The genetics of lupus: a functional perspective
Sandra G Guerra1,2, Timothy J Vyse1,2 and Deborah S Cunninghame Graham*1,2

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 × 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 × 10−8) in one or more GWASs, a meta-analysis, or replication studies. We have also included the Fcγ 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
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 × 10^{-8})

| Locus          | Gene                                      | Position         | Variant                | P value (significance) | OR (CI) (effect size) | Autoimmune disease associations | Function                             |
|----------------|-------------------------------------------|------------------|------------------------|------------------------|------------------------|----------------------------------|--------------------------------------|
| ITGAM          | Integrin alpha M                          | 16p11.2 (intronic) | rs9888739 (T)          | 1.61 × 10^{-23}        | 1.62 (1.47-1.78)        | Phagocytosis                      |                                      |
| FcyR           | Fcy receptors                             | Multiple (see text) | Multiple (see text)    | Multiple (see text)    | Multiple (see text)    | UC                              | Phagocytosis                         |
| PRDM1-ATG5     | PR domain zinc finger protein 1- autophagy-related 5 homolog | 6q21-22.1 (intergenic) | rs548234 (G)          | 5.18 × 10^{-12}        | 1.25 (1.17-1.33)        | Autophagy and B-cell differentiation |                                      |
| TNFAIP3        | Tumor necrosis factor-alpha-induced protein | 6q23 (exonic)    | rs2230926 (C)          | 1.37 × 10^{-17}        | 1.72 (1.52-1.94)        | RA, CeID, UC, and PS              | Ubiquitination                       |
| TNIP1          | TNFAIP3-interacting protein 1             | 5q22-q33.1 (intronic) | rs7708392 (C)         | 3.8 × 10^{-13}         | 1.27 (1.10-1.35)        | PS                              |                                      |
| UBE2L3         | Ubiquitin-conjugating enzyme E2L 3        | 22q11.2-q13.1 (upstream) | rs463426 (G)       | 1.48 × 10^{-16}        | 0.78 (0.74-0.83)        | CD, RA, and CeID                  |                                      |
| ETS1           | V-ETS avian erythroblastosis virus E26 oncogene homolog 1 | 11q23.3 (downstream) | rs6590330 (A)       | 1.77 × 10^{-25}        | 1.37 (1.29-1.45)        | RA                              | Lymphocyte development and activation |
| IKZF1          | IKAROS family zinc finger 1               | 7p12 (upstream)  | rs4917014 (C)         | 2.75 × 10^{-23}        | 1.23 (1.03-1.42)        | RA, IBD, T1D, and Graves’ disease |                                      |
| CD44           | CD44                                      | 11p13 (upstream) | rs507230               | 3.98 × 10^{-12}        | 0.71 (0.63-0.79)        | RA                              | B-cell activation and signaling      |
| BANK1          | B-cell scaffold protein with ankyrin repeats 1 | 4q22-q24 (exonic) | rs10516487 (G)       | 3.7 × 10^{-10}         | 1.38 (1.25-1.53)        | RA                              | B-cell activation and signaling      |
| BLK            | B lymphoid tyrosine kinase               | 8q23-p22 (upstream) | rs7812879 (A)         | 2.09 × 10^{-24}        | 0.69 (0.64-0.74)        | RA                              |                                      |
| LYN            | V-yes-1 Yamaguchi sarcoma viral-related oncogene homolog 1 | 8q13 (intrinsic) | rs7829816 (C)         | 5.40 × 10^{-9}         | 0.77 (0.70-0.84)        | RA                              |                                      |
| RasGRF3        | Ras guanyl releasing protein 3 (calcium and DAG-regulated) | 2p25.1-p24.1 (intrinsic) | rs13385731 (G)      | 1.25 × 10^{-15}        | 0.70 (0.64-0.76)        | RA                              |                                      |
| NCF2           | Neutrophil cytosolic factor 2             | 1q25 (intrinsic) | rs10911363 (T)        | 2.87 × 10^{-11}        | 1.18 (1.10-1.30)        | RA, IBD, T1D, and Sjogren’s syndrome | T-cell development and signaling |
| STAT4          | Signal transducer and activator of transcription 4 | 2q32-q32.3 (intrinsic) | rs7574865 (G)       | 5.17 × 10^{-42}        | 1.51 (1.43-1.61)        | RA                              |                                      |
| PTPN22         | Protein tyrosine phosphatase non-receptor type 22 | 1p13 (exonic) | rs2476601 (A)         | 3.4 × 10^{-12}         | 1.35 (1.24-1.47)        | T1D and Graves’ disease          |                                      |
| TNFSF4         | Tumor necrosis factor (ligand) superfamily member 4 | 1q25 (upstream) | rs2205960 (A)        | 2.5 × 10^{-12}         | 1.46 (1.37-1.56)        | T1D and Graves’ disease          |                                      |
| HLA-DRB1       | HLA class II histocompatibility antigen   | 6p21.3 (downstream) | rs3135394 (G)       | 2.0 × 10^{-10}         | 1.98 (1.84-2.14)        | T1D, RA, CeID, IBD, and CD       | Antigen presentation                 |
| SLC15A4        | Solute carrier family 15, member 4        | 12q24.32 (exonic) | rs10847697 (A)       | 3.54 × 10^{-11}        | 1.26 (1.17-1.34)        | RA                              |                                      |
| IRF5           | Interferon regulatory factor 5            | 7q32 (3’ untranslated region) | rs2070197 (C)   | 5.8 × 10^{-24}         | 1.88 (1.78-1.95)        | Rheumatic disease and RA         |                                      |
| IRF7           | Interferon regulatory factor 7            | 11p11.5 (downstream) | rs4963128 (T)       | 3.0 × 10^{-10}         | 0.78 (0.73-0.85)        | T1D                              |                                      |

