ubiquitination, and phagocytosis (Table 1). Therefore, this review aims to highlight the known function(s) of the associated loci and to indicate where further functional studies are needed to elucidate the pathogenic mechanisms in lupus.

## Contribution of apoptosis to SLE pathogenesis

Apoptosis is a well-defined process of programmed cell death and does not immediately release the intracellular content into the extracellular environment [7,8]. In healthy individuals, dead or dying cells are cleared by macrophages in an inherently anti-inflammatory way. However, in patients with SLE, apoptosis has been reported to be defective and plays a role in disease

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**Table 1. A summary of loci associated with systemic lupus erythematosus in one or more genome-wide association studies, a meta-analysis, and replication studies ( $P < 1.0 \times 10^{-8}$ )**

Locus	Gene	Position	Variant	P value (significance)	OR (CI) (effect size)	Autoimmune disease associations	Function
<i>ITGAM</i> <sup>a</sup>	Intergrin alpha M	16p11.2 (intronic)	rs9888739 (T)	$1.61 \times 10^{-23}$	1.62 (1.47-1.78)		Phagocytosis
<i>FcyR</i>	Fcy receptors	Multiple (see text)	Multiple (see text)	Multiple (see text)	Multiple (see text)	UC	Phagocytosis
<i>PRDM1-ATG5</i> <sup>b</sup>	PR domain zinc finger protein 1- autophagy-related 5 homolog	6q21-q22.1 (intergenic)	rs548234 (G)	$5.18 \times 10^{-12}$	1.25 (1.17-1.33)		Autophagy and B-cell differentiation
<i>TNFAIP3</i> <sup>b</sup>	Tumor necrosis factor-alpha-induced protein	6q23 (exonic)	rs2230926 (C)	$1.37 \times 10^{-17}$	1.72 (1.52-1.94)	RA, CeID, UC, and PS	Ubiquitination
<i>TNIP1</i> <sup>a</sup>	TNFAIP3-interacting protein 1	5q32-q33.1 (intronic)	rs7708392 (C)	$3.8 \times 10^{-13}$	1.27 (1.10-1.35)	PS	
<i>UBE2L3</i> <sup>b</sup>	Ubiquitin-conjugating enzyme E2L 3	22q11.2- q13.1 (upstream)	rs463426 (G)	$1.48 \times 10^{-16}$	0.78 (0.74-0.83)	CD, RA, and CeID	
<i>ETS1</i> <sup>b</sup>	V-ETS avian erythroblastosis virus E26 oncogene homolog 1	11q23.3 (downstream)	rs6590330 (A)	$1.77 \times 10^{-25}$	1.37 (1.29-1.45)	RA	Lymphocyte development and activation
<i>IKZF1</i> <sup>b</sup>	IKAROS family zinc finger 1	7p12 (upstream)	rs4917014 (C)	$2.75 \times 10^{-23}$	1.23 (1.03-1.42)		
<i>CD44</i> <sup>d</sup>	CD44	11p13 (upstream)	rs507230	$3.98 \times 10^{-12}$	0.71 (0.63-0.79)		
<i>BANK1</i> <sup>c</sup>	B-cell scaffold protein with ankyrin repeats 1	4q22-q24 (exonic)	rs10516487 (G)	$3.7 \times 10^{-10}$	1.38 (1.25-1.53)	RA	B-cell activation and signaling
<i>BLK</i> <sup>b</sup>	B lymphoid tyrosine kinase	8p23-p22 (upstream)	rs7812879 (A)	$2.09 \times 10^{-24}$	0.69 (0.64-0.74)	RA	
<i>LYN</i> <sup>a</sup>	V-yes-1 Yamaguchi sarcoma viral-related oncogene homolog	8q13 (intronic)	rs7829816 (C)	$5.40 \times 10^{-9}$	0.77 (0.70-0.84)		
<i>RasGRP3</i> <sup>b</sup>	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	2p25.1-p24.1 (intronic)	rs13385731 (G)	$1.25 \times 10^{-15}$	0.70 (0.64-0.76)		
<i>NCF2</i> <sup>f</sup>	Neutrophil cytosolic factor 2	1q25 (intronic)	rs10911363 (T)	$2.87 \times 10^{-11}$	1.18 (1.10-1.30)		
<i>STAT4</i> <sup>b</sup>	Signal transducer and activator of transcription 4	2q32.2-q 32.3 (intronic)	rs7574865 (A)	$5.17 \times 10^{-42}$	1.51 (1.43-1.61)	RA, IBD, T1D, and Sjögren's syndrome	T-cell development and signaling
<i>PTPN22</i> <sup>e</sup>	Protein tyrosine phosphatase non-receptor type 22	1p13 (exonic)	rs2476601 (A)	$3.4 \times 10^{-12}$	1.35 (1.24-1.47)	T1D and Graves' disease	
<i>TNFSF4</i> <sup>b</sup>	Tumor necrosis factor (ligand) superfamily member 4	1q25 (upstream)	rs2205960 (A)	$2.5 \times 10^{-32}$	1.46 (1.37-1.56)		
<i>HLA-DRB1</i> <sup>e</sup>	HLA class II histocompatibility antigen	6p21.3 (downstream)	rs3135394 (G)	$2.0 \times 10^{-60}$	1.98 (1.84-2.14)	T1D, RA, CeID, IBD, and CD	Antigen presentation
<i>SLC15A4</i> <sup>b</sup>	Solute carrier family 15, member 4	12q24.32 (exonic)	rs10847697 (A)	$3.54 \times 10^{-11}$	1.26 (1.17-1.34)		
<i>IRF5</i> <sup>e</sup>	Interferon regulatory factor 5	7q32 (3' untranslated region)	rs2070197 (C)	$5.8 \times 10^{-24}$	1.88 (1.78-1.95)	Rheumatic disease and RA	Interferon regulation and production
<i>IRF7</i> <sup>a</sup>	Interferon regulatory factor 7	11p15.5 (downstream)	rs4963128 (T)	$3.0 \times 10^{-10}$	0.78 (0.73-0.85)	T1D	

