Published in final edited form as:

Curr Opin Rheumatol. 2014 September ; 26(5): 482–492. doi:10.1097/BOR.0000000000000086.

Advances in lupus genetics and epigenetics

Yun Deng^a and Betty P. Tsao^a

^aDivision of Rheumatology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

Abstract

Purpose of review—Genome-wide association studies (GWAS) have identified more than 50 robust loci associated with SLE susceptibility, and follow-up studies help reveal candidate causative genetic variants and their biological relevance contributing to the development of SLE. Epigenetic modulation is emerging as an important mechanism for understanding how the implicated genes interact with environmental factors. We review recent progress towards identifying causative variants of SLE-associated loci and epigenetic impact to lupus, especially genetic-epigenetic interactions that modulate expression levels of SLE susceptibility genes.

Recent findings—A few SLE-risk loci have been refined to localize likely causative variants responsible for the observed GWAS signals. Few of such variants disrupt coding sequences resulting in gain or loss of function for the encoded protein, while most fall in noncoding regions with potential to regulate gene expression through alterations in transcriptional activity, splicing, mRNA stability and epigenetic modifications. Multiple key pathways related to the SLE pathogenesis have been indicated by the identified genetic risk factors, including type I interferon signaling pathway that can also be regulated by epigenetic changes occurred in SLE.

Summary—These findings provide novel insights of the disease pathogenesis, and promise better diagnostic accuracy and new therapeutic targets for patient management.

Keywords

genetics; epigenetics; causative variant; molecular pathways; systemic lupus erythematosus

INTRODUCTION

The GWAS approach based on its ability to screen hundreds of thousands of single nucleotide polymorphisms (SNPs) across the genome in a hypothesis-free manner has accelerated the discovery of genetic variations contributing to systemic lupus erythematosus (SLE). Eight GWAS in SLE (four in European-derived [1–4] and four in Asian populations [5–8]) and subsequent meta-analysis and large-scale replication studies have identified a rapidly expanding number of risk loci exceeding the genome-wide significance level ($P < 5 \times 10^{-8}$) that are located within or near genes encoding products contributing to the

Correspondence to Betty P. Tsao, PhD, 900 Veteran Avenue, Warren Hall 14-224, Los Angeles, CA 90095. Tel: 310-825-8906; btsao@mednet.ucla.edu.

CONFLICTS OF INTEREST

There are no conflicts of interest.

pathogenesis of SLE. In some cases, follow-up fine mapping using increased dense markers, imputation and target resequencing help localization of candidate causative variants that explain observed GWAS signals. Only few of such variants disrupt protein-coding sequences and most lie in noncoding regions of the genome. The emergence of genomic and epigenomic datasets, such as eQTL (expression quantitative-trait loci) and ENCODE (Encyclopedia of DNA Elements) [9], have revolutionized functional annotation of noncoding variants with potential impact on gene regulation through alterations in transcriptional activity, splicing, mRNA stability and epigenetic modifications. Here, we discuss non-HLA SLE-associated loci grouped by biological pathways, highlighting those that have causative variants implicated with their functional roles experimentally investigated.

Environmental exposures of genetically-predisposed individuals may modify SLE risk genes epigenetically, resulting in the development of SLE manifestations. Epigenetic processes refer to heritable modifications that regulate gene expression and alter cellular functions without changes in the genomic sequence. Commonly described epigenetic mechanisms include DNA methylation, histone modification and microRNAs (miRNAs). A recent study has revealed epigenomic elements enriched in the promoters of autoimmunity susceptibility genes [10²²], suggesting that epigenetic modifications may amplify genetic risks for autoimmune diseases. We summarize important findings in epigenetic changes and highlight genetic-epigenetic interactions that operate in variants associated with SLE susceptibility.

SLE SUSCEPTIBILITY GENES STRATIFIED BY BIOLOGICAL PATHWAYS

Non-HLA SLE-associated genes are summarized in Table 1. We discuss genes that have the most likely causative variants implicated and functional consequences relevant to the disease pathogenesis.

Type I interferon (IFN) pathway

Integration of data from GWAS, gene expression microarrays and serologic studies supports that dysregulation of type I IFN serves as a central driver of SLE pathogenesis [55]. The diverse mechanisms by elevated type I IFN affecting SLE development include promoting differentiation of monocytes and plasmacytoid dendritic cells, activation of autoreactive B and T cells, production of autoantibodies and expression of proinflammatory cytokines and chemokines [56]. Over half of the currently identified SLE susceptibility genes encode proteins that can be directly or indirectly linked to type I IFN production or signaling [55].

Binding of immune complexes containing self-antigens and nucleic acids by pattern recognition receptors, such as TLR7, is a likely major trigger of type I IFN production in SLE. The importance of TLR7 upregulation in mediating autoimmune responses has been clearly demonstrated in murine lupus models [57–59]. Our group has identified a functional SNP at 3′ untranslated region (UTR) exhibiting consistent association with SLE in four major ancestries [25,26²²]. This SNP maps within a binding site for miRNA-3148 conferring allelic modulation of *TLR7* expression. The SLE-risk allele confers decreased degradation of *TLR7* transcripts, resulting in elevated *TLR7* levels and heightened downstream IFN response [26²²].

IRF5, IRF7 and IRF8, a family of transcription factors downstream of endosomal TLRs, are required for activating transcription of IFN- α and IFN-inducible genes. Genetic variants in or near these three genes have been associated with SLE susceptibility [3,16–20,22,24]. In particular, SLE-associated variants of *IRF5* and *IRF7* have functional impact on increased serum IFN- α and such impact depends on the presence of specific autoantibodies [21,60]. A cis-eQTL SNP located within the SLE-associated haplotype not only is associated with *IRF7* expression but also confers trans-eQTL effect on regulating type I IFN response in activated but not unstimulated dendritic cells [61^{***}], highlighting the importance for using appropriate activated *ex vivo* cells to explore functional roles of the disease-associated variants.

Other genes related to the type I IFN pathway that are associated with increased risk for SLE include *IFIH1* [11^{***}], *STAT4* [3,5,13,14], *TYK2* [12] and *SLC15A4* [5,20,23]. *IFIH1*, a cytosolic sensor of dsRNA, promotes IRF7/3 phosphorylation and type I IFN production. Three independent variants at *IFIH1* (one intronic and two missense SNPs) account for genetic association in multiple ancestries [11^{***}]. Risk alleles of both missense variants confer increased apoptosis and elevated expression of inflammation-related genes. The intronic risk allele leads to decreased *IFIH1* transcript levels by disruption of binding to protein complex including nucleolin and lupus autoantigen Ku70/80, which would be expected to promote autoantibody generation.

Nuclear factor κ B (NF κ B) pathway

Genes that function in the NF κ B pathway downstream of TLR engagement have been associated with increased SLE risk in multiple ancestries. For example, *TNFAIP3* encodes a deubiquitinating enzyme (A20) that participates in the termination of NF κ B signaling. A pair of tandem polymorphic dinucleotides (TT>A), downstream of the *TNFAIP3* promoter, have been nominated as causal variants responsible for disease association with *TNFAIP3* [27^{***}]. The SLE-associated TT>A risk alleles with inefficient delivery of NF κ B to the *TNFAIP3* promoter via long-range DNA looping attenuate A20 expression, leading to enhanced NF- κ B pathway activity that contributes to SLE. Located on the X chromosome, the S196F variant of *IRAK1* captures the association signals of a SLE risk haplotype shared by multiple ancestries [28^{***},29^{***}]. The risk 196F allele confers increased NF κ B activity and is associated with decreased mRNA levels of *MECP2*, but not *IRAK1*, suggesting contributions of both *IRAK1* and *MECP2* to SLE susceptibility [28^{***},62]. Studies in murine lupus models indicate a pivotal role of *Irak1* in activation of NF κ B and induction of IFN- α/γ [63]. *MECP2* is a transcriptional regulator involved in modulating expression of methylation-sensitive genes [29^{***}]. Functional consequences of the *MECP2* risk haplotype will be discussed in DNA methylation section.

