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Recent insights into the genetic basis of systemic lupus erythematosus

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Abstract

Many identified genetic risk factors for SLE contribute to the function of the immune system, which has expanded our understanding of disease pathogenesis. We outline the genetic variants in the recently identified SLE-associated loci, the immunologic pathways affected by these gene products, and the disease manifestations linked to these loci. Pathways potentially influenced by SLE risk variants include: apoptosis, DNA degradation and clearance of cellular debris; antigen-presentation; type I interferon, Toll-like receptor and NFκB activation; defective clearance of immune complexes containing nuclear antigens; B- and T-cell function and signaling; and monocyte and neutrophil function and signaling. These identified SLE susceptibility loci are predominantly common variants that have been confirmed among multiple ancestries, suggesting shared mechanisms in disease etiology. Ongoing genetic studies continue the investigation of specific functional variants, and their potential consequences upon immune dysregulation, enhancing our understanding of links between genotypes and specific disease manifestations. The next generation sequencing explores the identification of causal rare variants that may contribute robust genetic effects to developing SLE. Novel insights coming from genetic studies of SLE provide the opportunity to elucidate pathogenic mechanisms as well as contribute to the development of innovative therapeutic targets for this complex disease.

Keywords

Systemic lupus erythematosus; Genetic; Genome wide association studies; Interferon pathway; Cell signaling

Systemic lupus erythematosus (SLE) is a complex, autoimmune disease characterized by diverse clinical phenotypes and the presence of antibodies to nuclear components. Genetic, epigenetic, environmental and hormonal factors interact to contribute to immunologic abnormalities leading to disease pathogenesis[1]. The disease is variable in presentation and outcome among individuals and across ancestral groups[2;3], and worldwide epidemiologic heterogeneity has been documented[4]. Despite this variability, a genetic basis of SLE has been established, with over 40 susceptibility loci identified at present.

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Initial work exploring SLE genetics included targeted and genome-wide linkage analysis in multiplex families as well as candidate gene association studies. More recently, platforms designed to identify common variants have been used to genotype up to 0.6 million single nucleotide polymorphisms (SNPs) in each of 7 genome-wide association (GWA) studies (4 in European-derived populations, 3 in Asians), and in a series of large-scale replication studies of individuals of European, Asian and multiracial (including African-American, and Hispanics enriched in Amerindian) descent. Results from these studies have identified a growing number of novel risk loci, and confirmed disease associations with previously established risk loci. Many such loci are located either within or near genes encoding products with functional relevance to the pathogenesis of SLE, implicating the involvement of specific immune pathways. These loci thus provide an opportunity to investigate how the genetics of SLE may elucidate its pathophysiology, provide drug targets and allow for prediction of disease course.

In each GWA study, the strongest association resides within the HLA region, an extensively studied locus due to the importance of the major histocompatibility complex (MHC) to development of autoimmunity. Associations of highly conserved and extended haplotypes bearing class II alleles *HLA-DRB1*03:01* and *HLA-DRB1*15:01*[5] with SLE are well-established in European populations. Recently, a high-density transancestral mapping study of the MHC region in SLE of European and Filipino ancestries identified new independent loci including *MSH5* (MutS protein homolog 5) involved in DNA repair and meiotic recombination, HLA-DPB1, and HLA-G involved in maternal-fetal tolerance [6]. Below, we highlight additional SLE-associated loci that have reached GWA significance after correcting for multiple testing.

Immunologic pathways affected by SLE susceptibility variants

Current understanding of SLE pathogenesis can group gene products of identified SLE-associated gene variants into pontentially influcenced mechanistic pathways, such as: (1) DNA degradation, apoptosis and clearance of cellular debris, e.g. *TREX1* (three prime repair exonuclease 1), and *DNASE1* (deoxyribonuclease 1); (2) defective clearance of immune complexes (ICs) containing nuclear antigens, e.g. complement components, and *FCGR*s (Fc fragment of IgG, low affinity receptors); (3) Toll-like receptor (TLR) and type I interferon (IFN) pathway activation, e.g. *TLR7*, *IRF5* (interferon regulatory factor 5), and *STAT4* (signal transducer and activator of transcription 4); (4) NFκB signaling, e.g. *TNFAIP3* (tumor necrosis factor, alpha-induced protein 3; (5) B cell function and signaling, e.g. *BANK1* (B-cell scaffold protein with ankyrin repeats 1), and *BLK* (B lymphoid tyrosine kinase); (6) T-cell signaling and function, e.g. *PTPN22* (protein tyrosine phosphatase, non-receptor type 22), and *TNFSF4* (tumor necrosis factor superfamily, member 4); and (7) monocyte and neutrophil signaling and function, e.g. *ITGAM* (integrin, alpha M); (see Table 1 and the text below for a description of additional genes in each pathway).