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**Table 1. Continued**

Locus	Gene	Position	Variant	P value (significance)	OR (CI) (effect size)	Autoimmune disease associations	Function
<i>IRF8<sup>f</sup></i>	Interferon regulatory factor 8	16q24.1 (downstream)	rs2280381 (A)	$1.24 \times 10^{-8}$	1.17 (1.10-1.24)	UC and MS	
<i>IFIH1<sup>f</sup></i>	Interferon-induced helicase C domain-containing protein 1	2q24 (exonic)	rs1990760 (T)	$1.63 \times 10^{-8}$	1.23 (1.09-1.39)		
<i>TYK2<sup>f</sup></i>	Tyrosine kinase 2	19p13.2 (intronic)	rs280519 (A)	$3.88 \times 10^{-8}$	1.29 (1.15-1.47)	MS	
<i>LRRC18-WDFY4<sup>b</sup></i>	Leucine-rich repeat containing 18-WD repeat and FYVE domain-containing protein 4	10q11.22-q11.23 (intergenic)	rs1913517 (A)	$7.22 \times 10^{-12}$	1.24 (1.17-1.32)		Unknown function
<i>PXK<sup>a</sup></i>	PX domain containing serine/threonine kinase	3p14.3 (intronic)	rs6445975 (C)	$7.10 \times 10^{-9}$	1.25 (1.16-1.35)	RA	
<i>JAZF1<sup>e</sup></i>	Juxtaposed with another zinc finger gene 1	7p15 (intronic)	rs849142 (T)	$1.5 \times 10^{-9}$	1.19 (1.13-1.26)		
<i>UHRF1BP1<sup>e</sup></i>	UHRF-binding protein 1	6q23 (exonic)	rs11755393 (G)	$2.2 \times 10^{-8}$	1.17 (1.10-1.24)		
<i>XKR6<sup>a</sup></i>	XK, Kell blood group complex subunit-related family, member 6	8p23.1 (intronic)	rs6985109 (G)	$2.51 \times 10^{-11}$	1.23 (1.16-1.30)		

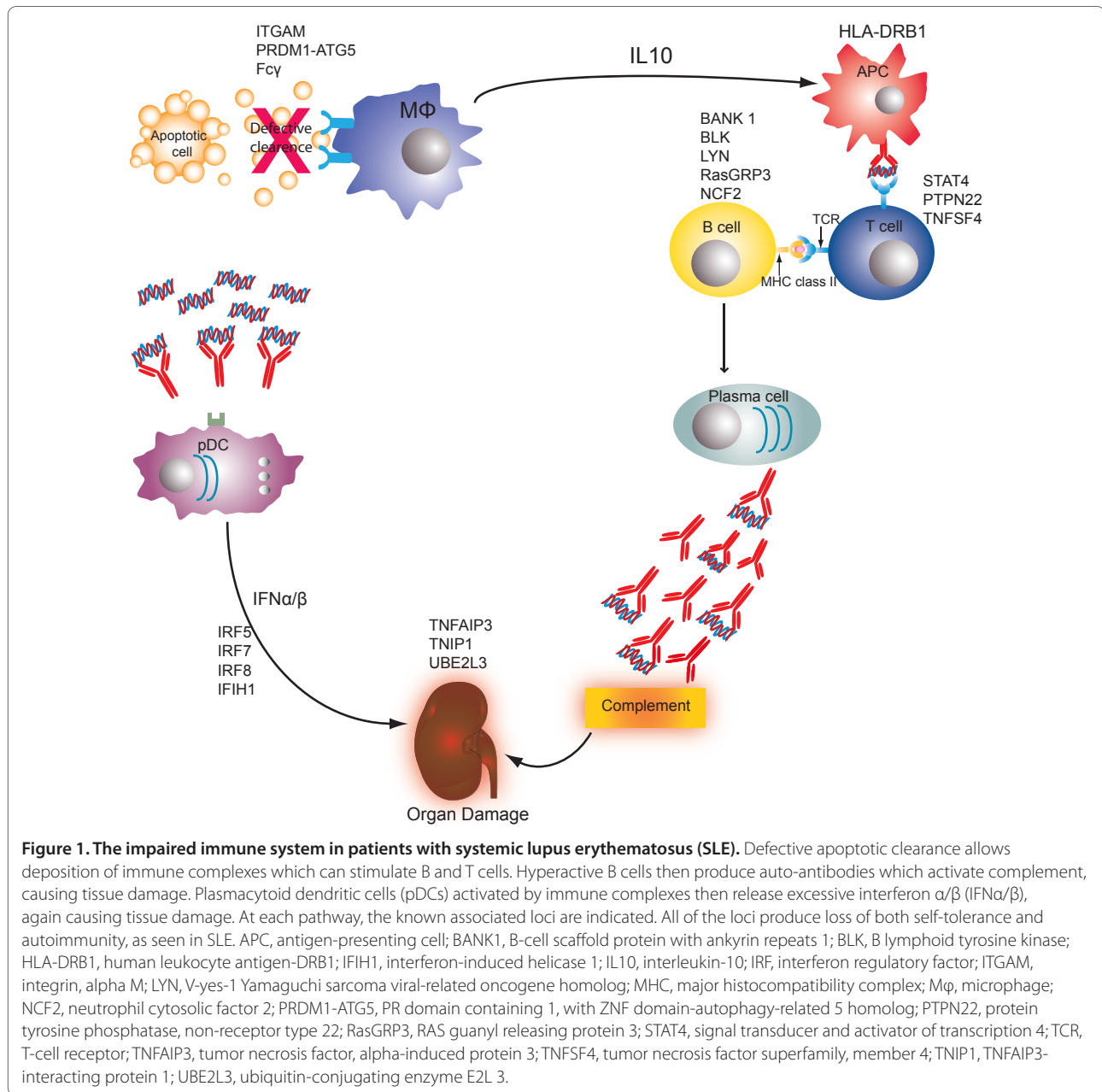
Odds ratios (ORs) and confidence intervals (CIs) are noted with the primary function of each locus. The genome-wide association studies from which this table was generated were conducted by <sup>a</sup>Harley and colleagues [95] (1,846 systemic lupus erythematosus (SLE) women cases and 1,825 controls), <sup>b</sup>Han and colleagues [53] (1,047 Han Chinese cases and 1,205 controls), and <sup>c</sup>Kozyrev and colleagues [59] (279 Swedish SLE cases and 515 controls). The meta-analysis study was conducted by <sup>d</sup>Ramos and colleagues [58] (939 Caucasian cases and 3,398 controls). The replication studies were conducted by Han and colleagues [53] (3,152 Han Chinese cases and 7,050 controls), <sup>e</sup>Gateva and colleagues [6] (1,963 cases and 4,329 controls), and <sup>f</sup>Cunningham-Graham and colleagues [69] (870 UK SLE cases and 5,551 controls). All loci that have been reported to be associated with other autoimmune diseases – Crohn's disease (CD), celiac disease (CeID), irritable bowel syndrome (IBD), multiple sclerosis (MS), psoriasis (PS), rheumatoid arthritis (RA), type 1 diabetes (T1D), and ulcerative colitis (UC) – are also stated [58].

