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Genetic Factors Predisposing to Systemic Lupus Erythematosus and Lupus Nephritis

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Abstract

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease characterized by a loss of tolerance to self-antigens and the production of high titers of serum autoantibodies. Lupus nephritis can affect up to 74% of SLE patients, particularly those of Hispanic and African ancestries, and remains a major cause of morbidity and mortality. A genetic etiology in SLE is now well substantiated. Thanks to extensive collaborations, extraordinary progress has been made in the last few years and the number of confirmed genes predisposing to SLE has catapulted to approximately 30. Studies of other forms of genetic variation, such as CNVs and epigenetic alterations, are emerging and promise to revolutionize our knowledge about disease mechanisms. However, to date little progress has been made on the identification of genetic factors specific to lupus nephritis. On the near horizon, two large-scale efforts, a collaborative meta-analysis of lupus nephritis based on all genome-wide association data in Caucasians and parallel scans in four other ethnicities, are poised to make fundamental discoveries in the genetics of lupus nephritis. Collectively, these findings will demonstrate that a broad array of pathways underlines the genetic heterogeneity of SLE and lupus nephritis, and provide potential avenues for the development of novel therapies.

Keywords

Systemic Lupus Erythematosus (SLE); genetics; lupus nephritis

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Introduction

Systemic Lupus Erythematosus (SLE [MIM 152700]) is a chronic inflammatory disease characterized by a loss of tolerance to self-antigens and the production of high titers of autoantibodies directed against native DNA and other cellular constituents. Approximately 90% of individuals affected with SLE are female, predominately of childbearing age. SLE patients can present with a wide spectrum of clinical manifestations involving multiple organ systems. The prevalence of SLE in the U.S. is estimated between 0.05% and 0.1% of the population; The disease disproportionately affects African Americans (prevalence estimates: 0.009%, white men; 0.066%, white women; 0.038%, African-American men; and 0.282%, African-American women) [1]. About one-half of SLE patients will manifest the more severe complications of the disease, which can include nephritis, central nervous system vasculitis, pulmonary hypertension, interstitial lung disease, and stroke.

Lupus nephritis (LN) is among the most common clinical complication of SLE, occurring in up to 74% percent of patients and accounting for significant morbidity and mortality particularly among ethnic minorities [2]. The current paradigm is that LN results from immune complex deposition in the renal glomeruli leading to complement activation, chronic inflammation and renal insufficiency defined by histopathology and the presence of proteinuria and cellular casts.

Multiple lines of indirect evidence support a genetic etiology in SLE and LN. Twin studies estimated that the rate of SLE concordance in monozygotic twins is 24%-35%, compared to 2%–5% in dizygotic twin pairs [3,4]. Familial aggregation studies in SLE show that 10%-12% of patients with SLE have first or second degree family members with the disease, compared to < 1% of controls [5,6]. In SLE, the sibling risk ratio (λ_S) is estimated to be between 20 and 40 [7]. In addition, a genetic component to the susceptibility of LN is supported by an over-representation of LN among children with SLE, familial aggregation of end-stage renal disease (ESRD) among African Americans with LN [8] and linkage studies of LN 9.

Recently, more direct evidence for the role of genetic variation in the pathogenesis SLE and LN has emerged. Until 2007, only a handful of candidate gene polymorphisms had been convincingly implicated is SLE risk. Remarkable technological advances such as high-throughput genotyping, the completion of the human genome sequence and the International HapMap Project and parallel development of analytic and bioinformatic methods have occurred. Funding from the Alliance for Lupus Research has facilitated the development of the International Consortium on Systemic Lupus Erythematosus Genetics (SLEGEN; www.slegen.org) Collaborations between industry (e.g., Genentech) and academic institutions facilitated pooling of patient samples and leveraged recent technological advances to permit genome-wide searches for genetic polymorphisms predisposing to SLE and its complications. These efforts and those of many individual researchers have triggered an explosion of discoveries on the genetics of SLE. In spite of the complex genetic architecture of SLE, these discoveries demonstrate that a broad array of pathways underlines the genetic heterogeneity of SLE. Currently, the number of validated genetic regions predisposing to SLE is approximately 30. Current follow up efforts are now focused on precisely identifying the causative genetic variants and their effects, and the biological mechanisms through which they predispose to SLE. Research in LN has not attained the same level of maturity as it has in SLE. For example, no large-scale genome-wide association study (GWAS) for LN has been published. Consistent with the pre-GWAS era, the literature on LN genetics is remarkable for the lack of strength and consistency of associations of variants across different study designs and diverse populations.