Genetic variation in DNA degradation, apoptosis and clearance of cellular debris pathways

The proper disposal of intracellular constituents or infectious agents in a regulated manner may function inappropriately in SLE, leading to abundance of self-antigens. Several variants of genes related to these pathways contribute to both monogenic and polygenic forms of SLE. Recessive mutations typically lead to Aicardi Gutieres syndrome with deficiency of TREX1 - an exonuclease involved in cell death, DNA degradation, and cellular response to oxidative damage; deep sequencing of *TREX1* identified novel frameshift or missense mutations in patients with SLE but not controls[7]. A large, multiethnic case-control study subsequently confirmed a *TREX1* SLE risk haplotype associated with neurological

manifestations in patients of European ancestry[8] (see Table 2 for candidate genes and associated sub-phenotypes). Similarly, mutations of *ACP5* (acid phosphatase 5, tartrate resistant), which cause spondyloenchondrodysplasia due to deficiency of TRAP (tartate-resistant acid phosphatase), a protein that functions in lysosomal digestion, lead to elevated IFN-α activity and a spectrum of autoimmune diseases including SLE [9]. Rare mutations of *DNASE1*, encoding the major nuclease present in serum, urine and secreta and its homolog, *DNASE1L3* (deoxyribonuclease 1-like 3) have been identified in several patients with SLE from homogeneous and potentially consanguineous populations[10;11]. Additionally, SLE-associated variants have been described in European and Asian populations of *ATG5* (autophagy related 5), encoding a protein that contributes to caspase-dependent apoptosis from FAS and TNF- ligands, and degradation of cytoplasmic constituents [12].

Genetic variants of immune complex clearance and phagocytosis pathways

Defective clearance of ICs containing nuclear antigens in SLE leads to deposition in target organs. The incidence of SLE or lupus-like manifestations in individuals with a complete deficiency, due to a homozygous mutation, in one of the classical complement pathway genes ranges from 10–93% (C1Q and C1R/C1S, >90% penetrance; C4A and C4B, 75%; C2, 10–20%) [13]. *C1Q* and *C4A* – which had previously been described in monogenic forms of SLE – have also been implicated in polygenic SLE and with various clinical phenotypes[14]. Genetic variants of *CFHR1* and *CFHR3* (complement factor H related genes), which may contribute to alternative complement pathway regulation among other functions, have also been associated with SLE risk in multiple ancestral groups[15].

FcγR gene variants with function in IC clearance are relevant in the development of several autoimmune diseases[16]. The Fc receptor gene family region is complex and includes gene duplications and copy number variations, creating challenges to the investigation of gene structure. Inconsistencies between FcγRs genetic studies in SLE have been attributed to ethnic differences and disease heterogeneity, as well as genotyping error. However, the role of FcγR variants to risk of SLE is highlighted by several variants, including H131R of *FCGR2A*, F158V of *FCGR3A*, and I187T of *FCGR2B*, which have been associated with SLE susceptibility in several ancestral populations, and with specific disease profiles[17]. In addition, decreased copy numbers of *FCGR3B,* correlating with protein expression and IC clearance, is associated with SLE[18]. FcγRII and FcγRIII, the low-affinity receptors for IgG-Fc region, are important in phagocytosis, presentation of complexed antigen, and cytokine response after receptor cross-linking. The FcγRs are predominantly activating, except FcγRIIB which can inhibit signaling through other FcγRs and the B cell receptor, neutrophils and macrophages[19]; interestingly, a *FCGRIIB* functional SNP abrogates receptor function in SLE patients of both European and Southeast Asian ancestries[20]. Further investigation of functional consequences of the FcγR gene variants in SLE is warranted and will help to characterize their contributions to disease pathogenesis.