manifestation [9]. Patients with SLE demonstrate defective clearance of apoptotic cells, which evokes a secondary transition into necrotic cell death [10]. During apoptosis, cells shrink and change morphology by engulfing self-antigens, forming membrane-bound blebs that are exposed on the cell surface. Once engulfed, these blebs carry on their surface intracellular proteins, which can act as a source of auto-antigens, a tendency that is enhanced if clearance is defective [11,12]. With defective clearance of apoptotic blebs, cells undergo secondary necrosis, releasing nuclear auto-antigens [13]. This process triggers the production of inflammatory cytokines and interferon-alpha (IFN $\alpha$ ) [10], promoting lymphocyte loss of self-tolerance, auto-antibody production, and IC deposition. The ICs can bind low-affinity Fc $\gamma$ RIIa, expressed on plasmacytoid dendritic cells (pDCs). After endocytosis of the ICs, Toll-like receptor 7/9 (TLR7/9) is activated through the DNA/RNA presented by IC [14] and this in turn stimulates the production of IFN by pDCs (Figure 1). This production of IFN propagates chronic inflammation and loss of tolerance, both of which are hallmarks of SLE. It has also been reported

that patients with SLE have an increased rate of lymphocyte apoptosis [15], which is possibly due to increased activation of these cells. Mutations in a number of loci associated with SLE have been reported to propagate defective clearance of apoptotic cells and increased apoptosis.

#### **ITGAM**

*ITGAM* encodes the  $\alpha$ -chain of  $\alpha$ M $\beta$ 2-integrin (*CD11b*) [16] and plays a role in phagocytosis and leukocyte adhesion [17]. GWASs have reported that variants at this locus are associated with SLE, and single-nucleotide polymorphism (SNP) rs9888739 showed the strongest association ( $P = 1.61 \times 10^{-23}$ , odds ratio (OR) = 1.62). However, a trans-ancestral study in European-Americans and African-Americans [18] indicated the causal variant as rs1143679, which has been reported to cause two functional changes in *ITGAM*. The first of these functional changes is an amino acid mutation at R77H (Arg-His) which modifies the tertiary and quaternary structures of the  $\alpha$ M $\beta$ 2 ligand-binding domain [18].  $\alpha$ M $\beta$ 2-integrin interacts with a number of ligands such as



intracellular adhesion molecule 1 (ICAM-1) and the complement C3 degradation product, C3bi; these ligands play a role in leukocyte activation, migration, and phagocytosis [16]. Variants in the  $\alpha M\beta 2$  ligand-binding domain may alter binding affinity, hence leukocyte trafficking, phagocytosis [16], and IC clearing [19]. The second functional change is with rs1143679, which impairs the phagocytosis of C3bi-coated particles [20] and propagates the deficient clearance of ICs and increased inflammation [20]. However, the exact mechanism of how both of these variants influence the pathogenesis of SLE warrants further investigation.