The role of other forms of genetic variation is an exciting new frontier. Some copy number variants have already been shown to be important for SLE [10]. Epigenetic variation, (i.e., heritable change in genome function that occur without a change in DNA sequence) is clearly involved in the pathogenesis of SLE [11]. Such change may be the result of environmental exposures and can have a profound impact on gene expression. Given its potential importance, epigenomics has recently been included on the NIH Roadmap (http://nihroadmap.nih.gov/epigenomics). These new findings are creating new hypothesis about mechanisms of disease that may be potential therapeutic targets, and will revolutionize our knowledge of SLE.

Early discoveries

The major histocompatibility complex (MHC) was the first region reported as associated with SLE 12,13, and the dissection of its effects is still an area of active research. The extended MHC is a gene dense, transcriptionally active, 7.6 Mb interval on chromosome 6p21.3. It comprises the classical human leukocyte antigen (HLA) class I and class II regions that encode the genes involved in antigen presentation. In addition, it comprises the class III region that contains many immune genes, such as cytokines and early complement components, as well as genes of unknown function.

The class II alleles *HLA-DR2* (*DRB1*1501*) and *HLA-DR3* (*DRB1*0301*) have been the most consistent genetic risk factors associated with SLE in Caucasian populations. and studies suggest that these alleles confer an overall 2-to-3-fold increased risk for SLE [14]. Interestingly, *HLA-DQ* and *–DR* alleles show strong associations with SLE autoantibodies [15,16]. Despite the higher incidence and severity of SLE in African-Americans, HLA Class II associations with SLE in African-American populations are not consistent 14. Likewise, reports of HLA-DRB1*15 association with LN are largely discordant across diverse populations 17,[18] and the combined effect of HLA-DRB1*15 and HLA-DQA1*01 alleles, which was associated with a significant synergistic increased risk of LN compared to SLE patients without LN among Northern Italians, remains unconfirmed (OR=65.9, 95% CI 9.4-1,326) [19]. There is a need for additional studies that include sufficiently large and homogeneous sets of well-characterized LN and comparison groups to discover the role of the MHC in LN.

In spite of the fact that several genes within the MHC Class II and Class III regions have also shown associations with SLE, the high and extensive linkage disequilibrium (LD) present in the HLA region make identification of the causative genetic variation difficult to determine. Several reports have shown associations with multiple genes, including the *tumor necrosis factor α* (*TNF* or *TNFA*) in the class III region, or *TAP1* and *TAP2* genes in class II. However, only a few have shown to be distinct from the HLA alleles consistently associated with SLE. The ATP-binding cassette transporter *TAP2* gene [20] in class II has shown association separate from the *HLA-DR2* and *–DR3* alleles. A heterodimer formed by the TAP proteins transports peptides from the cytoplasm into the lumen of the endoplasmic reticulum for assembly with HLA class I or class II molecules. The first large analysis of the MHC revealed a distinct signal in the *superkiller viralicidic activity 2* (*SKIV2L*) gene [15] in class III, which is thought to be an RNA helicase and is highly expressed in T, B and dendritic cells [15]. Interestingly, the signal in the *SKIV2L* gene excludes the TNF-308G/A promoter polymorphism. Two large high-resolution analyses of this region have demonstrated evidence for distinct effects due to variation in different genes. Barcellos and colleagues [21] report several independent regions including the *G-protein-coupled receptor olfactory receptor 2* (*OR2H2*) gene in the extended class I region, *c-AMP responsive element binding protein-like 1* (*CREBL1*) within the class III region, and *MHC class I polypeptide-related sequence B* (*MICB*), which can activate the cytolytic response of natural killer cells. Rioux and colleagues [22] report separate effects within

HLA-DRA, near the ring finger *TRIM31* in class I, and the transmembrane protein *NOTCH4* in class III regions.