B and T cell signaling

Multiple loci that mediate signaling transduction in B and T cells are associated with SLE, supporting a central role of dysregulated lymphocytes in the pathogenesis of SLE.

The R620W SNP of *PTPN22* is a well-characterized functional variant associated with multiple autoimmune diseases including SLE. Both humans carrying the risk 620W allele and knockin mice expressing the analogous 619W mutation show altered T-cell receptor

(TCR) and BCR signaling as well as enhanced B cell autoreactivity, illustrating the consequences of the risk variant in modulating T and B cell tolerance and autoimmunity [30–34]. Efforts to elucidate the role of R620W in nonlymphocytes have revealed that the risk 620W allele is associated with reduced TRAF3 (TNF receptor-associated factor 3) autopolyubiquitination and diminished TLR-induced type I IFN production in myeloid cells [64], but with enhanced functions in neutrophils including increased transendothelial migration, Ca²⁺ release and ROS (reactive oxygen species) production [65]. Taken together, this *PTPN22* polymorphism affects multiple signaling pathways in diverse immune cell types contributing to autoimmunity.

CSK encoding c-Src tyrosine kinase can regulate activation of Src kinases (e.g. LYN) by physically interaction with LYP (encoded by *PTPN22*) in lymphocytes. Association of *CSK* with SLE identified in European population has been localized to an intronic SNP as causal [44]. The SLE-risk allele is associated with high *CSK* expression, increased phosphorylation of Lyn, enhanced BCR-mediated activation of mature B cells and expansion of transitional B cells, suggesting *CSK* involved in multiple development stages of B cells [44]. Integrating gene-expression data with SLE-associated loci has implicated transitional B cells to be appropriate for investigating functional consequences of risk alleles [66], such as *CSK*.

BANK1, encoding an adaptor/scaffold protein, facilitates the release of intracellular calcium and alter the B cell activation threshold [2]. Three functional *BANK1* variants including one intronic and two missense SNPs have been associated with SLE in multiple ancestries, which contributes to sustained BCR signaling and B cell hyperactivity characteristic of SLE [2]. *BLK* encodes a member of the Src family kinases functioning in intracellular signaling and the regulation of B cell proliferation, differentiation and tolerance [1]. Risk alleles of the *BLK* promoter variants account for genetic associations in multiethnic populations, and reduce promoter activity in B cell lines representing different B cell developmental stages, which suggests that decreased *BLK* expression may affect B cell development and impair functional responses in B cells [41^{***}].

IL-10 is a pivotal cytokine which inhibits T cells and antigen-presenting cells while enhances B cell survival and activity [67]. Our group has identified an *IL10* upstream SNP that tags a risk haplotype associated with SLE in European population [36^{***}]. The SLE-risk allele is associated with increased *IL10* expression by preferentially binds to the phosphorylated transcription factor Elk-1. Interestingly, SLE patients with active disease show enhanced phosphorylated Elk-1 in nuclei and elevated co-expression of IL-10 and phosphorylated Elk-1 in peripheral lymphocytes, suggesting the involvement of aberrant Elk-1 activation in development of SLE.

IKZF1 regulates lymphocyte differentiation, proliferation and BCR signaling [68]. The first evidence supporting *IKZF1* as SLE susceptibility gene comes from a Chinese GWAS [5]. Recently, a trans-eQTL study has revealed the SLE-associated SNP at upstream of *IKZF1* that alters the *IKZF1* levels in *cis* and regulates expression of *CIQB* and five type I IFN response genes in *trans*, thereby reinforcing the importance of *IKZF1* in SLE [40^{***}]. This study illustrates how trans-eQTL mapping helps yield insights into downstream effects of the disease-associated variants.

Other genes with roles in B and T cell functions associated with SLE susceptibility are summarized in Table 1, and most of them await delineation of functional mechanisms by which the associated variants affect disease risk.

Immune complex (IC) clearance

Defective clearance of ICs and apoptotic cells leads to initiation and maintenance of autoimmune responses and chronic inflammation in SLE. Polymorphisms in multiple members of this pathway have been associated with SLE, for example missense variants of *FCGR2A/FCGR3A* and *ITGAM* and decreased copy number variations of *FCGR3B* (reviewed in [47]). CD11b encoded by *ITGAM* together with CD18 form the complement receptor 3 (CR3) with functions in binding to tissue deposited ICs as well as leukocyte phagocytosis, apoptosis, adhesion and migration via interaction with a range of ligands, such as ICAM1 that has also show association with SLE susceptibility [46]. The SLE-risk allele of *ITGAM* which encodes an amino acid change from Arg to His at position 77 (R77H) in CD11b impairs the CR3-mediated phagocytosis in monocytes, neutrophils and macrophages [48–50]. Given its location within an active chromatin region in *ITGAM*, the SLE-risk 77H allele confers reduced transcriptional enhancer activity and is associated with decreased *ITGAM* expression at both mRNA and protein levels in monocytes [69].

NADPH oxidase-dependent ROS pathway

ROS produced by NADPH (nicotinamide adenine dinucleotide phosphate) oxidase complex are essential in defense against invading pathogens and are likely to promote cellular and tissue damage owing to their highly reactive nature [70]. Considering the pro-inflammatory effect, ROS have been implicated in promoting autoimmune diseases, such as SLE, rheumatoid arthritis (RA), thyroiditis and type 1 diabetes [71*, 72–74]. A surprising finding of a polymorphism in the rat *Ncf1* gene (encoding a subunit of NADPH oxidase complex) leading to low NADPH oxidase activity and reduced ROS production associated with severe arthritis in rodents provides new insight of an anti-inflammatory role for ROS involved in autoimmune diseases [75,76]. In fact, increasing evidence supports that ROS are not only proinflammatory byproducts of cellular responses to infectious or inflammatory stimuli but act as fine-tuning regulators of autoimmune responses varying in time, location and extent of the ROS production (reviewed in [77]). Consistently, a mutation (H389Q) in human *NCF2* gene (encoding another subunit of NADPH oxidase complex) has been identified to associate with SLE risk in European population, which is also accompanied by decreased NADPH oxidase activity and ROS production [51]. A large-scale trans-ancestral replication study has confirmed this mutation with SLE susceptibility in African-American and Hispanic populations but not in Koreans (due to the absence of minor allele), and identified additional independently associated variants at *NCF2* in all of the three non-European populations [52].

Other Loci

Other pathways implicated by genetic findings have potential relevance to the SLE pathogenesis, including cell-cycle regulation (*CDKN1B*), autophagy (*ATG5* and *DRAM1*) and DNA demethylation (*TET3*); however, further functional characterization is required

[38]. In addition, SLE-associated loci (e.g. *TMEM39A*, *UHRF1BP1* and *CLEC16A*) with unknown immune function require further fine mapping and characterization of functional pathways contributing to the development of SLE [24,53,54].

CONNECTING GENOTYPE TO PHENOTYPE IN SLE

Recent genotype-phenotype association studies provide insights into genetic effects on clinical subphenotypes. Multiple established SLE-risk loci are associated with anti-dsDNA autoantibody (e.g. *HLA-DR2/DR3*, *STAT4*, *IRF5/IRF7*, *IFIH1*, *ITGAM* and *UBE2L3*) [78] and/or renal disorders (e.g. *ITGAM*, *STAT4*, *TNFSF4*, *TNFAIP3* and *TNIP1*) [79,80]. In addition, the apolipoprotein L1 nephropathy risk alleles G1/G2 strongly impact the risk and the time of end-stage renal disease (ESRD) in African Americans with lupus nephritis (LN), which may partly explain the increased risk of LN-ESRD in African Americans due to the high frequency of these alleles in African Americans but near absence in European Americans [81]. An analysis of specific manifestations with 22 validated SLE-susceptibility loci has showed cumulative genetic associations with age at diagnosis, anti-dsDNA autoantibody, oral ulcers, immunological and hematologic disorders, single marker association with renal disorders and arthritis, and no genetic association with malar/discord rash, photosensitivity, serositis and neurological disorder [82]. Such measures will be improved as more new SLE-risk loci are emerging, which help enhance the link between genotype and phenotype in SLE.