Continued overleaf
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 (IFNα) [10], promoting lymphocyte loss of self-tolerance, auto-antibody production, and IC deposition. The ICs can bind low-affinity FcγRIIa, 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 α-chain of αMβ2-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 ($P = 1.61 \times 10^{-21}$, 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 αMβ2 ligand-binding domain [18]. αMβ2-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 αMβ2 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-kB)-derived pro-inflammatory responses. This occurs through the ubiquitination of IKKγ and phosphorylation of Ikβα [30,31], facilitating the release of NF-kB (Figure 2). A20 is a key regulator of NF-kB 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 \( (P = 1.37 \times 10^{-17}, \text{OR} = 1.72) \) 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-kB activity [34]. Variants at this locus could potentially lead to reduced inhibitory activity of NF-kB and reduced expression of A20.

Owing to increased NF-κB signaling, TNfaip3–/– mice develop spontaneous inflammation and lymphocyte cell death [35]. This shows the importance of TNFAIP3 in NF-kB 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-kB 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-kB [36]. However, overexpression of TNIP1 inhibits NF-kB activation by TNF [37]. Variants in TNIP1 could potentially play a role in negatively regulating the NF-kB pathway [38]. SNP rs7708392 has been reported to play a role in TNIP1 splicing, rendering the inhibition of the NF-kB 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-kB 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 \( (\text{rs}463426, P = 1.48 \times 10^{-16}, \text{OR} = 0.78) \).