Genetic variants of the toll-like receptor and type I interferon pathway

Increased expression of type I IFN and type I IFN-inducible genes is observed commonly in patients with SLE, suggesting a major role in disease pathogenesis, and leading to development of anti-IFN-α therapy[21]. Likely candidates for triggers of type I IFN activation are binding of pattern recognition membrane and cytosolic receptors by exogenous viral agents or endogenous nucleic acids. Variants have been associated with risk of SLE; for example a functional 3′ untranslated region (UTR) SNP of the X-linked *TLR7* that confers elevated TLR7 expression and an increased IFN response has been associated with SLE in East Asians[22], which was subsequently confirmed in European-American, African-American and Hispanic populations[23].

Variation in genes coding for transcription factors downstream of TLRs, including IRF5[24;25], IRF7[26], and IRF8[27;28], has been associated with SLE susceptibility. Robust associations of four *IRF5* functional variants in multiple ancestries define haplotypes associated with increased, decreased, or neutral levels of risk for SLE, with functional consequences on expression of IRF5, IFN-α and IFN-inducible chemokines[29]. Similarly, a nonsynonymous *IRF7* SNP (Q412R) confers increased IRF7 and downstream IFN pathway activation in European-, Asian-, and African-American patients with SLE [26]; additional *IRF7* risk alleles in patients with SLE are associated with anti-dsDNA antibodies (European-American and Hispanic-American individuals), and anti-Sm antibodies (African-American and Japanese individuals)[30;31]. *IRF8* and susceptibility to SLE in a large multiethnic cohort was recently described[28]. *IRF8* encodes a transcription factor that acts in the type I IFN pathway, and also plays a role in B cell and macrophage development[32], however the causal variant in *IRF8* has not yet been identified.

Several additional genes within or downstream of the type I IFN pathway have been associated with risk of SLE, including *STAT4, IFIH1* (interferon induced with helicase C domain 1), *TYK2* (tyrosine kinase 2), and *PRDM1* (PR domain zinc finger protein 1)[27;33]. IFIH1 detects RNA prior to type I IFN pathway activation; an allele of *IFIH1* was associated with anti-dsDNA antibodies among patients of multiple ancestries with SLE[34]. *PRDM1* encodes BLIMP-1 that acts as a repressor of IFN-β gene expression, is an essential regulator of T-cell homeostasis, and may regulate both B-cell and T-cell differentiation. TYK2 interacts directly with the type I IFN receptor upon engagement with IFN-α or –β and contributes to downstream phosphorylation of STAT family and other transcription factors. *STAT4*, encoding a protein that promotes transcription after type I IFN receptor activation, has been associated with increased susceptibility to SLE in several ancestral backgrounds[12;35;36], several sub-phenotypes and an early age of diagnosis [37;38]. The genetic control of IFN activity in SLE was recently expanded to include a functional SLE risk variant in *MIR146A*, encoding a negative regulator of the type I IFN pathway. Decreased levels of miR-146A seen in PBMCs from Han Chinese patients with SLE may be due to decreased binding of transcription factor Ets-1 at the *MIR146A* promoter variant location[39]; genetic variation in *ETS1* has also been associated with risk of SLE (see B cell section below).

Genetic variation of the NFκB pathway

Genes that play a role in the NFκB pathway downstream of TLR engagement have also been associated with increased SLE susceptibility in multiple ancestries. For example, both risk and protective haplotypes of *IRAK1* (interleukin-1 receptor-associated kinase 1) have been associated with SLE[40]. The X-linked *IRAK1* gene encodes a kinase that acts as the Myd88 complex on/off switch for activation of the NFκB inflammatory pathway. *TNFAIP3,* also associated with SLE and subphenotypes including renal disease[41;42], encodes A20, a deubiquitinating enzyme which inhibits NFκB, leading to protein degradation and interactions that inhibit NFκB activity and TNF-mediated programmed death. A dinucleotide polymorphism just downstream of *TNFAIP3* promoter region was linked to decreased expression of A20 in patients with SLE of Korean and European ancestry, and may be the risk haplotype functional variant[43]. *TNIP1* (TNFAIP3 interacting protein 1), encoding the A20-interacting protein, has also been associated with SLE risk[33;35]. Additional genes within the NFκB pathway associated with SLE susceptibility include: *SLC15A4* (solute carrier family 15, member 4) encoding a peptide transporter that participates in NOD1-dependent NFκB signaling[35]; *PRKCB* (protein kinase C, beta) which is involved in B-cell receptor mediated NFκB activation[44]; and *UBE2L3* (ubiquitin-conjugating enzyme E2L 3), encoding the enzyme UBCH7 which participates in ubiquitination of an NFκB precursor, and may have a role in cell proliferation[45]. A risk