A strong relationship has long been noted between deficiencies of early classical pathway complement components (C1q, C2, and C4) and the development of SLE [23,24,25]. The complement system consists of approximately 30 plasma and cell-surface proteins that function to mediate inflammatory responses to immune complexes and to assist in the clearance of pathogens. Individuals that are homozygous deficient in *C1q* develop a severe and early onset form of SLE with severe glomerulonephritis and skin manifestations 26. Complete C2 and C4 deficiencies are rare (one in 10,000 and less than one in 10,000, respectively) and often result in a mild form of SLE that affects mostly the joints and skin [26,14]. In spite of being rare, these recessive deletions are strong genetic risk factors for SLE 27, underscoring the importance of rare variants in disease risk. Recent work has shown that both of C4 isoforms, C4A and C4B, harbor copy number variants (CNV) that predispose to SLE 28 (discussed below).

The Fc gamma (Fcγ) receptors, *FcγRI* (*CD64*), *FcγRII* (*CD32*) and *FcγRIII* (*CD16*), have been consistently and strongly associated with both susceptibility and severity of SLE [29]. These genes are closely linked at chromosome 1q23 and function to bind and clear IgG antibodies and IgG-containing immune complexes from the circulation. SLE patients show a higher frequency of the low binding affinity F176V mutation in the mature sequence for *FcγRIIIa* [30], in which individuals with the V/V genotype can bind IgG1 and IgG3 more efficiently. African-American SLE patients are enriched for the IgG2 low binding affinity allele H131R of *FcγRIIa* [31], in which H/H homozygotes bind IgG2 more avidly than R/R homozygotes. The T allele of the T232I polymorphism of *FcγRIIb* is also associated with SLE, especially in Asians [32,33], underscoring the importance of ethnicity. In the case of both FcγRIIa and FcγRIIIa, the low affinity allele is further enriched in patients that have lupus nephritis, suggesting Fc receptors may influence clinical manifestations and that the relevant Fc receptor depends on ethnicity. A meta-analysis of the H131R variant of *FcγRIIa* reported an increased risk of SLE (but not LN) for individuals with two copies of the risk allele (R/R) [34]. However, a meta-analysis of the V158F variant of *FcγRIIIa* [35] observed an increased risk of lupus nephritis for individuals with two copies of the risk allele (F/F). These meta-analyses suggest that for *FcγRIIIa* may be comparatively more functionally deleterious. Evidence that the *FcγRIIIa*-F176 allele co-segregates with LN may reflect a combined deleterious genetic effect consistent with direct functional evidence that low-affinity binding receptors specific for IgG isotypes reduce the efficiency of the mononuclear phagocyte system to clear immune complexes resulting in their deposition in the renal glomeruli [30,31]. In addition, evidence from an inception cohort of SLE patients showed that among Hispanics with LN, the alternate high-binding FCGR3A-V176 allele is associated with progression to ESRD[32], perhaps reflecting an alternative etiologic mechanism. Recently, a copy number variation in *FcγRIIIb* has also been associated with SLE [10] (discussed below).

Much interest was initially created by the *programmed cell death 1* gene (*PDCD1*) after Prokunina et al. [36], following-up a linkage study, first reported its association with SLE. *PDCD1* is an excellent functional candidate for SLE, given its role in apoptosis, and the fact that its deletion results in a lupus-like phenotype in animal models, including lupus-like glomerulonephritis, arthritis, and cardiomyopathy [37,38]. Nevertheless, further reports have yielded inconsistent results [39,40,41,42], suggesting that the causal variant either has opposing biological effects or tags different causal variants in different populations or specific disease features. Variation in this gene also may be associated with LN [43,44,45]. These independent findings were confirmed in a meta-analysis reported by Lee et al. [46], lending credence for *PCDC1* as a LN susceptibility marker (OR=2.27).