**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.
ETS1 has been reported as a negative regulator of B-cell differentiation and T helper 17 (Th17) 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 Th17 cells [49-51]. While having increased proliferation of Th17 cells causes increased inflammation through the secretion of interleukin-17 (IL-17), ETS1-deficient Th cells secrete higher amounts of anti-inflammatory cytokine IL-10 [52]. Interestingly, these ETS1-deficient Th cells have reduced secretion of IL-2, which is a potent Th17 inhibitor [52]. The top associated variant at this locus, rs6590330 (P = 1.77 × 10⁻²⁰, 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 × 10⁻¹³, 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+ T helper cells (Th1/Th2), 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 × 10⁻¹⁹, OR = 1.38). After B-cell activation, BANK1 becomes tyrosine-phosphorylated, resulting in phosphorylation of type 1 inositol-1,2,4-triphosphate (IP3R). 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 IP3R, 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 × 10⁻²⁴, OR = 0.69) and LYN (rs7829819, P = 5.40 × 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⁻/⁻ mice [65]. Compared with BLK, which affects pre-BCR signaling, active BLK enhances BCR responsiveness [66]. Blk⁻/⁻ 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 × 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 × 10⁻¹¹, OR = 1.18) has been shown to have reached genomewide 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⁺CD4⁻CD8⁻ T cells and Th17 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+CD25+ 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 Th1 transcription factor that has been reported to mediate Th1 T-cell response, Th1 cytokines, IL-12 and IL-23 [74,75], and IFNγ signaling [76,77]. rs7574865 has been reported to have the strongest association with SLE (*P* = 5.17 × 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 Th1 T-cell response, increasing IFNγ release [81]. As seen in Figure 1, this influx of IFNγ would target organs such as the kidneys, propagating further IFNγ release and chronic inflammation. rs7574865 may act to increase *STAT4* expression and hence IFNγ 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 × 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+ and CD8+ T cells [89]. The strongest association in *TNFSF4* is with the upstream variant rs2205960 (*P* = 2.5 × 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 × 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 (IFNα and IFNβ) and also mediate the Th1 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 the causal effect of SLE or whether it further propagates systems. However, it is unclear whether elevated IFN is mechanistic between the innate and adaptive immune tissue damage [14]. IFN also acts as a bridging cytokines, contributing to chronic inflammation and disease.

**IFN, 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 × 10^{-24}, OR = 1.88; P = 3.0 × 10^{-19}, OR = 0.78; and P = 1.24 × 10^{-6}, 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 poly-A binding 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 × 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 IFNα and NF-kB 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 IFNγ and LCK [58]. Variants in *CD44* alone have been shown to be associated with SLE [58]. CD4+ and CD8+ T cells of patients with SLE have been shown to overexpress *CD44*, causing an influx of IFNγ, 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-trisphosphate; LD, linkage disequilibrium; MHC, major histocompatibility complex; NF-κB, 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; TL1R7/9, Toll-like receptor 7/9

Competing interests

The authors declare that they have no competing interests.

Author details

1Department of Medical and Molecular Genetics, Division of Genetics and Molecular Medicine, King’s College London, Great Maze Pond, London, SE1 9RT, UK. 2Academic department of Rheumatology, Division of Immunology, Infection and Inflammatory Diseases, School of Medicine, King’s College London, Great Maze Pond, London, SE1 9RT, UK.

Published: 29 May 2012

References

1. Perl A: Pathogenic mechanisms in systemic lupus erythematosus. Autoimmunity 2010, 43:1-6.
2. Johnson AE, Gordon C, Palmer RG, Bacon PA: The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. Arthritis Rheum 1995, 38:551-558.
3. Lipsky PE: Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity. Nat Immunol 2001, 2:764-766.
4. Block SR, Winfield JB, Lockshin MD, D’Angelo WA, Christian CL: Studies of twins with systemic lupus erythematosus. A review of the literature and presentation of 12 additional sets. Am J Med 1975, 59:533-552.
5. Deapen D, Escalante A, Weinrib L, Horwitz D, Bachman B, Roy-Burman P, Walker A, Mack TM: A revised estimate of twin concordance in systemic lupus erythematosus. Arthritis Rheum 1992, 35:311-318.
6. Gateva V, Sandling JK, Hom G, Taylor KE, Chung SA, Sun X, Ortmann W, Kosoy R, Ferrera RC, Nordmark G, Gunnarsson I, Svenningson E, Padyukov L, Sturfelt G, Jönsson A, Bengtsson AA, Rantapää-Dahlgqvist S, Baechler EC, Brown EE, Alarcón GS, Edberg JC, Ramsey-Goldman R, McGwin G Jr., Reville JD, Vilà LM, Kimberly RF, Manzi S, Petri MA, Lee A, Gregersen PK, et al: A large-scale replication study identifies TNF1P, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. Nat Genet 2009, 41:1228-1233.
7. Kerr JF, Wyllie AH, Currie AR: Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972, 26:239-257.
8. Salmon M, Gordon C: The role of apoptosis in systemic lupus erythematosus. Rheumatol Oxford 1999, 38:1177-1183.
9. Bannister KM, Hay J, Clarkson AR, Woodroffe AJ: Fc-specific reticuloendothelial clearance in systemic lupus erythematosus and glomerulonephritis. Am J Kidney Dis 1984, 2:387-392.
10. Munoz LE, Lauber K, Schiller M, Manfredi AA, Herrmann M: The role of defective clearance of apoptotic cells in systemic autoimmunity. Nat Rev Rheumatol 2010, 6:280-289.
11. Herrmann M, Voll RE, Zöller OM, Hagenhofer M, Pönnner BB, Kalden JR: Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. Arthritis Rheum 1998, 41:241-250.
12. Suber T, Rosen A. Apoptotic cell blebs: repositories of autoantigens and contributors to immune context. Arthritis Rheum 2009, 60:2216-2219.