EPIGENETICS IN SLE

The disease concordance rate of SLE in monozygotic twins (24–58%) suggests epigenetic contribution to the disease development. Dysregulated epigenetic modifications, including DNA methylation, histone modification and noncoding RNA, can affect the expression and function of genes participating in pathogenic processes of SLE.

DNA hypomethylation

DNA methylation usually occurs at the 5' position of cytosine in the context of CpG dinucleotides distributed in genomes exhibiting suppressive effects on gene expression. A role of DNA hypomethylation in SLE has been demonstrated in studies showing demethylating drugs-induced T cell autoreactivity and lupus-like symptoms in mice and impaired DNA methylation in CD4⁺ T cells from active SLE patients (reviewed in [83]). Many methylation-sensitive genes are overexpressed in SLE CD4⁺ T-cells, functionally contributing to SLE development, including CD11A causing autoreactivity, perforin increasing apoptosis, CD70 and CD40L enhancing B-T cell interaction for autoantibody production (reviewed in [84]). Genome-wide DNA methylation analysis have showed severe hypomethylation of type I IFN-regulated genes in SLE CD4⁺ T cells, CD19⁺ B cells and CD14⁺ monocytes, suggesting epigenetically-mediated type I IFN hyper-responsiveness in SLE patients [85,86]. Interestingly, healthy individuals carrying the SLE-risk *IRAK1-MECP2* haplotype (mentioned in the NFκB pathway section) with increased levels of a specific *MECP2* transcript isoform in stimulated T-cells showed a similar hypomethylation of IFN-regulated genes, providing evidence for genetic-epigenetic interaction associated

with SLE-risk variants [29^{***}]. How DNA hypomethylation occurs in SLE patients are discussed in a recent review [87^{**}].

Histone modification changes

Various combinations of the histone modifications, including acetylation, phosphorylation, methylation, ubiquitylation and citrullination of histone tails, can affect DNA replication, transcription and chromatin structure [88]. In some cases, specific histone modifications associated with gene expression are defined, such as H3 and H4 hyperacetylation or H3 trimethyl-lysine4 (H3K4me3) present in many active genes, while H3 trimethyl-lysine9 or trimethyl-lysine27 in repressed genes [89]. Changes in histone modifications have been reported in SLE cells, leading to aberrant gene expressions that may contribute to SLE pathogenesis. For example, monocytes from SLE patients are characterized by global H4 hyperacetylation in parallel with increased expression of genes involved in type I IFN and NFκB pathways [90]. By integrating genetic and epigenetic datasets, active histone marks are enriched in the promoters of SLE- and RA-susceptibility genes in EBV-transformed lymphoblastoid cell lines, suggesting a regulatory role of epigenomic elements for functions and cellular specificity of these autoimmune-associated genes [10^{***},91^{***}].

MiRNA dysregulation

MiRNAs representing a large class of small noncoding RNAs regulate gene expression by targeting specific mRNAs for degradation or translation inhibition [92]. Increasing evidence supports miRNAs playing an essential role in the development, homeostasis and function of innate and adaptive immunity that dysregulation of these processes may induce autoimmunity and inflammation (reviewed in [93]). Studies of miRNA expression profiles in blood cells, plasma and target tissues from SLE patients have revealed unique miRNA signatures when compared with healthy individuals and dysregulation of miRNAs associated with disease activity and major organ involvement, suggesting miRNAs as biomarkers for SLE patients [94^{***},95^{*}]. These dysregulated miRNAs are mainly involved in three types of biological processes relevant to the SLE pathogenesis (Table 2): (1) hyperactivation of type I IFN pathway (e.g. miR-146a) [96], (2) exacerbation of inflammatory responses by increasing cyto/chemokines secretion (e.g. miR-125a, miR-23b) [97,98], and (3) reduction of DNA methylation by directly or indirectly inhibiting DNA methyltransferase 1 (e.g. miR-126, miR-148a, miR-21) [101,102]. Of interest, the SLE-risk allele of *miR146a* promoter variant confers lower levels of its transcript due to decreased binding of transcription factor Ets-1 [15]. Given of the great potential for variation in miRNA target sites, some SLE-associated SNPs located in 3'UTR could regulate gene expression through introducing or abolishing miRNA binding sites (e.g. *TLR7*) [26^{***}], providing a miRNA-based genetic-epigenetic interaction for dissecting functional consequences of SLE-associated variants.

CONCLUSION

GWAS and follow-up studies have rapidly advanced our understanding of SLE genetics. Future challenges include discovery of new associations responsible for the missing heritability of SLE and identification of causal variants with functional characterization at

each locus. It is likely that genetic variants may not explain all variations in gene functions contributing to SLE. Identifying epigenetic modulation and genetic-epigenetic interaction will unravel new mechanisms to understand how SLE susceptibility genes affect disease risk and phenotypic expression. Integration of genetic knowledge with diverse epigenomic and biological studies has already guided drug discovery for RA [103²²], and such systematic strategy will be applied to SLE in the near future.

Acknowledgments

This work was supported by grants from the US National Institutes of Health (RO1AR043814 and R21AR065626) and the Alliance for Lupus Research.

References

1. Hom G, Graham RR, Modrek B, et al. Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. *N Engl J Med*. 2008; 358:900–909. [PubMed: 18204098]
2. Kozyrev SV, Abelson AK, Wojcik J, et al. Functional variants in the B-cell gene BANK1 are associated with systemic lupus erythematosus. *Nat Genet*. 2008; 40:211–216. [PubMed: 18204447]
3. Harley JB, Alarcon-Riquelme ME, Criswell LA, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXX, KIAA1542 and other loci. *Nat Genet*. 2008; 40:204–210. [PubMed: 18204446]
4. Graham RR, Cotsapas C, Davies L, et al. Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus. *Nat Genet*. 2008; 40:1059–1061. [PubMed: 19165918]
5. Han JW, Zheng HF, Cui Y, et al. Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. *Nat Genet*. 2009; 41:1234–1237. [PubMed: 19838193]
6. Yang W, Shen N, Ye DQ, et al. Genome-Wide Association Study in Asian Populations Identifies Variants in ETS1 and WDFY4 Associated with Systemic Lupus Erythematosus. *PLoS Genet*. 2010; 6:e1000841. [PubMed: 20169177]
7. Okada Y, Shimane K, Kochi Y, et al. A genome-wide association study identified AFF1 as a susceptibility locus for systemic lupus erythematosus in Japanese. *PLoS Genet*. 2012; 8:e1002455. [PubMed: 22291604]
8. Lee HS, Kim T, Bang SY, et al. Ethnic specificity of lupus-associated loci identified in a genome-wide association study in Korean women. *Ann Rheum Dis*. 2013 Epub ahead of print.
9. ENCODE Project Consortium. A user's guide to the encyclopedia of DNA elements (ENCODE). *PLoS Biol*. 2011; 9:e1001046. [PubMed: 21526222]
10. ■ Dozmorov MG, Wren JD, Alarcon-Riquelme ME. Epigenomic elements enriched in the promoters of autoimmunity susceptibility genes. *Epigenetics*. 2014; 9:276–285. This study evaluates transcription factors, histone modifications and chromatin state data from the ENCODE project and identifies specific transcription factors, H3K4me1 and H3K4me2 marks enriched in SLE- and RA-susceptibility gene promoters, providing evidence of distinct epigenomic elements as a regulatory basis for pathways, functions and cellular specificity of autoimmune disease-related genes. [PubMed: 24213554]
11. ■ Moliner JE, Maiti AK, Sun C, et al. Admixture Mapping in Lupus Identifies Multiple Functional Variants within IFIH1 Associated with Apoptosis, Inflammation, and Autoantibody Production. *PLoS Genet*. 2013; 9:e1003222. This genome-wide admixture mapping study reveals three independently associated variants in the *IFIH1* gene and explains their molecular basis for SLE pathogenesis. [PubMed: 23441136]
12. Cunningham DS, Morris DL, Bhangale TR, et al. Association of NCF2, IKZF1, IRF8, IFIH1, and TYK2 with systemic lupus erythematosus. *PLoS Genet*. 2011; 7:e1002341. [PubMed: 22046141]