### Fcγ receptors

The *FCGR* genes encode diverse Fcγ receptors that recognize the Fc portion of immunoglobulin G (IgG) molecules. Several missense polymorphisms in *FCGR2A*, *FCGR2B*, and *FCGR3A* [21-23] are associated with SLE. Three of the five *FCGR* genes (*FCGR3A*, *FCGR2C*, and *FCGR3B*) have been reported to show CNV [24] and expression of Fcγ receptors on the cell surface is dependent on the number of copies expressed [25,26]. A CNV that resulted in a reduced number of *FCGR3B* molecules expressed on the cell surface of neutrophils is associated with SLE. The exact mechanism by which the CNV

incorporating *FCGR3B* promotes disease is not fully established, although reduced binding of ICs by neutrophils is a possible mechanism.

### The role of ubiquitination in SLE

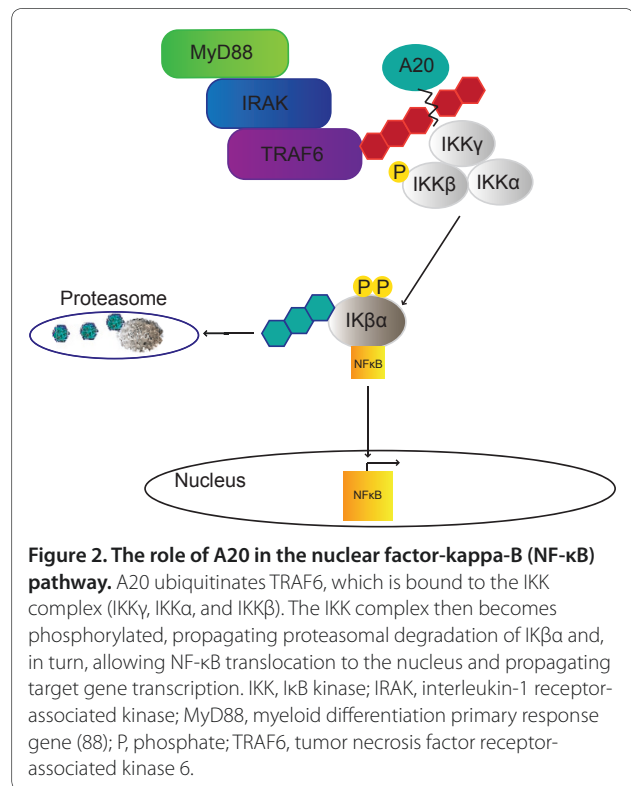
Ubiquitination is still an incompletely understood biochemical process by which proteins are post-translationally modified through the addition of single ubiquitin molecules or polyubiquitin chains. During ubiquitination, proteins may be tagged for proteolytic degradation by the proteasome. Ubiquitination has also been reported to regulate transcription factors and intracellular kinase activity [27]. Genes that encode these different components of the protein modification system have been reported to be associated with SLE.

#### *TNFAIP3* and *TNIP1*

*TNFAIP3* encodes the ubiquitin-editing enzyme A20 [28,29], which alters ubiquitin patterns, which then alter targeting for proteasome degradation and termination of nuclear factor-kappa-B (NF- $\kappa$ B)-derived pro-inflammatory responses. This occurs through the ubiquitination of IKK $\gamma$  and phosphorylation of IKK $\beta$  [30,31], facilitating the release of NF- $\kappa$ B (Figure 2). A20 is a key regulator of NF- $\kappa$ B through ubiquitin modifications of receptor-interacting protein kinase (RIP) and tumor necrosis factor receptor-associated kinase 6 (TRAF6) [32]. Multiple associations have been found in *TNFAIP3* in a range of autoimmune diseases [28]; of these associations, rs2230926 has shown the strongest significance ( $P = 1.37 \times 10^{-17}$ , OR = 1.72) in SLE. This non-synonymous SNP [33] causes an amino acid change from a Phe-Cys. This amino acid change propagates A20 protein to be less effective at inhibiting tumor necrosis factor (TNF)-induced NF- $\kappa$ B activity [34]. Variants at this locus could potentially lead to reduced inhibitory activity of NF- $\kappa$ B and reduced expression of A20.

Owing to increased NF- $\kappa$ B signaling, *Tnfaip3*<sup>-/-</sup> mice develop spontaneous inflammation and lymphocyte cell death [35]. This shows the importance of *TNFAIP3* in NF- $\kappa$ B regulation through the ubiquitination of adaptors such as RIP [35]. Therefore, it can be seen that *TNFAIP3* is an important locus that contributes to SLE pathogenesis through its downregulation. The downregulation of *TNFAIP3* facilitates hyperactive NF- $\kappa$ B signaling, chronic inflammation, and reduced apoptosis, all characteristics of SLE.