13. Muhaz LE, Jankic C, Grossmayer GE, Frey B, Vol RE, Kem P, Kalden JR, Schett G, Fiebich B, Herrmann M, Gaypl US. Remnants of secondarily necrotic cells fuel inflammation in systemic lupus erythematosus. Arthritis Rheum 2009, 60:1713-1714.

14. Ellion K, Stone W. Type I interferon and systemic lupus erythematosus. J Interferon Cytokine Res 2011, 31:803-812.

15. Lorenz HM, Grunke M, Hieronymus T, Herrmann M, Kuhnel A, Manger B, Elkon KB, Stone VV: Guerra.

20. MacPherson M, Lek HS, Prescott A, Fagerholm SC:

21. Karassa FB, Trikalinos TA, Ioannidis JP: http://arthritis-research.com/content/14/3/211

26. Morris DL, Roberts AL, Witherden AS, Tarzi R, Barros P, Whittaker JC, Cook TH, Fietkau R, Herrmann M, Gaipl US:

40: molecules in lymphocytes from patients with systemic lupus erythematosus contribute to immune context.

Fietkau R, Herrmann M, Gaipl US:

22. Brown EE, Edberg JC, Kimberly RP:

23. Mac-1 integrin compromises leukocyte adhesion and phagocytosis. Harley JB, Nath SK:

39: The genetics of systemic lupus erythematosus-associated R77H substitution in the CD11b chain of the Mac-1 integrin compromises leukocyte adhesion and phagocytosis. J Biol Chem 2011, 286:17303-17310.

29. Han S, Kim-Howard X, Deshmukh H, Karnavati Y, Viswanathan P, Guthridge JM, Harley JB. A nonsynonymous functional variant in integrin-alpha(M) (encoded by ITGAM) is associated with systemic lupus erythematosus. Nat Genet 2008, 40:152-154.

30. Anaya JM, Kim-Howard X, Prahalad S, Chernyasky A, Cañas C, Rojas-Villaraga A, Bohnack J, Jonsson R, Bolstad AI, Brun JG, Cobb B, Moser KL, James JA, Jarrett NH, Nath SK. Evaluation of genetic association between an ITGAM non-synonymous SNP (rs1143679) and multiple autoimmune diseases. Arthritis Res Ther 2010, 2011, 1171-1180.

32. Adrianto I, Wen F, Templeton A, Wiley G, King JB, Lessard CJ, Bates JS, Hu Y, Kawasaki A, Ito S, Furukawa H, Hayashi T, Goto D, Matsumoto I, Kusaoi M, Hitotsumatsu O, Ahmad RC, Tavares R, Wang M, Philpott D, Turer EE, Lee BL, Shiffin N, Advincula R, Malynn BA, Werts C, Ma A. The ubiquitin-editing enzyme A20 restricts nucleotide-binding oligomerization domain containing 2-triggered signals. Immunity 2008, 28:381-390.