13. Namjou B, Sestak AL, Armstrong DL, et al. High-density genotyping of STAT4 reveals multiple haplotypic associations with systemic lupus erythematosus in different racial groups. *Arthritis Rheum.* 2009; 60:1085–1095. [PubMed: 19333953]
14. Sanchez E, Comeau ME, Freedman BI, et al. Identification of novel genetic susceptibility loci in African American lupus patients in a candidate gene association study. *Arthritis Rheum.* 2011; 63:3493–3501. [PubMed: 21792837]
15. Luo X, Yang W, Ye DQ, et al. A functional variant in microRNA-146a promoter modulates its expression and confers disease risk for systemic lupus erythematosus. *PLoS Genet.* 2011; 7:e1002128. [PubMed: 21738483]
16. Graham RR, Kozyrev SV, Baechler EC, et al. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. *Nat Genet.* 2006; 38:550–555. [PubMed: 16642019]
17. Graham RR, Kyogoku C, Sigurdsson S, et al. Three functional variants of IFN regulatory factor 5 (IRF5) define risk and protective haplotypes for human lupus. *Proc Natl Acad Sci U S A.* 2007; 104:6758–6763. [PubMed: 17412832]
18. Sigurdsson S, Goring HH, Kristjansdottir G, et al. Comprehensive evaluation of the genetic variants of interferon regulatory factor 5 (IRF5) reveals a novel 5 bp length polymorphism as strong risk factor for systemic lupus erythematosus. *Hum Mol Genet.* 2008; 17:872–881. [PubMed: 18063667]
19. Lofgren SE, Yin H, Delgado-Vega AM, et al. Promoter insertion/deletion in the IRF5 gene is highly associated with susceptibility to systemic lupus erythematosus in distinct populations, but exerts a modest effect on gene expression in peripheral blood mononuclear cells. *J Rheumatol.* 2010; 37:574–578. [PubMed: 20080916]
20. Gateva V, Sandling JK, Hom G, et al. A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. *Nat Genet.* 2009; 41:1228–1233. [PubMed: 19838195]
21. Niewold TB, Kelly JA, Kariuki SN, et al. IRF5 haplotypes demonstrate diverse serological associations which predict serum interferon alpha activity and explain the majority of the genetic association with systemic lupus erythematosus. *Ann Rheum Dis.* 2012; 71:463–468. [PubMed: 22088620]
22. Fu Q, Zhao J, Qian X, et al. Association of a functional IRF7 variant with systemic lupus erythematosus. *Arthritis Rheum.* 2011; 63:749–754. [PubMed: 21360504]
23. Baccala R, Gonzalez-Quintal R, Blasius AL, et al. Essential requirement for IRF8 and SLC15A4 implicates plasmacytoid dendritic cells in the pathogenesis of lupus. *Proc Natl Acad Sci U S A.* 2013; 110:2940–2945. [PubMed: 23382217]
24. Lessard CJ, Adrianto I, Ice JA, et al. Identification of IRF8, TMEM39A, and IKZF3-ZBP2 as susceptibility loci for systemic lupus erythematosus in a large-scale multiracial replication study. *Am J Hum Genet.* 2012; 90:648–660. [PubMed: 22464253]
25. Shen N, Fu Q, Deng Y, et al. Sex-specific association of X-linked Toll-like receptor 7 (TLR7) with male systemic lupus erythematosus. *Proc Natl Acad Sci U S A.* 2010; 107:15838–15843. [PubMed: 20733074]
26. ■ Deng Y, Zhao J, Sakurai D, et al. MicroRNA-3148 modulates allelic expression of toll-like receptor 7 variant associated with systemic lupus erythematosus. *PLoS Genet.* 2013; 9:e1003336. This study establishes the *TLR7* 3'UTR SNP as a causal variant associated with SLE in multiple ancestries, which confers allelic effect on transcript turnover via differential binding to the epigenetic factor miR-3148. [PubMed: 23468661]
27. ■ Wang S, Wen F, Wiley GB, et al. An enhancer element harboring variants associated with systemic lupus erythematosus engages the TNFAIP3 promoter to influence A20 expression. *PLoS Genet.* 2013; 9:e1003750. This study provides functional evidence supporting a causal role for TT>A risk variants in the genetic predisposition to SLE. [PubMed: 24039598]
28. ■ Kaufman KM, Zhao J, Kelly JA, et al. Fine Mapping of Xq28: Both MECP2 and IRAK1 Contribute to Risk for Systemic Lupus Erythematosus in Multiple Ancestral Groups. *Ann Rheum Dis.* 2013; 72:437–444. This fine mapping study identifies a risk haplotype tagged by rs1059702 associated with SLE in four major ancestries. This SNP leads to an amino acid change in *IRAK1* with known function of increasing NFκB activity and is associated with low *MECP2* expression

levels in PBMCs, suggesting both *IRAK1* and *MECP2* contribute to SLE susceptibility. [PubMed: 22904263]