*TNIP1*, an adaptor protein that binds to A20, has also been reported to be associated with SLE. *TNIP1* is expressed on lymphocytes and its expression is induced by NF- $\kappa$ B [36]. However, overexpression of *TNIP1* inhibits NF- $\kappa$ B activation by TNF [37]. Variants in *TNIP1* could potentially play a role in negatively regulating the NF- $\kappa$ B pathway [38]. SNP rs7708392 has been reported to play a role in *TNIP1* splicing, rendering the inhibition



**Figure 2. The role of A20 in the nuclear factor-kappa-B (NF- $\kappa$ B) pathway.** A20 ubiquitinates TRAF6, which is bound to the IKK complex (IKK $\gamma$ , IKK $\alpha$ , and IKK $\beta$ ). The IKK complex then becomes phosphorylated, propagating proteasomal degradation of IKK $\beta$  and, in turn, allowing NF- $\kappa$ B translocation to the nucleus and propagating target gene transcription. IKK, I $\kappa$ B kinase; IRAK, interleukin-1 receptor-associated kinase; MyD88, myeloid differentiation primary response gene (88); P, phosphate; TRAF6, tumor necrosis factor receptor-associated kinase 6.

of the NF- $\kappa$ B pathway less effective. This would propagate pro-inflammatory responses and chronic inflammation. This variant has been shown to be associated with Caucasian and Asian populations [36].

#### *UBE2L3*

*UBE2L3* is a ubiquitin-carrier enzyme gene and is expressed widely on all lymphocytes [39]. It plays a key role in the maturation of transcription factors (for example, p53 and p105, the latter of which is an NF- $\kappa$ B precursor) [40,41]. This enzyme regulates IFN through TLR7/9 [42,43]. The exact mechanism of *UBE2L3* is still not fully understood, but variants in this locus have been shown to be associated with SLE (rs463426,  $P = 1.48 \times 10^{-16}$ , OR = 0.78).

#### Abnormalities of lymphocyte development in SLE

SLE is associated with multiple dysfunctions in many lymphocyte subsets. SLE T cells have been reported to show inappropriate tissue homing, increased secretion of pro-inflammatory cytokines [44], and activation of both dendritic cells (DCs) and B cells [45]. A number of loci have been found to be associated with lymphocyte differentiation and SLE, as described below.

#### *ETS1* and *IKZF1*

*ETS1* and *IKZF1* are transcription factors that regulate lymphocyte differentiation and lymphocyte development



[46,47]. *ETS1* has been reported as a negative regulator of B-cell differentiation and T helper 17 ( $Th_{17}$ ) cell proliferation [48]. Patients with SLE demonstrate a reduced expression of *ETS1*, which may contribute to abnormal B-cell differentiation into immunoglobulin-secreting plasma cells and an increased number of  $Th_{17}$  cells [49-51]. While having increased proliferation of  $Th_{17}$  cells causes increased inflammation through the secretion of interleukin-17 (IL-17), *ETS1*-deficient  $Th_1$  cells secrete higher amounts of anti-inflammatory cytokine IL-10 [52]. Interestingly, these *ETS1*-deficient  $Th_1$  cells have reduced secretion of IL-2, which is a potent  $Th_{17}$  inhibitor [52]. The top associated variant at this locus, rs6590330 ( $P = 1.77 \times 10^{-25}$ , OR = 1.37), could potentially play a role in decreasing *ETS1* expression.

Patients with SLE have also been reported to express low *IKZF1* levels in peripheral blood [48]. The strongest association found at this locus is rs4917014 ( $P = 2.75 \times 10^{-23}$ , OR = 1.23) [53], which may play a role in downregulating *IKZF1* expression. This reduced level of expression contributes to SLE pathogenesis through interactions with other genes; for example, *IKZF1* has been reported to play a role in trans-activating *STAT4*, a confirmed risk locus in SLE [54]. *IKZF1* is important for lymphocyte differentiation [55] and regulation of self-tolerance through B-cell receptor (BCR) signaling [56]. Downregulation of this locus would therefore promote loss of self-tolerance, a hallmark of SLE.

### Inappropriate B-cell physiology in SLE

Hyperactive B cells play an important role in the pathogenesis of SLE. With the production of auto-antibodies and prolonged cell life, B-cell regulation is important in the maintenance of immune balance. B cells of patients with SLE have been shown to present auto-antigens, induce CD4<sup>+</sup> T helper cells ( $Th_1/Th_2$ ), inhibit T regulatory cells, and secrete pro-inflammatory cytokines [57]. A number of key loci have been reported to be associated with SLE and are described below.

#### *BANK1*, *BLK*, and *LYN*

The gene products of *BANK1*, *BLK*, and *LYN* operate in the BCR signaling pathway and have been reported to be associated with SLE [58], which together attest to the importance of this pathway in disease pathogenesis. rs10516487, located in the *BANK1*-binding region [59], has shown the strongest association with SLE ( $P = 3.1 \times 10^{-10}$ , OR = 1.38). After B-cell activation, *BANK1* becomes tyrosine-phosphorylated, resulting in phosphorylation of type 1 inositol-1,2,4-triphosphate (IP(3)R). This phosphorylation event serves to augment calcium mobilization and hence B-cell activation [60]. The associated variant at *BANK1* increases its expression by influencing splicing efficiency, creating a splicing

enhancer [59]. The expression increase propagates stronger binding affinity between *BANK1* and IP(3)R, resulting in hyper-responsiveness [61]. Cells expressing the risk allele of this variant also have higher protein levels, which can sustain BCR signaling and hyperactive B cells, as shown in SLE [59].