The association of the missense SNP R620W of the *protein tyrosine phosphatase PTPN22* was first reported in type 1 diabetes [47], and quickly replicated in SLE by Kyogoku and colleagues [48]. Even though a recent meta-analysis corroborated this polymorphism's association with SLE [49], it is not a major risk allele for SLE susceptibility in all Caucasian individuals [50]. *PTPN22* is an important example of a real risk polymorphism that has a significant North-South European gradient in allele frequency, underscoring the importance that admixture must be considered in candidate gene analyses [51]. The PTPN22 gene product, the lymphoid specific phosphatase Lyp, binds to the Src thyrosine kinase Csk to inhibit T cell activation. The R620W amino acid change disrupts binding of Lyp to Csk [47], with a likely stronger suppression of T cell signaling as a consequence. This could, in turn, lead to the persistence of autoreactive T cells that would otherwise have been deleted.

The clear role of the interferon pathway in SLE [52] prompted Sigurdsson and colleagues [53] to perform a genetic association study of 11 interferon genes. This analysis led to the identification of the *interferon regulatory factor 5* (*IRF5*) and *tyrosine kinase 2* (*TYK2*) genes. Upon activation, IRF5 activates transcription of type I IFN and pro-inflammatory cytokines such as TNFα, IL-12 and IL-6 [54]. A large meta-analysis firmly cemented the original rs2004640 SNP as a significant risk factor for SLE [55]. Subsequent work by Graham and colleagues [56] has elegantly shown how specific combinations of several polymorphisms in the *IRF5* region interact to increase disease risk. Specifically, the combinations of three functional alleles (at a splice site, at an in-frame deletion, and at a polyadenylation signal) define three distinct levels of risk to SLE. Their work illustrates how there may be multiple functional variants in a gene and how the most significant variant may be a proxy for a haplotype of multiple variants. The evidence for *TYK2* has recently become compelling, with two recent replication studies confirming its association with SLE [57,58].

Recent genes

The *signal transducer and activator of transcription* (*STAT4*) gene was first identified in rheumatoid arthritis on a fine-mapping analysis of a linkage peak [59,60], and the polymorphism was simultaneously replicated in SLE with an even stronger association [60]. A careful analysis of a large sample revealed associations with severe SLE nephritis, double-stranded DNA autoantibodies and younger age of onset [61]. Nevertheless, association analyses with LN have yielded inconsistent results. Interestingly, it has been suggested that two independent functional variants affect the levels of *STAT4* expression [62]. STAT4 is a transcription factor that transmits signals induced by several growth factors and cytokines, including IFNα [63]. Mice deficient for *STAT4* develop accelerated nephritis [64], which supports the association results. In addition, it was recently shown that the risk allele of *STAT4* was associated with increased sensitivity to IFNα signaling in lupus patients [65], providing biologic relevance for *STAT4* in the IFNα pathway.

Two neighbor genes on chromosome X, *interleukin-1 receptor-associated kinase 2* (*IRAK2*) and *methyl CpG binding protein 2* (*MECP2*) have shown association to SLE, raising the possibility that the higher prevalence of SLE in females may be due in part to the effects of genes on this chromosome. In 2007 Jacob et al. [66] first implicated *IRAK1*, and recently, using a combination of genetic studies in patient cohorts and functional studies in animal models, established a critical role for *IRAK1* in SLE pathogenesis [67]. IRAK1 is a serine/threonine protein kinase involved in the signaling cascade of the Toll/IL-1 receptor (TIR) family, and a potent activator of NFκB with roles in both innate and adaptive immunity [68]. Jacob et al. 67 hypothesized that variation in *IRAK1* may increase the risk of SLE by virtue of its role in the induction of IFN-α and IFN-γ, as a regulator of the NFκB pathway, and in TLR signaling. Challengingly, *MECP2*, which is only 2 kb from *IRAK1*, has also been associated with SLE [69,57,70]. Furthermore, Webb et al. [70] identified several genes that are dysregulated in B cells

from lupus patients with the *MECP2* risk haplotype, including a number of overexpressed IFN-regulated genes. They posit that the *MECP2* risk haplotype may play a role in the IFN signature observed in lupus patients. MECP2 is a chromatin-condensing protein with an important role in DNA methylation, thus involved in regulation of gene expression. It binds methylated DNA, recruits histone deacetylase or CREB1, and functions as a transcription repressor or activator for genes with CG-rich promoter sequences [70]. It is also a regulator of *IRAK1* expression [71, 72]. Epigenetic defects have a clear role in SLE pathogenesis [11], which makes of MECP2 both a likely and exciting candidate. Both *IRAK1* and *MECP2* lie in the same haplotype block, sharing several SNPs in high LD (r^2>0.80) according to the HapMap data (release 24) in Caucasians. It remain to be shown which of the two genes, or both, is the putative candidate. Nevertheless, these reports refute the paradigm that gender imbalance in SLE is solely due to sex hormones and support the hypothesis that genetic variation on chromosome X contributes to risk.