29. ■ Koelsch KA, Webb R, Jeffries M, et al. Functional characterization of the *MECP2/IRAK1* lupus risk haplotype in human T cells and a human *MECP2* transgenic mouse. *J Autoimmun.* 2013; 41:168–174. This study identifies that the SLE-risk haplotype confers increased expression level of *MECP2* transcript isoform 2 in stimulated T cells and is associated with DNA methylation changes in multiple genetic loci, providing evidence for genetic-epigenetic interaction in SLE. [PubMed: 23428850]
30. Vang T, Congia M, Macis MD, et al. Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant. *Nat Genet.* 2005; 37:1317–1319. [PubMed: 16273109]
31. Arechiga AF, Habib T, He Y, et al. Cutting edge: the *PTPN22* allelic variant associated with autoimmunity impairs B cell signaling. *J Immunol.* 2009; 182:3343–3347. [PubMed: 19265110]
32. Zhang J, Zahir N, Jiang Q, et al. The autoimmune disease-associated *PTPN22* variant promotes calpain-mediated Lyp/Pep degradation associated with lymphocyte and dendritic cell hyperresponsiveness. *Nat Genet.* 2011; 43:902–907. [PubMed: 21841778]
33. Menard L, Saadoun D, Isnardi I, et al. The *PTPN22* allele encoding an R620W variant interferes with the removal of developing autoreactive B cells in humans. *J Clin Invest.* 2011; 121:3635–3644. [PubMed: 21804190]
34. Dai X, James RG, Habib T, et al. A disease-associated *PTPN22* variant promotes systemic autoimmunity in murine models. *J Clin Invest.* 2013; 123:2024–2036. [PubMed: 23619366]
35. Manku H, Langefeld CD, Guerra SG, et al. Trans-ancestral studies fine map the SLE-susceptibility locus *TNFSF4*. *PLoS Genet.* 2013; 9:e1003554. [PubMed: 23874208]
36. ■ Sakurai D, Zhao J, Deng Y, et al. Preferential Binding to Elk-1 by SLE-Associated Risk Allele Upregulates Expression. *PLoS Genet.* 2013; 9:e1003870. This study identifies the *IL10* upstream SNP rs3122605 as the likely causal variant responsible for the genetic association with SLE in European Americans. The risk allele preferentially binds to the activated Elk-1 conferring elevated IL10 expression. [PubMed: 24130510]
37. Wang C, Ahlford A, Jarvinen TM, et al. Genes identified in Asian SLE GWASs are also associated with SLE in Caucasian populations. *Eur J Hum Genet.* 2013; 21:994–999. [PubMed: 23249952]
38. ■ Yang W, Tang H, Zhang Y, et al. Meta-analysis followed by replication identifies loci in or near *CDKN1B*, *TET3*, *CD80*, *DRAM1*, and *ARID5B* as associated with systemic lupus erythematosus in Asians. *Am J Hum Genet.* 2013; 92:41–51. This study using meta-analysis of prior Asian GWAS results followed by large-scale replication identifies additional novel genetic associations with SLE exceeding the GWAS significance. [PubMed: 23273568]
39. Hughes T, Kim-Howard X, Kelly JA, et al. Fine-mapping and transethnic genotyping establish *IL2/IL21* genetic association with lupus and localize this genetic effect to *IL21*. *Arthritis Rheum.* 2011; 63:1689–1697. [PubMed: 21425124]
40. ■ Westra HJ, Peters MJ, Esko T, et al. Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat Genet.* 2013; 45:1238–1243. This eQTL meta-analysis identifies *trans* eQTLs for 233 SNPs that are associated with complex traits, yielding insights into downstream effects of disease-associated variants. [PubMed: 24013639]
41. ■ Guthridge JM, Lu R, Sun H, et al. Two Functional Lupus-Associated *BLK* Promoter Variants Control Cell-Type- and Developmental-Stage-Specific Transcription. *Am J Hum Genet.* 2014; 94:586–598. This study identifies two causal variants within the *BLK* promoter associated with SLE susceptibility by modulating *BLK* transcription in B cells and altering immune responses. [PubMed: 24702955]
42. Lessard CJ, Adrianto I, Kelly JA, et al. Identification of a systemic lupus erythematosus susceptibility locus at 11p13 between *PDHX* and *CD44* in a multiethnic study. *Am J Hum Genet.* 2011; 88:83–91. [PubMed: 21194677]
43. Yang J, Yang W, Hirankarn N, et al. *ELF1* is associated with systemic lupus erythematosus in Asian populations. *Hum Mol Genet.* 2011; 20:601–607. [PubMed: 21044949]
44. Manjarrez-Orduno N, Marasco E, Chung SA, et al. *CSK* regulatory polymorphism is associated with systemic lupus erythematosus and influences B-cell signaling and activation. *Nat Genet.* 2012; 44:1227–1230. [PubMed: 23042117]

45. Sheng YJ, Gao JP, Li J, et al. Follow-up study identifies two novel susceptibility loci PRKCB and 8p11. 21 for systemic lupus erythematosus. *Rheumatology (Oxford)*. 2011; 50:682–688. [PubMed: 21134959]
46. Kim K, Brown EE, Choi CB, et al. Variation in the ICAM1-ICAM4-ICAM5 locus is associated with systemic lupus erythematosus susceptibility in multiple ancestries. *Ann Rheum Dis*. 2012; 71:1809–1814. [PubMed: 22523428]
47. Deng Y, Tsao BP. Genetic susceptibility to systemic lupus erythematosus in the genomic era. *Nat Rev Rheumatol*. 2010; 6:683–692. [PubMed: 21060334]
48. Rhodes B, Furnrohr BG, Roberts AL, et al. The rs1143679 (R77H) lupus associated variant of ITGAM (CD11b) impairs complement receptor 3 mediated functions in human monocytes. *Ann Rheum Dis*. 2012; 71:2028–2034. [PubMed: 22586164]
49. Fossati-Jimack L, Ling GS, Cortini A, et al. Phagocytosis is the main CR3-mediated function affected by the lupus-associated variant of CD11b in human myeloid cells. *PLoS One*. 2013; 8:e57082. [PubMed: 23451151]
50. Zhou Y, Wu J, Kucik DF, et al. Multiple lupus-associated ITGAM variants alter Mac-1 functions on neutrophils. *Arthritis Rheum*. 2013; 65:2907–2916. [PubMed: 23918739]
51. Jacob CO, Eisenstein M, Dinayer MC, et al. Lupus-associated causal mutation in neutrophil cytosolic factor 2 (NCF2) brings unique insights to the structure and function of NADPH oxidase. *Proc Natl Acad Sci U S A*. 2012; 109:E59–67. [PubMed: 22203994]
52. Kim-Howard X, Sun C, Molineros JE, et al. Allelic heterogeneity in NCF2 associated with systemic lupus erythematosus (SLE) susceptibility across four ethnic populations. *Hum Mol Genet*. 2014; 23:1656–1668. [PubMed: 24163247]
53. Zhang Y, Yang W, Mok CC, et al. Two missense variants in UHRF1BP1 are independently associated with systemic lupus erythematosus in Hong Kong Chinese. *Genes Immun*. 2011; 12:231–234. [PubMed: 21326321]
54. Zhang Z, Cheng Y, Zhou X, et al. Polymorphisms at 16p13 are associated with systemic lupus erythematosus in the Chinese population. *J Med Genet*. 2011; 48:69–72. [PubMed: 20805369]
55. Bronson PG, Chaivorapol C, Ortmann W, et al. The genetics of type I interferon in systemic lupus erythematosus. *Curr Opin Immunol*. 2012; 24:530–537. [PubMed: 22889593]
56. Ardoin SP, Pisetsky DS. Developments in the scientific understanding of lupus. *Arthritis Res Ther*. 2008; 10:218. [PubMed: 18947369]
57. Deane JA, Pisitkun P, Barrett RS, et al. Control of toll-like receptor 7 expression is essential to restrict autoimmunity and dendritic cell proliferation. *Immunity*. 2007; 27:801–810. [PubMed: 17997333]
58. Christensen SR, Shupe J, Nickerson K, et al. Toll-like receptor 7 and TLR9 dictate autoantibody specificity and opposing inflammatory and regulatory roles in a murine model of lupus. *Immunity*. 2006; 25:417–428. [PubMed: 16973389]
59. Barrat FJ, Meeker T, Chan JH, et al. Treatment of lupus-prone mice with a dual inhibitor of TLR7 and TLR9 leads to reduction of autoantibody production and amelioration of disease symptoms. *Eur J Immunol*. 2007; 37:3582–3586. [PubMed: 18034431]
60. Salloum R, Franek BS, Kariuki SN, et al. Genetic variation at the IRF7/PHRF1 locus is associated with autoantibody profile and serum interferon-alpha activity in lupus patients. *Arthritis Rheum*. 2010; 62:553–561. [PubMed: 20112359]
61. Lee MN, Ye C, Villani AC, et al. Common genetic variants modulate pathogen-sensing responses in human dendritic cells. *Science*. 2014; 343:1246980. This study identifies 121 common genetic variants associated in *cis* with variation in the induction of gene expression in DCs and localizes causal variants to binding sites of pathogen-activated STAT and IRF transcription factors. It also identifies a common *IRF7* variant associated in *trans* with type I IFN induction in response to influenza infection. [PubMed: 24604203]
62. Liu G, Tsuruta Y, Gao Z, et al. Variant IL-1 receptor-associated kinase-1 mediates increased NF-kappa B activity. *J Immunol*. 2007; 179:4125–4134. [PubMed: 17785851]
63. Jacob CO, Zhu J, Armstrong DL, et al. Identification of IRAK1 as a risk gene with critical role in the pathogenesis of systemic lupus erythematosus. *Proc Natl Acad Sci U S A*. 2009; 106:6256–6261. [PubMed: 19329491]