haplotype of *UBE2L3* confers increased UBCH7 expression in patients with SLE[46]; a variant contained in this haplotype has been associated with the presence of anti-dsDNA antibodies[38].

Genetic variation of B cell signaling and function

DNA or RNA released from dying or damaged cells can be recognized by autoreactive B-cells leading to activation and production of autoantibodies that, together with additional autoantigens, form ICs that drive other proinflammatory responses. This critical role of B-cells in the development of autoimmunity has led to the development of several targeted therapies, including anti-BLyS (B lymphocyte stimulator) and anti-CD20. Several B-cell related gene variants are involved in cell signaling and have been associated with SLE susceptibility in multiple ancestral backgrounds. For example, *BLK*, encoding a protein functioning in intracellular signaling and regulation of proliferation, differentiation, and tolerance of B-cells[35;36;47]; and *BANK1*, whose gene product facilitates the release of intracellular calcium, altering the B-cell activation threshold[36;48;49]; and *LYN*, encoding a binding partner of BANK1 that mediates B-cell inhibition[50]. Three functional variants of *BANK1*, including R61H, A383T and rs17266594 (affecting alternative splicing) have been identified which contribute to sustained B-cell receptor signaling and B-cell hyperactivity[48].

Other genes with roles in B-cell function associated with SLE susceptibility in single ancestry groups include those that encode: ETS1 (Ets-1 protein, or p54), which negatively regulates B-cell and Th17-cell differentiation[49]; IKZF1 (IKAROS family zinc finger 1), which regulates lymphocyte differentiation, proliferation and B-cell receptor signaling[27]; AFF1 (AF4/FMR2 family member 1), which functions in normal lymphocyte development[51]; RASGRP3 (ras guanyl-releasing protein 3) which transmits B-cell signals via Ras-ERK after B-cell receptor ligation, with potential impact on immunoglobulin production and B-cell proliferation[35]; IL21 which sustains antibody production, mediates antibody class switching and promotes differentiation of Th17 cells (association with SLE described in European and Hispanic ancestry)[52]; and IL10 which inhibits T-cells and antigen presenting cells while enhancing B-cell survival and activity[33]. Ongoing work from our laboratory has identified a functional SNP in the 5′ region of *IL10* which is associated with higher mRNA and protein expression in SLE[53].

Genetic variation of T cell signaling and function

Hyperactive B-cells, resulting from T-cell and antigen stimulation, increase the production of autoantibodies in SLE. T-cell directed therapies, including CTLA4 (cytotoxic T lymphocyte antigen 4) fusion proteins, have been developed to modulate T-cell costimulation. The production of superoxide by NADPH oxidase in leukocytes stimulated by autoantigens may be affected by an amino acid change (H389Q) in *NCF2* (neutrophil cytosolic factor 2), a SLE susceptibility gene encoding a subunit of the oxidase enzyme, implicating a role for decreased reactive oxygen species in SLE pathogenesis[27;54]. Two genes important to T-cell signaling, R620W of *PTPN22* and *TNFSF4* have been associated with SLE risk[55]: PTPN22 is critical for T-cell signaling; TNFSF4 (or OX40L) induces co-stimulatory signals that induce activation and differentiation of B-cells and inhibit T regulatory cells. Variants of *PTPN22* have been associated with both gain of function and loss of function in patients with SLE[56]. Additionally, *CD44* encodes a cell-surface protein that regulates lymphocyte activation and apoptosis, among other functions; specific transcript isoforms in T-cells from patients with SLE suggests a role for CD44 in SLE pathogenesis[57;58].