A single risk haplotype upstream from the *tumor necrosis factor* (TNF) *superfamily member OX40L* (*TNFSF4*) gene is a risk factor for SLE and correlates with increased expression of TNFSF4 [73,74]. This gene, which locates within an interval showing genetic linkage with SLE, is expressed on activated antigen-presenting cells (APCs) and vascular endothelial cells. It interacts with its single receptor OX40, which is expressed on activated T cells, to sustain the survival of activated T cells. Cunninghame Graham et al. [73] hypothesize that increased expression of *TNFSF4* predisposes to SLE either by quantitatively augmenting T cell-APC interaction or by influencing the functional consequences of T cell activation via TNFRSF4.

Variation in the promoter of the *pentraxin C-reactive protein* (*CRP*) gene has been associated with SLE or SLE nephritis in Caucasian and African ethnicities [75,76,77]. CRP is a plausible candidate for SLE susceptibility: it is an important innate immune modulator that facilitates the clearance of cellular debris and apoptotic bodies, and defects in clearance of apoptotic debris is thought to be important in the promotion and development of autoantibodies in patients with SLE [75]. In addition, the low CRP levels observed in SLE patients are influenced by genetic variation in the *CRP* promoter, and might contribute to altered handling of self-antigens [75]. Evidence of associations between CRP variants and LN is inconclusive.

Motivated by its function, Lee-Kirsh and colleagues [78] sequenced the gene encoding the 3′-5′ DNA exonuclease *TREX1* and found monoallelic frameshift or missense mutations and one 3′ UTR variant of *TREX1* present in 2% individuals with SLE but absent in controls. TREX1, the major mammalian intracellular DNase, causes single-stranded DNA damage during caspase-independent apoptosis activated by granzyme A [78]. Defective TREX1 might result in the failure to degrade ssDNA or dsDNA leading to immune activation and development of autoantibodies to these macromolecules [79]. In addition, TREX1 is an essential negative regulator of the IFN-stimulatory DNA response [80].

The GWAS era

Two high density GWAS [81,82] and a candidate gene study of a linkage peak [83] have simultaneously reported a novel association of the *integrin-α_M* (*ITGAM*) with SLE. Work by Nath and colleagues [83] suggest that the putative polymorphism is a functional nonsynonymous R77H substitution that alters the structure and function of the ITGAM protein. A recent meta-analysis further confirms the strength of the association in patients of European and African ancestry, but not in Asians, which is indicative of a population-specific risk [84]. *ITGAM* encodes the α-chain of $\alpha_M\beta_2$-integrin (also known as Mac-1, CD11b/CD18, and complement receptor type 3). It forms a heterodimer with integrin-β_2 (ITGB2) that regulates immune complex clearance, which appears impaired in SLE patients, and leukocyte adhesion and migration from the bloodstream via interactions with a wide range of structurally unrelated ligands, including

intracellular adhesion molecule (ICAM) -1 and ICAM-2, C3bi, fibrinogen, and others [83]. *ITGAM* expression is increased on neutrophils in SLE patients with active disease and may contribute to endothelial injury [85]. Although preliminary work is suggestive and *ITGAM* is a very interesting candidate gene for LN, to date published evidence for association has not convincingly established the *ITGAM* – LN relationship.

Variants in the *B-lymphoid tyrosine kinase* (*BLK*) promoter region were independently identified in three GWAS [86,81,82]. The risk allele at *BLK* is associated with reduced expression of BLK in B-cell lines [82]. BLK is a Src family kinase that interacts with the B-cell receptor complex and mimics pre-B cell receptor signaling in mice [87]. The importance of B-cell receptor signaling in establishing the B-cell repertoire has lead Hom et al. [82] to speculate that altered protein levels of BLK may influence tolerance mechanisms in B cells.