Associated allelic variants in *BLK* (rs7812879,  $P = 2.09 \times 10^{-24}$ , OR = 0.69) and *LYN* (rs7829819,  $P = 5.40 \times 10^{-9}$ , OR = 0.77), in comparison with *BANK1*, have been shown to decrease their respective expressions [61,62]. *LYN* kinase mediates inhibitory signals from CD22, which modulates the B-cell activation threshold [63]. Downregulation of *LYN* causes hyper-responsiveness of BCR stimulation, triggering autoimmunity [64] as shown in *Lyn*<sup>-/-</sup> mice [65]. Compared with *BLK*, which affects pre-BCR signaling, active *BLK* enhances BCR responsiveness [66]. *Blk*<sup>-/-</sup> mice have shown no phenotype [67]; thus, an interaction with *BANK1* could potentially explain the association with SLE [61]. As *LYN* and *BLK* share similarities of genomic structure [64], it is believed that, in BCR signaling, *BLK* plays a role similar to that of *LYN*.

#### *RasGRP3*

*RasGRP3* regulates Ras-ERK signaling, which is crucial in lymphocyte development and activity [68], and is involved in B-cell proliferation and immunoglobulin production [53]. rs13385731 ( $P = 1.25 \times 10^{-15}$ , OR = 0.70) at the *RasGRP3* locus has been reported to be associated with SLE and may cause an underexpression of *RasGRP3*, which blocks its inhibitory role in B-cell proliferation.

#### *NCF2*

*NCF2* is a cytosolic subunit of NADPH oxidase, which is expressed on B cells [69]. It is thought to play a role in the increased production and release of free radicals, propagating B-cell activation. rs10911363 ( $P = 2.87 \times 10^{-11}$ , OR = 1.18) has been shown to have reached genome-wide significance in SLE [69] and could play a role in increased *NCF2* expression in patients with SLE.

### Dysregulation of T cells in SLE

Patients with SLE demonstrate an increased number of CD3<sup>+</sup>CD4<sup>-</sup>CD8<sup>-</sup> T cells and  $Th_{17}$  cells and a variable effect on T regulatory cells [44]. These T-cell subsets together lead to increased inflammation, B-cell interaction, and tissue damage [45]. SLE T cells engage the CD3-TCR faster and earlier, leading to increased signaling and intracellular calcium levels. These increased calcium levels may lead to increased expression of CD40L, increasing transcription of cAMP-responsive element modulator (CREM), which would produce hyperactive T cells [70]. However, data on T regulatory cell expression in SLE have been variable. Some reports

suggest that T regulatory cells, such as CD4<sup>+</sup>CD25<sup>+</sup> T cells, are deficient in SLE [71]. However, others report enrichment for this cell type [72,73], perhaps relating to heterogeneity in the definitions of regulatory cells using cell-surface markers. It has also been reported that SLE T cells, compared with control T cells, undergo an increased rate of apoptosis, which again will contribute to SLE pathogenesis. As described below, there are a number of associated loci whose gene products play a key role in T-cell development and TCR signaling and have been reported to be associated with SLE.

#### **STAT4**

*STAT4* is a Th<sub>1</sub> transcription factor that has been reported to mediate Th<sub>1</sub> T-cell response, Th<sub>1</sub> cytokines, IL-12 and IL-23 [74,75], and IFN $\gamma$  signaling [76,77]. rs7574865 has been reported to have the strongest association with SLE ( $P = 5.17 \times 10^{-42}$ , OR = 1.51) and has also been described for other autoimmune diseases such as rheumatoid arthritis (RA) [74], Sjögren's syndrome [78], inflammatory bowel disease, and type 1 diabetes (T1D) [79]. rs7574865 has been described as being associated with many SLE clinical features, such as lupus nephritis [80]. *STAT4* propagates a Th<sub>1</sub> T-cell response, increasing IFN $\gamma$  release [81]. As seen in Figure 1, this influx of IFN $\gamma$  would target organs such as the kidneys, propagating further IFN $\gamma$  release and chronic inflammation. rs7574865 may act to increase *STAT4* expression and hence IFN $\gamma$  production. Further reports have shown that other associated variants, such as rs7582694 (intronic), show overexpression of the risk allele (C) in mesenchymal cells but not in B cells [82]. This *STAT4* risk allele was also reported to be overexpressed in cells carrying the risk haplotype in comparison with cells not carrying this haplotype [82].

#### **PTPN22**

*PTPN22* encodes the lymphoid tyrosine phosphate protein, LYP, which is involved in the downregulation of T-cell activation through the interaction with cytoplasmic tyrosine kinase (CSK) and suppression of T regulatory cells [83]. rs2476601 ( $P = 3.4 \times 10^{-12}$ , OR = 1.35) has been reported to be associated with SLE and also with T1D and RA [84]. Furthermore, a trans-ancestral study has shown that rs2476601 is associated with SLE in Europeans, Hispanics, and African-Americans [85]. The associated variant causes the amino acid change of Arg-Try, preventing *PTPN22* interaction with CSK [86,87]. However, the experimental evidence suggests that rs2476601 reduces TCR signaling [88]. Furthermore, *PTPN22* expressing the associated risk allele (A) has been reported to bind CSK less effectively than those expressing the G allele, producing hyper-responsive T cells [85]. Therefore, the current

experimental evidence does not give us the full understanding of *PTPN22* function and warrants further investigation.