64. Wang Y, Shaked I, Stanford SM, et al. The autoimmunity-associated gene PTPN22 potentiates toll-like receptor-driven, type 1 interferon-dependent immunity. *Immunity*. 2013; 39:111–122. [PubMed: 23871208]
65. Bayley R, Kite KA, McGettrick HM, et al. The autoimmune-associated genetic variant PTPN22 R620W enhances neutrophil activation and function in patients with rheumatoid arthritis and healthy individuals. *Ann Rheum Dis*. 2014 Epub ahead of print. This study investigates the effects of R620W variant on neutrophil functions.
66. Hu X, Kim H, Stahl E, et al. Integrating autoimmune risk loci with gene-expression data identifies specific pathogenic immune cell subsets. *Am J Hum Genet*. 2011; 89:496–506. [PubMed: 21963258]
67. Pestka S, Krause CD, Sarkar D, et al. Interleukin-10 and related cytokines and receptors. *Annu Rev Immunol*. 2004; 22:929–979. [PubMed: 15032600]
68. Wojcik H, Griffiths E, Staggs S, et al. Expression of a non-DNA-binding Ikaros isoform exclusively in B cells leads to autoimmunity but not leukemogenesis. *Eur J Immunol*. 2007; 37:1022–1032. [PubMed: 17357110]
69. Maiti AK, Kim-Howard X, Motghare P, et al. Combined protein- and nucleic acid-level effects of rs1143679 (R77H), a lupus-predisposing variant within ITGAM. *Hum Mol Genet*. 2014 Epub ahead of print.
70. Lambeth JD, Krause KH, Clark RA. NOX enzymes as novel targets for drug development. *Semin Immunopathol*. 2008; 30:339–363. [PubMed: 18509646]
71. Shah D, Mahajan N, Sah S, et al. Oxidative stress and its biomarkers in systemic lupus erythematosus. *J Biomed Sci*. 2014; 21:23. This review provides available evidence for the involvement of cellular oxidants in the SLE pathogenesis and current biomarkers of oxidative stress linking with disease complication. [PubMed: 24636579]
72. Filippin LI, Vercelino R, Marroni NP, Xavier RM. Redox signalling and the inflammatory response in rheumatoid arthritis. *Clin Exp Immunol*. 2008; 152:415–422. [PubMed: 18422737]
73. Burek CL, Rose NR. Autoimmune thyroiditis and ROS. *Autoimmun Rev*. 2008; 7:530–537. [PubMed: 18625441]
74. Chen J, Gusdon AM, Thayer TC, Mathews CE. Role of increased ROS dissipation in prevention of T1D. *Ann N Y Acad Sci*. 2008; 1150:157–166. [PubMed: 19120287]
75. Olofsson P, Holmberg J, Tordsson J, et al. Positional identification of Ncf1 as a gene that regulates arthritis severity in rats. *Nat Genet*. 2003; 33:25–32. [PubMed: 12461526]
76. Hultqvist M, Olofsson P, Holmberg J, et al. Enhanced autoimmunity, arthritis, and encephalomyelitis in mice with a reduced oxidative burst due to a mutation in the Ncf1 gene. *Proc Natl Acad Sci U S A*. 2004; 101:12646–12651. [PubMed: 15310853]
77. Hultqvist M, Olsson LM, Gelderman KA, Holmdahl R. The protective role of ROS in autoimmune disease. *Trends Immunol*. 2009; 30:201–208. [PubMed: 19356981]
78. Chung SA, Taylor KE, Graham RR, et al. Differential Genetic Associations for Systemic Lupus Erythematosus Based on Anti-dsDNA Autoantibody Production. *PLoS Genet*. 2011; 7:e1001323. [PubMed: 21408207]
79. Sanchez E, Nadig A, Richardson BC, et al. Phenotypic associations of genetic susceptibility loci in systemic lupus erythematosus. *Ann Rheum Dis*. 2011; 70:1752–1757. [PubMed: 21719445]
80. Caster DJ, Korte EA, Nanda SK, et al. ABIN1 dysfunction as a genetic basis for lupus nephritis. *J Am Soc Nephrol*. 2013; 24:1743–1754. [PubMed: 23970121]
81. Freedman BI, Langefeld CD, Andringa KK, et al. End-stage renal disease in African Americans with lupus nephritis is associated with APOL1. *Arthritis Rheumatol*. 2014; 66:390–396. [PubMed: 24504811]
82. Taylor KE, Chung SA, Graham RR, et al. Risk alleles for systemic lupus erythematosus in a large case-control collection and associations with clinical subphenotypes. *PLoS Genet*. 2011; 7:e1001311. [PubMed: 21379322]
83. Hedrich CM, Tsokos GC. Epigenetic mechanisms in systemic lupus erythematosus and other autoimmune diseases. *Trends Mol Med*. 2011; 17:714–724. [PubMed: 21885342]
84. Javierre BM, Richardson B. A new epigenetic challenge: systemic lupus erythematosus. *Adv Exp Med Biol*. 2011; 711:117–136. [PubMed: 21627046]

85. ■ Absher DM, Li X, Waite LL, et al. Genome-wide DNA methylation analysis of systemic lupus erythematosus reveals persistent hypomethylation of interferon genes and compositional changes to CD4⁺ T-cell populations. *PLoS Genet.* 2013; 9:e1003678. This genome-wide DNA methylation analysis in CD4⁺ T cells, CD19⁺ B cells and CD14⁺ monocytes uncovers a profound hypomethylation of type I IFN-regulated genes, and identifies widespread moderate changes in methylation in T cells that are best explained by SLE-related compositional changes to the CD4⁺ population. [PubMed: 23950730]
86. Coit P, Jeffries M, Altorok N, et al. Genome-wide DNA methylation study suggests epigenetic accessibility and transcriptional poising of interferon-regulated genes in naive CD4⁺ T cells from lupus patients. *J Autoimmun.* 2013; 43:78–84. [PubMed: 23623029]
87. ■ Zhang Y, Zhao M, Sawalha AH, et al. Impaired DNA methylation and its mechanisms in CD4(+)T cells of systemic lupus erythematosus. *J Autoimmun.* 2013; 41:92–99. This review discusses the potential mechanisms leading to DNA hypomethylation in SLE. [PubMed: 23340289]
88. Esteller M. Cancer epigenomics: DNA methylomes and histone-modification maps. *Nat Rev Genet.* 2007; 8:286–298. [PubMed: 17339880]
89. Ballestar E. Epigenetic alterations in autoimmune rheumatic diseases. *Nat Rev Rheumatol.* 2011; 7:263–271. [PubMed: 21343899]
90. Zhang Z, Song L, Maurer K, et al. Global H4 acetylation analysis by ChIP-chip in systemic lupus erythematosus monocytes. *Genes Immun.* 2010; 11:124–133. [PubMed: 19710693]
91. ■ Trynka G, Sandor C, Han B, et al. Chromatin marks identify critical cell types for fine mapping complex trait variants. *Nat Genet.* 2013; 45:124–130. This study examines the cell type-specific overlap between histone markers and GWAS SNPs associated with several traits. H3K4me3 peaks overlaps with 31 RA-associated SNPs within CD4⁺ regulatory T cells. [PubMed: 23263488]
92. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell.* 2004; 116:281–297. [PubMed: 14744438]
93. Xiao C, Rajewsky K. MicroRNA control in the immune system: basic principles. *Cell.* 2009; 136:26–36. [PubMed: 19135886]
94. ■ Shen N, Liang D, Tang Y, et al. MicroRNAs--novel regulators of systemic lupus erythematosus pathogenesis. *Nat Rev Rheumatol.* 2012; 8:701–709. This comprehensive review summarizes current insights into miRNA biogenesis and functions in regulation of immune responses, discusses the roles of miRNAs in SLE pathogenesis and underscore the future therapeutic potential of targeting miRNAs in the management of SLE. [PubMed: 23070646]
95. ■ Carlsen AL, Schetter AJ, Nielsen CT, et al. Circulating microRNA expression profiles associated with systemic lupus erythematosus. *Arthritis Rheum.* 2013; 65:1324–1334. This study evaluates the specific expression patterns of cell-free circulating miRNAs in SLE. [PubMed: 23401079]
96. Tang Y, Luo X, Cui H, et al. MicroRNA-146A contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins. *Arthritis Rheum.* 2009; 60:1065–1075. [PubMed: 19333922]
97. Zhao X, Tang Y, Qu B, et al. MicroRNA-125a contributes to elevated inflammatory chemokine RANTES levels via targeting KLF13 in systemic lupus erythematosus. *Arthritis Rheum.* 2010; 62:3425–3435. [PubMed: 20589685]
98. Zhu S, Pan W, Song X, et al. The microRNA miR-23b suppresses IL-17-associated autoimmune inflammation by targeting TAB2, TAB3 and IKK-alpha. *Nat Med.* 2012; 18:1077–1086. [PubMed: 22660635]
99. Stagakis E, Bertsias G, Verginis P, et al. Identification of novel microRNA signatures linked to human lupus disease activity and pathogenesis: miR-21 regulates aberrant T cell responses through regulation of PDCD4 expression. *Ann Rheum Dis.* 2011; 70:1496–1506. [PubMed: 21602271]
100. Fan W, Liang D, Tang Y, et al. Identification of microRNA-31 as a novel regulator contributing to impaired interleukin-2 production in T cells from patients with systemic lupus erythematosus. *Arthritis Rheum.* 2012; 64:3715–3725. [PubMed: 22736314]