The *B-cell scaffold protein with ankyrin repeats 1* (*BANK1*) is another B-cell molecule originally identified through a GWAS of nonsynomymous SNPs [88]. The variants identified affect regulatory sites and key functional domains of BANK1, leading the authors to hypothesize that variation in *BANK1* can contribute to sustained B-cell receptor signaling, breakage of B-cell tolerance, autoantibody production and B-cell hyperactivity characteristic of SLE.

A GWA study reported a new association of the *tumor necrosis factor alpha-induced protein 3* (*TNFAIP3*) gene with SLE [86]. A relatively uncommon risk haplotype spanning *TNFAIP3* (minor allele frequencies ~5%) seems to confer a relatively high risk of SLE (odds ratio about 2.3). Studies in LN have yielded inconsistent results. TNFAIP3 catalyzes the ubiquitin modification of adaptor proteins downstream of TNFR, TLR and IL1R, and is a negative regulator of the NF-κB pathway [86].

The most recent GWAS was performed in a Chinese Han population and underscores the genetic heterogeneity of disease susceptibility between different ethnic populations [89]. This study confirmed seven of the previously reported loci in populations of European ancestry (*BLK*, *IRF5*, *STAT4*, *TNFAIP3*, *TNFSF4*, near *ATG5*, and near *UBE2L3*), and identified nine new loci. The most significant new loci include the transcription factors *ETS1* and *IKAROS family zinc finger 1* (*IKZF1*), the GTPase *RAS guanyl releasing protein 3* (*RASGRP3*), the transporter *SLC15A4*, and the *TNFAIP3 interacting protein 1* (*TNIP1*). As the authors indicate, these new genes corroborate the role for biological pathways already implicated in disease susceptibility: immune complex processing (*SLC15A4*), Toll-like receptor function and type I interferon production (*TNIP1*), and immune signal transduction in lymphocytes (*ETS1*, *RASGRP3* and *IKZF1*) [89].

A recent meta-analysis of GWAS has confidently validated three loci reported by Harley and colleagues [81]: the *ubiquitin-conjugating enzyme E2L 3 isoform 1* (*UBE2L3*), *pituitary tumour-transforming protein 1* (*PTTG1*), and *autophagy protein 5* (*ATG5*) [90]. A further large-scale replication by the same group confirmed these associations [58], as well as those in the *islet cell autoantigen 1* (*ICA1*) [81], and *nicotinamide nucleotide adenylyltransferase 2* (*NMNAT2*) genes [81]. Moreover, several new *loci* were identified in this Caucasian study: *TNIP1*, which was simultaneously reported in the Chinese Han GWAS [89], the *B-lymphocyte-induced maturation protein 1* (*BLIMP1*), also known as *PR-domain zinc finger protein 1* (*PRDM1*), *juxtaposed with another zinc finger gene 1* (*JAZF1*), *ICBP90 binding protein 1* (*UHRF1BP1*), and *interleukin-10* (*IL10*) [58].

The GWAS approach has also uncovered variants strongly associated with SLE in genes or regions of unknown immune function. Harley and colleagues [81] identified three such variants: in the *PX domain containing serine/threonine kinase* (*PXK*) gene, in *KIAA1542* (also known

as *PHD and ring finger domains 1* (*PHRF1*)), and in an intergenic region at 1q25.1. The two genes have been validated in a large replication study [58]. These intriguing associations clearly demonstrate that our understanding about SLE is only partial, and remind us that exciting new mechanisms await to be discovered.

Currently there are efforts to combine the existing genome-wide association data [86,81,82] to complete a robust meta-analysis for SLE, LN and age of onset to SLE in Caucasians. The meta-analysis of LN will be the first GWAS for LN and it holds great potential to uncover SNPs predisposing to LN previously masked by a lack of strong evidence for susceptibility to SLE alone. Genotyping of GWAS for SLE and LN in multiple other ethnicities are also being completed and will address a disappointing gab in our knowledge of risk factors for minority populations. Together their results should provide valuable information on ethnic heterogeneity in the causes of SLE and LN and help us to leverage the differences in linkage disequilibrium to better isolate regions of interest.