35. Adiriano I, Wen F, Templeton A; Wiley G, King JB, Lessard CJ, Bates JS, Hu Y, Kelly JA, Kaufman KM, Guthridge JM, Alarcón-Riquelme MJ, Arcelus JF, Manger B, Elkon KB, Stone VV: Guerra.
patients with systemic lupus erythematosus. *Rheumatol Int* 2011, 31:819-822.

48. Yang W, Shen N, Ye DQ, Liu Q, Zhang Y, Qian XH, Hanikarn N, Ying D, Pan HF, Mok CC, Chan TM, Wong RW, Lee KW, Mok MK, Wong SN, Leung AM, Li XP, Avhingsanoy W, Wong CM, Lee TL, Ho MH, Lee PJ, Chang YK, Li PH, Li RJ, Zhang J, Wong WH, Ng IO, Lau CS, Sham PC, Lau M. Asian Lupus Genetics Consortium: Genome-wide association study in Asian populations identifies variants in ET1 and WDFY4 associated with systemic lupus erythematosus. *PLoS Genet* 2010, 6:e1000841.

49. Bories JC, Willerford DM, Gevin D, Davidson L, Camus A, Martin P, Stelbelin D, Alt FW. Increased T-cell apoptosis and terminal B-cell differentiation induced by inactivation of the Ets-1 proto-oncogene. *Nature* 1995, 377:635-638.

50. Eyquem S, Chemin K, Fasseu M, Chopin M, Sigaux F, Cumano A, Bories JC. The dual nature of Ets-1: focus to the pathogenesis of systemic lupus erythematosus. *Autoimmun Rev* 2011, 10:439-443.

51. Han JW, Zheng HF, Cui Y, Sun LD, Ye DQ, Li J, Shen SK, Li J. Ets-1: focus to the pathogenesis of systemic lupus erythematosus (SLE); Role of peptide tolerance. *Autoimmun Rev* 2011 Oct 7. [Epub ahead of print].

52. Sudoes A, Lopez P, Gomez J, Gutierrez C. Enrichment of CD4+ CD25high T cell population in patients with systemic lupus erythematosus treated with glucocorticoids. *Ann Rheum Dis* 2006, 65:1512-1517.

53. Lin SC, Chen KH, Lin CH, Kuo CC, Ling QD, Chan CH. The quantitative analysis of peripheral blood FOXP3-expressing T cells in systemic lupus erythematosus and rheumatoid arthritis patients. *Eur J Clin Invest* 2007, 37:987-996.

54. Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, de Bakker P, Li J, Lee HS, Baitiswalla F, Li W, Masters SL, Boyt MG, Carulli JP, Padyukov L, Alldredson J, Kläreskog L, Chen WW, Amlis CI, Criswell LA, Seldin MF, Kastner DL, Gregersen PK. *STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus*. *N Engl J Med* 2007, 357:977-986.

55. Watford WT, Hissong BD, Bream JH, Kanno Y, Mual L, O'Shea JJ. Signaling by IL-12 and IL-23 and the immunoregulatory roles of STAT4. *Immunity* 2004, 20:139-156.

56. Farrar JD, Smith JD, Murphy TL, Leung S, Stark GR, Murphy KM. Selective loss of type I interferon-induced STAT activation caused by a nonsynonymous insertion in mouse Stat2. *Nat Immunol* 2011, 12:139-148.

57. Marion MC, Langefeld CD, Moser KL, Moser BLK. The B-cell-specific Src-family kinase Blk is dispensable for B-cell development and activation. *Mol Cell Biol* 2000, 20:1227-1233.

58. Stone J. *Regulation of Ras in lymphocytes: a get a GRP*. *Biochem Soc Trans* 2006, 34:858-861.

59. Cuningham Graham DS, Morris DL, Bhagnare TR, Criswell LA, Syvanen AC, Ronnblom L, Behrens TW, Graham RR. *Vys T J*. Association of NCF2, IKZF1, IFIH1, and TYK2 with systemic lupus erythematosus. *PLoS Genet* 2011, 7:e1002341.