#### **TNFSF4 (OX40L)**

*TNFSF4* is expressed on the surface of antigen-presenting cells (APCs), B cells, and macrophages, and its unique ligand CD123 (*OX40*) is expressed on activated CD4<sup>+</sup> and CD8<sup>+</sup> T cells [89]. The strongest association in *TNFSF4* is with the upstream variant rs2205960 ( $P = 2.5 \times 10^{-32}$ , OR = 1.46), and protective and risk haplotypes that carry alternate alleles of rs2205960 have been observed [90]. The risk haplotype has been reported to be associated with increased *TNFSF4* transcript levels [91,92]. This increased expression of *OX40L* promotes *OX40/OX40L* interactions and increases the co-stimulatory signal between APCs and T cells, and this in turn increases T-cell survival and thereby propagates autoimmunity. *OX40L* has been shown *in vitro* to inhibit the generation of IL-10-producing T regulatory cells needed for tolerance, and it is known that mutations in this pathway cause loss of tolerance and autoimmunity [93].

#### **Defective antigen presentation in SLE**

##### **HLA-DRB1/MHC**

The major histocompatibility complex (*MHC*) region has been shown to exert the strongest genetic association and effect in SLE to date; the top association was found at *HLA-DRB1* ( $P = 2.0 \times 10^{-60}$ , OR = 1.98). Studies examining the association with HLA class II have implicated both *HLA-DRB1\*03:01* and *HLA-DRB1\*15:01* [94] in SLE. The *MHC* is composed of 250 genes subdivided into three classes (I, II, and III) with a strong linkage disequilibrium (LD) spanning the region. There appear to be multiple independent signals at the *MHC* in SLE, accounting for the overall strength of the association seen with the region. One paper reported a 180-kb region of class II, spanning *HLA-DRB1*, *HLA-DQA1*, and *HLA-DQB* [95], whereas the second signal was found in a marker of the class III gene *SKIV2L*. Other immunologically relevant genes such as complement *C4A* and *C4B* are also in this region of *MHC*. The strong LD covering the extended *MHC* region makes it difficult to identify whether the association arises from the associated variants currently identified or from variants within this LD region. For this reason, further fine mapping of the region is needed and the region may also benefit from trans-ancestral mapping [96].

#### **The interferon signature and its regulation in SLE**

More than half of patients with SLE show a dysregulation in the expression of genes in the IFN pathway [97]. The type I IFNs are potent cytokines (IFN $\alpha$  and IFN $\beta$ ) and also mediate the Th<sub>1</sub> response, sustain activated T cells,

sustain B-cell survival, and lower the B-cell activation threshold [98]. These responses propagate pro-inflammatory cytokines, contributing to chronic inflammation and tissue damage [14]. IFN also acts as a bridging mechanism between the innate and adaptive immune systems. However, it is unclear whether elevated IFN is the causal effect of SLE or whether it further propagates disease intensity. Given the genetic role of *IRF5* and a number of other genes in the IFN pathway, it is likely that IFN exerts a pathway effect in the pathogenesis of disease.

#### ***IRF5, IRF7, and IRF8***

*IRF5*, *IRF7*, and *IRF8* are transcription factors that play a role in type 1 IFN signaling and immune cell development [99]. SNPs in *IRF5*, *IRF7*, and *IRF8* ( $P = 5.8 \times 10^{-24}$ , OR = 1.88;  $P = 3.0 \times 10^{-10}$ , OR = 0.78; and  $P = 1.24 \times 10^{-8}$ , OR = 1.17, respectively) (as shown in Table 1) have been shown to be associated with increased risk of SLE [98]. These variants have been shown to increase the levels of *IRF5*, *IRF7*, and *IRF8* transcript and protein expressions [100]. Of these three loci, *IRF5* exhibits the largest effect. An *IRF5* risk haplotype has been observed and carries multiple mutations, including rs2004640, which has been reported to create a novel splicing variant. Another variant found at the 3' untranslated region, rs10954213, has been reported to create a more functional polyadenylation site, which creates a more stable transcript [101]. Variants in the *IRF5* locus influence alternatively spliced transcripts, which alter or prolong *IRF5* expression. Hence, increased expression of *IRF5* propagates increased IFN $\alpha$  production. Little is reported for *IRF7* and *IRF8*; therefore, these loci warrant further investigation to determine the functional consequences of the associated variants.

#### ***IFIH1***

*IFIH1* is a DEAD box helicase that senses intracellular RNA and induces IFN (type 1) activation [102]. Variants at this locus have been associated with other autoimmune diseases such as T1D [103], autoimmune thyroid disease [104], and psoriasis [105]. The top associated SNP in SLE is rs1990760 ( $P = 1.63 \times 10^{-8}$ , OR = 1.23), which has been shown to increase expression of *IFIH1*. This increased expression could contribute to an IFN cascade initiated by nucleic acids.

#### ***TYK2***

*TYK2* plays an important role in the pro-inflammatory immune response, being involved in cytokine signaling and the phosphorylation of IFN receptors, triggering a type 1 IFN response [69]. Variants in *TYK2* have been reported to increase type 1 IFN gene expression [106] and deregulate the Th<sub>1</sub>/Th<sub>17</sub> response. Th<sub>17</sub> cells are

pro-inflammatory, and their differentiation is dependent on IL-6 and transforming growth factor-beta (TGF $\beta$ ), both of which are cytokines that are regulated by *TYK2* [107]. The top associated SNP in SLE, rs280519 ( $P = 3.88 \times 10^{-8}$ ), has been shown to play a role in increasing gene expression and IFN production. Variants propagating increased *TYK2* function have also been reported to lead to a pro-inflammatory phenotype with increased levels of Th<sub>1</sub>/Th<sub>17</sub> cells [107]. Multiple variants in *TYK2* have been reported to be associated with other autoimmune and inflammatory diseases [108].