Efforts are underway to integrate the genetics of all autoimmune diseases and there appears to be considerable overlap in the genetic causes among type 1 diabetes, rheumatoid arthritis, SLE, Crohn's disease, multiple sclerosis, inflammatory bowel disease and several other disorders. How this shared versus SLE distinct risk factors might inform for the genetics of LN is to be seen.

Other forms of genetic variation

A copy number variant is defined as a DNA segment that is 1 kb or larger and is present at variable copy number (excess or missing) in comparison with a reference genome [91]. It is estimated that 5% of the genome display CNV and is a major source of genetic variation 92. Associations of SLE with CNVs have been reported for two genes, *FCGR3B* and *C4*. Aitman and colleagues [93] first suggested that reduced *FCGR3B* copy number is a risk factor for glomerulonephritis in SLE patients, and then reported that low copy number at *FCGR3B* is associated with SLE [94]. Although this association has not been established, a recent study reports that the *FCGR3B* CNV correlates with protein expression, with neutrophil uptake of and adherence to immune complexes, and with soluble serum FCGR3B, suggesting that a low copy number at this variant may contribute to impaired immune complex clearance due to reduced *FCGR3B* expression [95].

Given the known individual variation in the complement component *C4* locus copy number and protein levels, Yang and colleagues [28] investigated whether *C4* CNVs are risk factors for SLE. Their results suggest that low gene copy number is a risk factor for and high copy number is a protective factor against susceptibility to SLE in Caucasians. Possibly, decreased copy number of the *C4* genes leads to impaired clearance of immune complexes and apoptotic debris, while an increased copy number increases their clearance.

There is no doubt that environmental exposures can trigger lupus. Not only there is incomplete concordance for SLE among monozygotic twins, but hormonal factors [96], exposure to tobacco smoke [97], infectious agents and certain chemicals [98] are among the known contributors to SLE risk. Recent evidence suggests that environmental exposures can trigger SLE through epigenetic mechanisms [11]. Epigenetics refers to heritable modifications of gene expression that do not involve changes in the DNA sequence. Epigenetic mechanisms comprise DNA methylation, histone modification, and microRNA interference. DNA methylation - the addition of a methyl group to cytosines in CG pairs-, and covalent histone modifications, are sensitive to environmental influences, such as a dietary deficiency that would deplete the availability of methyl donors or methylation inhibitors. DNA methylation, which induces a chromatin structure that is inaccessible for transcription, is clearly involved in the pathogenesis of SLE. For example, it has been demonstrated that cells from lupus patients are

hypomethylated [99,100], resulting in overexpression of methylation-sensitive genes and T cell autoreactivity [11]. DNA methylation also participates in X chromosome inactivation in females [101] and silencing of parasitic viral DNA [102,103], plausible processes that might increase risk to SLE when dysregulated. The aforementioned association of the *methyl CpG binding protein 2* (*MECP2*) gene with SLE provides further evidence for the importance of DNA methylation in the etiology of SLE. The availability of high throughput microarray-based epigenetic profiling will allow eagerly anticipated studies to clarify the role of these novel disease mechanisms.

The role of microRNA (miRNA) in the regulation of the immune system is becoming evident. miRNAs are small (22-24 nucleotides) noncoding RNA molecules that post-transcriptionally regulate gene expression by binding and targeting messenger RNA for degradation. Several miRNAs are known regulators of the immune response – for example, miR-181a regulates PTPN22, and miR-17-92 regulates PTEN [104]. miRNA profiling studies have shown differential expression of several miRNAs between lupus patients and controls 105,106. Tang et al. 107 have recently shown that miR-146 regulates IRF5, STAT1, IRAK1 and TRAF6, and that it is underexpressed in SLE patients. Given the role of these genes in the IFN pathway and the known correlation of IFN with disease activity, underexpression of miR-146 might contribute to the IFN signature seen in lupus patients. Given that miRNA-mediated regulation of these and other genes is important to keep the immune system in balance, variation in miRNA levels or their targets is likely to contribute to increased risk of SLE.

Conclusion

In the last few years we have witnessed tremendous progress in the identification of genetic factors that contribute to the risk of developing SLE. An important contribution to the progress in the genetics of SLE has been the unprecedented collaborations among various research groups. Unfortunately, less effort has been focused on the genetics of LN but this appears to be changing.