60. Lissia SN, Hoffman RW, Toscos GC. Abnormal early TCR/CD3-mediated signaling events of a SRNP-autoimmune lupus T cell clone. *Clin Immunol Immunopathol* 1998, 88:305-310.

61. Savila P, Hossain A, Hahn BH, Singh RP. Regulatory T cells in systemic lupus erythematosus (SLE); Role of peptide tolerance. *Autoimmun Rev* 2011 Oct 7. [Epub ahead of print].

62. Eto H, Kido E, Taniguchi T. IRF8, IFIH1, and TYK2 with systemic lupus erythematosus. *Nat Immunol* 2011, 13:102-109.

63. Docea PW, Alarcon-Riquelme ME, Langefeld CD, Moser KL. Increased T-cell apoptosis and terminal B-cell differentiation induced by inactivation of the Ets-1 proto-oncogene. *Nature* 1995, 377:635-638.

64. Han JW, Zheng HF, Cui Y, Sun LD, Ye DQ, Li J, Shen SK, Li J. Ets-1: focus to the pathogenesis of systemic lupus erythematosus (SLE); Role of peptide tolerance. *Autoimmun Rev* 2011 Oct 7. [Epub ahead of print].

65. Mirouabu A, Gadina M, Strober W, Visconti R, Fornace A, Montagna C, Feldman GM, Nishikomora R, O'Shea JJ. STAT4 serine phosphorylation is critical for IL-12/IFN-gamma production but not for cell proliferation. *Proc Natl Acad Sci U S A* 2002, 99:12281-12286.

66. Komman BD, Alba MJ, Le JM, Alexizos I, Smith JA, Nikolov NP, Kastner DL, Remmers EF, Illei GG. Variant form of STAT4 is associated with primary Sjogren's syndrome. *Genes Immun* 2008, 9:267-270.

67. Martínez A, Varadé J, Máquez A, Cént MC, Espino L, Perdigones N, Santiago JL, Fernández-Arquero M, de la Calle H, Arroyo R, Mendoza JL, Fernández-Gutierrez B, de la Concha EG, Urrelo E. Association of the STAT4 gene with increased susceptibility for some immune-mediated diseases. *Arthritis Rheum* 2008, 58:2598-2602.

68. Kawasaki A, Ito I, Hikami K, Ohashi J, Hayashi T, Goto D, Matsumoto I, Ito S, Tsutsuomi A, Koga M, Aramimi T, Graham RR, Hom G, Takasaki Y, Hashimoto H, Behrens TW, Sumida T, Tsuchiya N. Role of STAT4 polymorphisms in systemic lupus erythematosus in a Japanese population: a case-control association study of the STAT4-IL23R region. *Arthritis Res Ther* 2008, 10:R113.

69. Li P, Cao C, Luan H, Li C, Hu C, Zhang S, Zeng X, Zhang F, Zeng C, Li Y. Association of genetic variations in the STAT4 and IRF7/KIAA1542 regions with systemic lupus erythematosus in a Northern Han Chinese population. *Hum Immunol* 2011, 72:249-255.

70. Sigurdsson S, Nordmark G, Garnier S, Grundberg E, Kwan T, Nilsson O, Ronnblom L, Behrens TW. Genetic analyses of type I interferon pathway-related genes reveal multiple new loci associated with systemic lupus erythematosus. *Arthritis Rheum* 2011, 63:2049-2057.

71. Kazys, SV, Abeleson AK, Wójciak J, Zaghloul A, Linga Reddy MV, Sanchez E, Gunnarsdottir I, Svennungson E, Stufert G, Jonsen A, Truedsson L, Pons-Estel BA, Witte T, Dalfonso S, Barzone N, Daniell MG, Gutierrez C, Sauer A, Junker PA, Laupstrup H, González-Escribano MF, Martin J, Abrahamsen H, Alarcón-Riquelme ME. Functional variants in the 8b-cell gene BANK1 is associated with systemic lupus erythematosus. *Nat Genet* 2008, 40:211-216.