101. Zhao S, Wang Y, Liang Y, et al. MicroRNA-126 regulates DNA methylation in CD4+ T cells and contributes to systemic lupus erythematosus by targeting DNA methyltransferase 1. *Arthritis Rheum.* 2011; 63:1376–1386. [PubMed: 21538319]
102. Pan W, Zhu S, Yuan M, et al. MicroRNA-21 and microRNA-148a contribute to DNA hypomethylation in lupus CD4+ T cells by directly and indirectly targeting DNA methyltransferase 1. *J Immunol.* 2010; 184:6773–6781. [PubMed: 20483747]
103. ■. Okada Y, Wu D, Trynka G, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature.* 2014; 506:376–381. This study uses a systematic strategy to integrate RA-associated variants with diverse genomic and biological datasets to provide insights into the pathogenesis of RA and drive drug discovery for RA. [PubMed: 24390342]

KEY POINTS

- Over 50 loci associated with SLE susceptibility have been identified across multiple ancestries, and most encode gene products participating in the key pathways relevant to SLE pathogenesis.
- Few of candidate causative variants are located in the coding sequences to affect protein functions, whereas many reside within noncoding regions to regulate gene expression through transcriptional and posttranscriptional mechanisms.
- Epigenetic changes such as DNA methylation, histone modification and miRNA regulation in SLE represent an important layer to link genetics and gene expression with disease risk.
- Integration of genetic knowledge into diverse biological studies promises to identify specific immune cells and important (or novel) pathways that present therapeutic targets for SLE drug development.

Table 1

Non-HLA loci associated with SLE in the disease pathways*

Pathway	Chr	Gene	OR	Population	Likely Causative Variant (SLE-risk allele)	Ref
Type I IFN signaling						
	2q24	<i>IFIH1</i>	1.1–1.4	EA,AA	rs13023380 (A allele) results in decreased <i>IFIH1</i> transcript levels; rs1990760 (A946T; A allele) and rs10930046 (H460R; A allele) confer increased apoptosis and elevated inflammation-related gene expression.	11 ^{***} , 12
	2q32	<i>STAT4</i>	1.4–1.8	EU,EA,AS,HS,AA		3, 5–6, 13–14
	5q34	<i>miR146a</i>	1.3	AS		15
	7q32	<i>IRF5</i>	1.3–1.9	EU,EA,AA,AS,HS	Four functional SNPs define risk haplotypes associated with increased expression of IRF5 and IFN- α .	16–21
	11p15	<i>IRF7</i>	1.3–2.0	EU,EA,AA,AS	rs1131665 (Q412R; A allele) confers increased IRF7 and downstream IFN pathway activation.	3, 20, 22
	12q24.32	<i>SLC15A4</i>	1.1–1.3	EA,AS		5, 20, 23
	16q24	<i>IRF8</i>	1.2–1.3	EU,EA		12, 23–24
	19p13	<i>TYK2</i>	1.3	EA		12
	Xp22	<i>TLR7</i>	1.2–2.3	AS,EA,AA,HS	rs3853839 (G allele) confers increased <i>TLR7</i> expression and IFN response.	25, 26 ^{**}
NF-κB signaling						
	5q33.1	<i>TNIP1</i>	1.2–1.4	EA,AS		5, 20
	6q23	<i>TNFAIP3</i>	1.7–2.3	EU,EA,AS	TT>A polymorphic dinucleotide (deletion T followed by A transversion) with decreased NF- κ B binding to the promoter attenuates <i>TNFAIP3</i> expression.	4–5, 27 ^{**}
	22q11.21	<i>UBE2L3</i>	1.2–1.4	EU,EA,AS		3, 5, 20
	Xq28	<i>IRAK1/MECP2</i>	1.1–1.6	EA,AS,AA,HS	rs1059702 (S196F; A allele) tags a risk haplotype and confers increased NF- κ B activity.	28 ^{**} , 29 ^{**}
B and T cell signaling						
	1p13.2	<i>PTPN22</i>	1.4–2.4	EU,HS	rs2476601 (R620W; T allele) alters TCR and BCR signaling, and interferes with the removal of developing autoreactive B cells.	30–34
	1q25	<i>TNFSF4</i>	1.2–1.5	EU,EA,AS,AA,HS		3, 5, 35
	1q31-q32	<i>IL10</i>	1.2–1.3	EU,EA	rs3122605 (G allele) tags a risk haplotype associated with increased <i>IL10</i> expression.	20, 36 ^{**}
	2p25-p24	<i>RASGRP3</i>	1.2–1.4	AS,EU		5, 37
	3q13	<i>CD80</i>	1.3	AS		38 [*]
	4q21	<i>AFF1</i>	1.2	AS		7
	4q24	<i>BANK1</i>	1.2–1.4	EU,EA,AS,AA	rs10516487 (R61H; G allele) and rs3733197 (A383T; G allele) encode mutant BANK1; rs17266594 (T allele) alters splicing efficiency of <i>BANK1</i> transcript isoforms.	2, 6, 14
	4q26-q27	<i>IL21</i>	1.1–1.6	EA,AA		39