A recent estimate suggests that most of the genetic variation identified so far only explains about 8% of genetic SLE risk [58]. Once association to a region or polymorphism is established, identifying the true causal variant is extremely complicated and time consuming. Establishing the role for a gene in SLE pathogenesis requires multiple lines of evidence. Clearly, much remains to be done before the etiology of SLE and LN becomes fully understood. Despite these qualifications, the near-term potential to understand much of SLE's etiology has never looked so promising. Many of the SLE susceptibility genes have known immune functions and can be placed into several focal pathways. These pathways highlight the importance of immune complex clearance (complement and phagocytosis), lymphocyte signaling (T and B cell signaling) and the innate immune response (interferon and NFκB signaling) in SLE predisposition. Furthermore, genes without an apparent immunological function may reveal novel pathways, and other forms of genetic regulation, such as epigenetic modifications and miRNAs, promise to unveil novel disease mechanisms. The development of high-throughput methods (such as epigenomic arrays) and parallel analytical strategies (such as data integration) are expected to provide unprecedented novel insights about the genetic factors and immune pathways that contribute to the pathogenesis of SLE. A deeper knowledge about disease mechanisms will provide a clearer understanding of this complex trait, and provide an avenue for the development of much needed targeted therapies.

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Table 1

Summary of established genes implicated in SLE

Gene	Location	Known function	OR[a]	Variation	Discovery[b]
HLA-DR2, -DR3	6p21.32	Antigen presentation	2.4	haplotypes	1971 12,13
C2	6p21.32	Immune complex clearance	5.0	deletion	1972 23
C4	6p21.32	Immune complex clearance	4.3	CNV	1974 24
C1q	1p36.12	Immune complex clearance	10	deletion	1981 25
FCGR2A	1q23.3	Immune complex clearance	1.6	H131R	1996 31
FCGR3A	1q23.3	Immune complex clearance	1.4	F176V	1997 30
FCGR2B	1q23.3	Immune complex clearance	1.7	I232T	2002 32
PDCD1	2q37.3	T cell signaling	1.2	PD1.3G/A	2002 36
PTPN22	1p13.2	TCR and BCR signaling	1.4	R620W	2004 48
IRF5	7q32.1	Regulator of type I IFN production	1.6	SNPs	2005 53
TYK2	19p13.2	Regulator of type I IFN production	1.2	SNPs	2005 53
FCGR3B	1q23.3	Immune complex clearance	2.2	CNV	2006 93
STAT4	2q32.2	Transcriptional regulator of IFNγ signaling; apoptosis	1.5	SNPs	2007 60
IRAK1*	Xq28	Toll, IL1R and NFkB signaling	1.4	SNPs	2007 66
TREX1	3p21.31	Regulator of IFNα production	25	SNPs	2007 78
MECP2*	Xq28	Regulation of gene expression through DNA methylation	1.3	SNPs	2008 69
TNFSF4	1q25.1	T cell signaling	1.4	SNPs	2008 73
CRP	1q32.2	Immune complex clearance	1.3	-707 SNP	2008 75
ATG5	6q21	Unknown	1.2	SNP	2008 81
PTTG1	5q33.3	Unknown	1.2	SNP	2008 81
UBE2L3	22q11.21	Ubiquitination	1.2	SNP	2008 81
PXK	3q14.3	Unknown	1.2	SNP	2008 81
PHRF1	11p15.5	Unknown	1.2	SNP	2008 81
ICA1	7p21.3	Unknown	1.2	SNP	2008 81

Gene	Location	Known function	OR[a]	Variation	Discovery[b]
NMNAT2	1q25.3	Unknown	1.1	SNP	2008 81
ITGAM	16p11.2	Immune complex clearance; leukocyte adhesion	1.6	R77H	2008 81,82,83
TNFAIP3	6q23.3	TNFR and NFkB signaling; ubiquitination	2.0	SNPs	2008 86,108
BLK	8p23.1	B cell activation	1.3	SNP	2008 86,81,82
BANK1	4q24	B cell activation; BCR signaling	1.2	R61H	2008 88
TNIP1	2q35	NFkB signaling	1.3	SNP	2009 58,89

[a] OR: Approximate Odds Ratio

[b] Year first reported

* These genes lie in the same haplotype block