Genetic variation in monocytes and neutrophil signaling and function

Aberrant activation of monocytes and neutrophils, now recognized as important participants in SLE pathogenesis, includes the function of NETs (neutrophil extracellular traps) containing DNA and neutrophil-derived proteins which trigger for IFN-α release and can directly damage tissue[21]. Genetic variants related to adhesion and endothelial migration of both cell types have been associated with SLE susceptibility in multiple ancestries, specifically, R77H *ITGAM* and most recently the *ICAM* (intercellular adhesion molecule) locus[12;47;59;60]. *ITGAM* encodes the α chain of $\alpha_M\beta_2$ integrin, which regulates neutrophil and monocyte adhesion and migration from the bloodstream via interactions with a wide range of structurally unrelated ligands, including ICAM1 and ICAM2.

Ancestral Differences among SLE susceptibility genes

Most SLE-associated loci have been confirmed among multiple ancestries, suggesting common pathways play a role in disease pathogenesis. However, some susceptibility genes may be unique to particular populations: for instance, *PTPN22* SLE risk alleles have been observed in European-derived but not Asian or African-American populations[12;35;36], whereas loci within *ETS1*, *WDFY4* and *AFF1* have been associated with SLE only in Asian studies[49;51]. Variability in allelic frequency among populations explains the difference in effect of *PTPN22* R620W (rs2476601; European 2–15%; Asian nearly absent) and potentially *ETS1* rs1128334 (Chinese and Japanese 31–45%; European, Hispanic and African 6–11%). However, other differences in effect sizes are seen among populations, including an increased number of risk alleles for several SLE loci in Amerindian compared with European ancestry [61], and in southern Europeans compared with central Europeans[62]. Possible explanations for such diversity in results include: differences in allelic linkage, different gene-gene interactions, unique environmental exposures, and limitations of study design.

Genotype-phenotype effects in SLE

The diversity of clinical manifestations in SLE has generated significant interest in the potential for genetic prediction of disease sub-phenotypes. Insights into genotype effects on clinical/laboratory phenotypes have led to burgeoning understanding of the potential impact on SLE variability, and we will highlight some examples in the following paragraph. As described above, *ITGAM* has recently been associated with SLE in multiple ancestral groups. Upon subphenotype analysis, the *ITGAM* rs1143679 risk allele was found to consistently confer higher risk for lupus nephritis in SLE patients of European and Asian ancestry when compared to SLE patients without the risk allele[63;64]. Another robust example is that of *IRF5*, whereby *IRF5* haplotypes determine risk for increased increased IFN-alpha activity in SLE, which is influenced by the presence of autoantibody subsets[29]. There may, in fact, be baseline increases in IFN activity in healthy individuals based on *IRF5* haplotype, potentially leading to increased risk for development of autoantibodies and autoimmune disease[65]. An association of *ITGAM* and *STAT4* also with anti-dsDNA antibody positivity in human SLE among several population groups additionally suggests the possibility of “autoantibody propensity loci” in SLE[38], which may influence disease subphenotype. Cumulative evidence also points to HLA-DR2- and DR3- containing haploytpes as respectively contributing to genetic risk for presence of autoantibodies in SLE[66]; in a murine model, lupus-associated autoantigen proteins interact with HLA-DR3 and lead to autoreactive T cells activation, resulting in the production of autoantibodies[67]. Overall, however, the modest effects of most loci to date account for a small proportion of the heritability of SLE. Indeed there have been divergences in genotype-phenotype associations described by studies of different cohorts possibly due to differences in samples

sizes, or a lack of complete clinical information. Learning more loci to account for heritability will enhance the link between genotype/phenotype in SLE.

Gene-gene interaction in SLE

Recent descriptions of gene-gene interactions, or epistasis, may explain some of the missing heritability in SLE. Using novel analytic tools, potential epistasis has been identified between the HLA region and *CTLA4*, *ITGAM* and *IRF5*, *STAT4* and *IRF5*, *PDCD1* and *IL21* and between *BLK* and *BANK1* and *TNFSF4* in patients with SLE[68–71]. These early results, whereby the presence of certain risk alleles may influence other risk alleles at different loci, suggest additional complexity to the previously accepted model of additive heritability in SLE. These results represent early stages of epistasis study in SLE; we anticipate novel insights from further analyses of functional variant interactions derived from growing numbers of susceptibility loci.