Pathway	Chr	Gene	OR	Population	Likely Causative Variant (SLE-risk allele)	Ref
	6q21	<i>PRDM1</i>	1.2	EA		20
	7p12.2	<i>IKZF1</i>	1.2–1.4	EU,AS	rs4917014 (T allele) alters <i>IKZF1</i> levels in <i>cis</i> and regulates expression of <i>C1QB</i> and five type I IFN response genes in <i>trans</i> .	5, 12, 40**
	8p23	<i>BLK</i>	1.2–1.6	EU,EA,AS,AA	rs922483 (T allele) and tri-allelic SNP rs1382568 (A, C alleles) reduce <i>BLK</i> promoter activity.	1, 3, 5, 41**
	8q13	<i>LYN</i>	1.2–1.3	EU		3
	10q21	<i>ARID5B</i>	1.2	AS		38*
	11p13	<i>PDHX/CD44</i>	1.2–1.4	EA,AA,AS		42
	11q23.3	<i>ETS1</i>	1.2–1.4	AS,EU		5, 6, 37
	13q13	<i>ELF1</i>	1.3	AS		43
	15q24.1	<i>CSK</i>	1.3	EU	rs34933034 (A allele) is associated with increased <i>CSK</i> expression, Lyn phosphorylation, BCR-mediated activation of mature B cells and expansion of transitional B cells.	44
	16p11.2	<i>PRKCB</i>	1.2	AS		45
	17q21	<i>IKZF3</i>	1.2–1.9	EU,AA		24
Neutrophil and monocyte function						
	19p13	<i>ICAM1/4/5</i>	1.2	EU,AA,HS,AS		46
Immune complex clearance						
	1q23	<i>FCGR2A</i>	1.3–1.4	EU,EA,AA,AS	rs1801274 (H166R; T allele)	reviewed in 47
		<i>FCGR3A</i>	1.2–1.5	EU,AA	rs396991 (F176V; T allele)	
		<i>FCGR2B</i>	1.3–2.5	AS	rs1050501 (I232T; C allele)	
		<i>FCGR3B</i>	1.7–2.3	EU,AA	decreased copy number	
	16p11.2	<i>ITGAM</i>	1.3–2.1	EA,EU,AA,AS,HS	rs1143679 (R77H; A allele) impairs leukocyte phagocytosis	
NADPH oxidase-dependent ROS pathway						
	1q25	<i>NCF2</i>	1.2–2.8	EA,AA,HS	rs17849502 (H389Q; A allele) confers decreased NADPH oxidase activity and ROS production	51–52
Others						
	2p13	<i>TET3</i>	1.3	AS		38*
	3p14.3	<i>PXK</i>	1.2–1.3	EU,EA		3, 20
	3q13.33	<i>TMEM39A</i>	1.2–1.4	EU,AA,AS		24
	5q35	<i>PTTG1</i>	1.2	EU		3
	6p21	<i>UHRF1BP1</i>	1.2–1.5	EU,AS		20, 53
	6q21	<i>ATG5</i>	1.2–1.3	EU,AS		3, 5

Pathway	Chr	Gene	OR	Population	Likely Causative Variant (SLE-risk allele)	Ref
	7p15.2	JAZF1	1.2	EA		20
	8p23.1	XKR6	1.2–1.3	EU		3
	10q11.23	WDFY4	1.2–1.3	AS		6
	12p13	CDKN1B	1.2	AS		38*
	12q23	DRAM1	1.2	AS		38*
	16p13.13	CLEC16A	1.2	EU,AS		20, 54

* These loci are identified through GWAS, meta-analysis, candidate gene studies or replication studies. All achieve $p < 5 \times 10^{-8}$ in at least one study.

Abbreviation: AA, African American; AS, Asian; EA, European American; EU, European; HS, Hispanic.

ARID5B, AT rich interactive domain 5B; *AFF1*, AF4/FMR2 family member 1; *ATG5*, autophagy related 5; *BANK1*, B-cell scaffold protein with ankyrin repeats 1; *BLK*, B lymphoid tyrosine kinase; *CD44*, CD44 molecule; *CD80*, CD80 molecule; *CDKN1B*, cyclin-dependent kinase inhibitor 1B; *CLEC16A*, C-type lectin domain family 16 member A; *CSK*, c-src tyrosine kinase; *C1QB*, complement component 1 q subcomponent B chain; *DRAM1*, DNA-damage regulated autophagy modulator 1; *ELF1*, E74-like factor 1; *ETSI*, v-ets avian erythroblastosis virus E26 oncogene homolog 1; *FCGR2A*, Fc fragment of IgG low affinity IIa receptor; *FCGR3A*, Fc fragment of IgG low affinity IIIa receptor; *FCGR3B*, Fc fragment of IgG low affinity IIb receptor; *FCGR3C*, Fc fragment of IgG low affinity IIIc receptor; *ICAM1*, intercellular adhesion molecule 1; *ICAM4*, intercellular adhesion molecule 4; *ICAM5*, intercellular adhesion molecule 5; *IFIH1*, interferon induced with helicase C domain 1; *IKZF1*, IKAROS family zinc finger 1; *IKZF3*, IKAROS family zinc finger 3; *IL10*, interleukin 10; *IL21*, interleukin 21; *IRF5*, interferon regulatory factor 5; *IRF7*, interferon regulatory factor 7; *IRF8*, interferon regulatory factor 8; *IRAK1*, interleukin-1 receptor-associated kinase 1; *ITGAM*, integrin alpha M; *JAZF1*, JAZF zinc finger 1; *LYN*, v-yes-1 Yamaguchi sarcoma viral related oncogene homolog; *MECP2*, methyl CpG binding protein 2; *miR146a*, microRNA 146a; *NCF2*, neutrophil cytosolic factor 2; *PDHX*, pyruvate dehydrogenase complex component X; *PRDM1*, PR domain containing 1 with ZNF domain; *PRKCB*, protein kinase C beta; *PTPN22*, protein tyrosine phosphatase non-receptor type 22; *PTTG1*, pituitary tumor-transforming 1; *PXXK*, PX domain containing serine/threonine kinase; *RASGRP3*, RAS guanyl releasing protein 3; *SLC15A4*, solute carrier family 15 (oligopeptide transporter) member 4; *STAT4*, signal transducer and activator of transcription 4; *TET3*, tet methylcytosine dioxygenase 3; *TLR7*, toll-like receptor 7; *TNFRSF39A*, transmembrane protein 39A; *TNFAIP3*, tumor necrosis factor alpha-induced protein 3; *TNIP1*, TNFAIP3 interacting protein 1; *TNFSF4*, tumor necrosis factor superfamily member 4; *TYK2*, tyrosine kinase 2; *UBE2L3*, ubiquitin-conjugating enzyme E2L3; *UHRF1BP1*, UHRF1 binding protein 1; *WDFY4*, WDFY family member 4; *XKR6*, XK Kell blood group complex subunit-related family member 6.

Table 2

MiRNA dysregulation in SLE

Function	miRNA	Expression in SLE patients	Target gene	Ref
Hyperactivation of type I IFN pathway				
	miR-146a	downregulated in PBMCs	<i>IRAK1, TRAF6, IRF5, STAT1</i>	96
Aberrant cyto/chemokines release				
	miR-125a	downregulated in PBMCs	<i>KLF13</i>	97
	miR-23b	downregulated in kidney tissue	<i>TAB2, TAB3, CHUK</i>	98
	miR-21	upregulated in CD4 ⁺ T cells	<i>PDCD4</i>	99
	miR-31	downregulated in CD4 ⁺ T cells	<i>RHOA</i>	100
DNA hypomethylation				
	miR-126	upregulated in CD4 ⁺ T cells	<i>DNMT1</i>	101
	miR-21	upregulated in CD4 ⁺ T cells	<i>RASGRP1</i>	102
	miR-148a	upregulated in CD4 ⁺ T cells	<i>DNMT1</i>	102

Abbreviation: *CHUK*, conserved helix-loop-helix ubiquitous kinase; *DNMT1*, DNA methyltransferase 1; *IRF5*, interferon regulatory factor 5; *IRAK1*, interleukin-1 receptor associated kinase 1; *KLF13*, Kruppel-like factor 13; *PDCD4*, programmed cell death 4; *RASGRP1*, RAS guanyl releasing protein 1; *RHOA*, ras homolog family member A; *STAT1*, signal transducer and activator of transcription 1; *TAB2*, TGF- β activated kinase 1/MAP3K7 binding protein 2; *TAB3*, TGF- β activated kinase 1/MAP3K7 binding protein 3; *TRAF6*, tumor necrosis factor receptor-associated factor 6.