72. Yokoyama K, Su I, Tsuzuki T, Yasuda T, Mikoshiba K, Takahashitakayana S, Yamamoto T. BANK regulates BCR-induced calcium mobilization by promoting tyrosine phosphorylation of PI3K receptor. *EMBO J* 2002, 21:83-92.

73. Castillejo López J, Delgado-Vega AM, Wojsck J, Korzeczy S, Thavathinwi E, Wu Y, Sánchez E, Illam Dópolandó L, López-Egoicka JD, Fine I, Sánchez D, Dominguez N, Lu R, Bruns CM, Kaufman KM, Maser KL, Gilkeson GS, Gestegi bard J, Pons-Estel BA, Dalfonso S, Witte T, Calleglas J, Narley JH, Gaffney PM, Martin J, Guttridge JM, Alarcón-Riquelme ME. Genetic and physical interaction of the B-cell-specific Src-family kinase Blk with the B-cell gene BANK1 and BLK. *Ann Rheum Dis* 2011, 71:36-42.

74. Dukes K, Le CR, Younou P, Zoual M. Expression of B cell receptor-associated signaling molecules in human lupus. *Autoimmunity* 2001, 32:133-124.

75. Xu Y, Beaumont SJ, Halden KM, Hibbs ML, Willerford DM. The activation and subsequent regulatory roles of Lyn and CD19 after B cell receptor ligation independent. *J Immunol* 2002, 169:6910-6918.

76. Lu R, Vidal GS, Kelly JA, Delgado-Vega AM, Howard KX, Macviana SR, Dominguez N, Klein W, Burrell C, Narley JH, Kaufman KM, Brunner GR, Maser KL, Gilkeson PM, Gilkeson GS, Wakefield EK, Li QZ, Langefeld CD, Maroc JM, Divers J, Alarcón GS, Brown EE, Kimberly RP, Eldberg JG, Ramsey-Goldman R, Revell JS, McGown GJR, Vila LM, Petri MA, Bae SC, et al. Genetic associations of LYN with systemic lupus erythematosus. *Genes Immun* 2009, 10:397-403.
83. Aksoy R, Duman T, Keskin O, Duzgun N: No association of PTPN22 R620W gene polymorphism with rheumatic heart disease and systemic lupus erythematosus. *Mol Biol Rep* 2011, 38:5393-5396.

84. Criswell LA, Pfeffer KA, Lu MF, González-Barrón L, Scriver C, Monté CH, Chang SY, Garcia VE, McAllister LB, Jeffery DA, Lee AT, Batiwalla F, Remmers E, Criswell LA, Seldin MF, Kastner DL, Amos CI, Sninsky JJ, Gregersen PK: The type I interferon system in the etiopathogenesis of systemic lupus erythematosus. *Am J Hum Genet* 2005, 76:561-571.

85. Lea WW, Lee YH: The role of autophagy during the early neonatal starvation period. *Transl Res* 2010, 550-555.

86. Begovich AB, Carlton VE, Honigberg LA, Schrodi SJ, Chokkalingam AP, Criswell LA, Pfeiffer KA, Lum RF, Gonzales B, Novitzke J, Kern M, Moser KL, Tsao BP, Vyse TJ, Langefeld CD, Nath SK, Guthridge JM, Cobb BL, Bumpstead SJ, Casas JP, Cockett H, Corveaux A, D'Alessio D, D'Ambrosio D, D'Arcy P, Denuwila A, D'Edics S, Estivill X, Fitzgerald O, Freeman C, Granda D, Gray P, Hofer A, Huffman U, Hunt SE, Irvine AD, Jankowski J, et al: A genome-wide association study identifies nonsynonymous SNPs that identify the type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. *Nat Genet* 2006, 38:617-619.