Conclusion

SLE is a complex disorder, with many new genetic associations and implications to consider in the evolving understanding of its pathogenesis. Though increasing numbers of robust associations have been identified, causal variants of many predisposing loci for SLE pathogenesis are not presently known. Functional studies will be required to determine causal variants at each locus coupled with an exploration of how identified SLE susceptibility genes contribute to disease manifestations. Ultimately specific genetic profiles may be leveraged for the prediction of risk for SLE subphenotypes and disease course at diagnosis. Currently evolving information and technology has the potential to permit significant strides towards the goal of improved medical management in SLE, and ultimately preventative care in individuals at risk for SLE.

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- The majority of large-scale genetic studies in SLE have been undertaken in European-derived, and secondly Asian, populations; focusing on other genetic backgrounds will lead to greater understanding of common pathways to autoimmunity.
- Next generation sequencing techniques will continue to aid researchers in identifying novel rare and functional genetic variants which might account for the missing heritability in SLE.
- Major susceptibility genes shared among multiple ancestral groups will be important in drug development for novel therapy in SLE.

Table 1

Pathway-associated SLE candidate genes

Pathway	Gene
DNA degradation, apoptosis and clearance of cellular debris	FCGR2B, ACP5, TREX1, DNASE1, DNASE1L3, ATG5
TLR and type I IFN signaling	TLR7, IRF5, IRF7/PHRF1, IRF8, IRAK1, IFIH1, TYK2, PRDM1, STAT4, TREX1, ACP5
NFκB signaling	IRAK1, TNFAIP3, TNIP1, UBE2L3, SLC15A4, PRKCB
Immune complex processing and phagocytosis	C1Q, C1R/C1S, C2, C4A/B, FCGR2A/B, FCGR3A/B
B cell function and signaling	FCGR2B, BLK, LYN, BANK1, PRDM1, ETS1, IKZF1, AFF1, RASGRP3, IL10, IL21, NCF2, PRKCB, HLA- DR2 & DR3, MSH5, IRF8
T cell function and signaling	PTPN22, TNFSF4, CD44, ETS1, IL10, IL21, TYK2, STAT4, PRDM1, AFF1, IKZF1, HLA-DR2 & DR3
Neutrophil and monocyte function and signaling	ITGAM, ICAMs, FCGR2B, FCGR3A/B, IL10, IRF8

TLR, toll like receptor; IFN, interferon; NFκB, nuclear factor kappa B. See text for complete gene names.

Table 2

SLE disease phenotypes and associated candidate genes

Disease Phenotype	
Anti-nuclear antibodies	RASGRP3; ACP5; TREX1[9;72;73]
Anti-dsDNA antibodies	STAT4; HLA-DR2&DR3; IRF5; BLK; PDHF1/IRF7; ITGAM; ACP5; UBE2L3; IFIH1[30;31;34;38;74;75]
Anti-RBP antibodies	IL10; HLA-DR2&DR3; IRF5; PDHF1/IRF7; TLR7[22;30;31;75;76]
Immunological disorder	IL10; DNASE1L3; PDHF1/IRF7; ITGAM[10;30;31;77]
Anti-phospholipid syndrome	STAT4; BLK[78]
Malar rash	FCGR2A; RASGRP3; IKZF1[72;79]
Discoid rash	IL10; RASGRP3; LYN; SLC15A4; ITGAM[72;79]
Oral ulcers	STAT4 *[79]
Neurological disorder	IL10; TREX1[73;80]
Renal disorder	C1Q*; FCGR2A; FCGR3B; TNFSF4; IL10; STAT4; DNASE1L3; C4A&B; C2; TNFAIP3; IKZF1; C1R/C1S; ITGAM; ACP5[9;10;14;37;41;72;79;81;82]
Hematological disorder	IL21; TNFAIP3; LYN*; PDHX/CD44; ITGAM; ACP5[41;50;74;79;83]
Vasculitis	TNIP1[72]
Arthritis	C4A&B; ACP5[13;74]
Early age at disease onset	STAT4; ETS1[37;72]

RBP, ribosomal binding protein (included: Sm/RNP, SSA/SSB)

* These genes confer protection from associated clinical phenotype.