#### **Known intergenic interactions in SLE**

From the published GWASs, we are able to identify associated variants for SLE in intergenic regions in addition to those in coding regions of genes. When intergenic loci are identified, it is important to ascertain the functional consequence of the variant on the neighboring genes. Indeed, until a molecular mechanism is fully elucidated, one cannot conclude that any associated allele will primarily exert its pathological effect by influencing the function of the gene that is closest by genomic distance.

#### ***PRDM1-ATG5***

The *PRDM1-ATG5* gene region has shown a significant association with increased risk of SLE at the intergenic variant rs548234 ( $P = 5.1 \times 10^{-12}$ , OR = 1.25) [109]. This variant has been shown to increase the expression of *ATG5* in individuals who are homozygous for the C allele [109]. Since *ATG5* is important for the formation of autophagosomes [110], increased expression of this gene increases autophagy, which in turn stimulates the IFN $\alpha$  and NF- $\kappa$ B pathways [109] and exacerbates the immune response. However, *PRDM1* (*BLIMP1*) has been reported to play a role in B-cell differentiation [111], and so variants that affect *PRDM1* could allow plasma cell differentiation, which further propagates hyperactive B cells and auto-antibody production. *PRDM1* has also been reported to maintain immune tolerance and has been shown to alter DC function in female mice that lack *PRDM1* expression on DCs. These mice also develop lupus-like auto-antibodies [112]. Therefore, both *ATG5* and *PRDM1* could potentially have causal effects for lupus. Consequently, further experiments will be required to establish whether one (or perhaps both) of these genes plays a role in genetic susceptibility to SLE.

#### ***CD44-PDHX***

One trans-ancestral study (Europeans, African-Americans, and Asians) reported two intergenic SNPs between *PDHX-CD44* [113]. *PDHX* plays a role in the pyruvate dehydrogenase complex, and *CD44* is an integral cell



membrane glycoprotein, which plays a role in cell-cell interactions and regulation of IFN $\gamma$  and LCK [58]. Variants in *CD44* alone have been shown to be associated with SLE [58]. CD4<sup>+</sup> and CD8<sup>+</sup> T cells of patients with SLE have been shown to overexpress *CD44*, causing an influx of IFN $\gamma$ , inflammation, and tissue damage [113]. This fact suggests that the intergenic associations are pointing toward *CD44* as a more likely candidate gene for SLE than *PDHX*.

## Conclusions

In this review, we describe the key loci that have been associated with SLE to date. We have shown the importance of these genes in their most relevant related pathways (Figure 1). However, to fully understand these associations, fine-mapping studies using targeted genotyping chips, such as the ImmunoChip, will be required. These types of studies will lead to the identification of additional variants that can then be used for functional studies to elucidate the molecular mechanisms operating in lupus. The additional advantage of the ImmunoChip platform is that it allows us to look for a commonality of associations across immune-related diseases.

To date, in lupus, there have been a number of relatively small GWASs, which nonetheless have been quite successful in identifying the strongest causal genetic effects in terms of both significance, in which a *P* value quantifies whether the difference in allele frequency between SLE cases and healthy controls is likely to occur solely by chance, and the effect size, which quantifies the amount of the observed difference between affected and unaffected individuals. However, as previously mentioned, these studies have been able to identify only approximately 10% of the genetic heritability. GWASs in SLE which are much larger than those previously undertaken will be necessary in order to expand the number of SLE-associated loci significantly. To fully explore the genetics of SLE, it is important to study high-risk groups, such as those with African or Amerindian ancestry. This will allow greater understanding of SLE across different ethnicities and will allow fine mapping of the associated loci. Such studies are currently under way.

Finally, building upon these GWASs and replication studies, functional and targeted assays (for example, next-generation sequencing) are needed. These studies enable us to identify rare variants, using methods such as next-generation sequencing, and to provide greater understanding of the biology of SLE and hence the pathogenesis of this disease. In summary, the genetics of SLE is still not fully understood, but by undertaking additional genetic studies and consequential functional assays we will obtain a much greater understanding of the etiology of the disease.

## Autoimmune Basis of Rheumatic Diseases

This article is part of a series on *Systemic lupus erythematosus*, edited by David Pisetsky, which can be found online at <http://arthritis-research.com/series/lupus>

This series forms part of a special collection of reviews covering major autoimmune rheumatic diseases, available at: <http://arthritis-research.com/series/abrd>

## Abbreviations

APC, antigen-presenting cell; BCR, B-cell receptor; CNV, copy number variation; CSK, cytoplasmic tyrosine kinase; DC, dendritic cell; GWAS, genome-wide association study; IC, immune complex; IFN, interferon; IL, interleukin; IP(3)R, type 1 inositol-1,2,4-triphosphate; LD, linkage disequilibrium; MHC, major histocompatibility complex; NF- $\kappa$ B, nuclear factor-kappa-B; OR, odds ratio; pDC, plasmacytoid dendritic cell; RA, rheumatoid arthritis; RIP, receptor-interacting protein kinase; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism; TCR, T-cell receptor; Th, T helper; T1D, type 1 diabetes; TLR7/9, Toll-like receptor 7/9.

## Competing interests

The authors declare that they have no competing interests.

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