87. Sutherland A, Davies J, Owen CJ, Vakkakkara S, Walker C, Cheetham TD, James RA, Perros P, Donaldson PT, Cordell HJ, Quinton R, Pearce SH: Genetic polymorphism at the interferon-induced helicase (IFIH1) locus contributes to Graves' disease susceptibility. *J Clin Endocrinol Metab* 2007, 92:3338-3341.

88. Mustelin T, MacMurray J, Meloni GF, Lucarelli P, Pellecchia M, Eisenbarth GS, Comings D: A functional variant of lymphoid tyrosine phosphatase is associated with Graves' disease. *J Clin Endocrinol Metab* 2004, 89:37-43.

89. Vang T, Cengia M, Macis MD, Musumeci L, Onii V, Zavattari P, Nika K, Touts M, Tasker K, Cucca F, Mustelin T, Bottini N: Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant. *Nat Genet* 2005, 37:1317-1321.

90. Gough P, Amett FC, Tan FK, Assassi S, Divecchia D, Paz G, McNeary T, Draeger H, Reveille JD, Mayes MD, Agarwal SK: Association of TNFSF4 (OX40L) polymorphisms with susceptibility to systemic sclerosis. *Ann Rheum Dis* 2010, 69:530-533.

91. Cunningham-Graham DS, Graham RR, Manku H, Wagner S, Reid J, Timms K, Gutin A, Cunninghame Graham DS, Manku H, Wagner S, Reid J, Timms K, Gutin A, Lanchbury JS, Vyse TJ: Association of IFIH1 with increased sensitivity to IFN-alpha and serologic autoimmunity in lupus patients. *J Immunol* 2011, 187:1298-1303.

92. Smyth DJ, Cooper JD, Bailey R, Field S, Bumrun O, Smink LJ, Guja C, Ionescu-Tirgoviste C, Widmer B, Dunger DB, Savage DA, Walker NM, Clayton DG, Todd JA: A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. *Nat Genet* 2011, 43:89-90.

93. Järvinen TM, Hellquist A, Koskinen E, Einarsdottir E, Koskinen LL, Jeskanen L, Ranki A, Kere J, Saarialho-Kere U: Tyrosine kinase 2 and interferon regulatory factor 5 polymorphisms are associated with discoid and subacute cutaneous lupus erythematosus. *Exp Dermatol* 2010, 19:123-131.

94. Iwashita M, Akimoto T, Muramoto R, Yokoyama M, Ohno Y, Sekine Y, Maeda H, Shimoda K, Onitani K, Matuda T: Involvement of tyrosine kinase 2 in both the IL-12/Th1 and IL-23/Th17 axes in vivo. *J Immunol* 2011, 187:181-189.

95. Tao JH, Zou YF, Feng XL, Li J, Wang J, Fan YF, Ye DQ: Meta-analysis of TYK2 gene polymorphisms in association with susceptibility to autoinimmune and inflammatory diseases. *Mol Biol Rep* 2011, 38:4663-4672.

96. Zhou XJ, Lu XL, Lv JC, Yang HZ, Qin LX, Zhao MH, Su Y, UZ, Zhang H: Genetic association of PRDM1-ATG5 intergenic region and autophagy with systemic lupus erythematosus in a Chinese population. *Am J Hum Genet* 2011, 70:1330-1337.

97. Kuma A, Hatano M, Matsui M, Yamamoto A, Nakaya H, Yoshimoto T, Osłomyś H, Tokuhisa T, Mizushima N: The role of autophagy during the early neonatal starvation period. *Nature* 2004, 432:1032-1036.

98. Garaud JC, Schickel JN, Blaison G, Knapp AM, Dembele D, Ruer-Laventie J, Tomaszewski D, Legendre A, Thévenet D, Garaud JC, Joffre B, Mouttet A, Blain S, Tissier R, Guillaume P, Fournier M, Guerra SG: Identification of a systemic lupus erythematosus susceptibility variant of IFIH1. *Cite this article as doi:10.1186/ar3844*.