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Genetic Susceptibility to Lupus: New Insights from fine mapping and genome-wide association studies

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Abstract

Genome-wide association studies and fine mapping of candidate regions have rapidly advanced our understanding of the genetic basis of systemic lupus erythematosus (SLE or lupus). More than 20 robust associations have now been identified and confirmed, and have provided insights at the molecular level that refine our understanding of the involvement of processes involved in the host immune response. In addition, genes with as yet unknown roles in SLE pathophysiology have been identified. These findings provide new routes toward improved clinical management of this complex disease.

Introduction

Systemic lupus erythematosus (SLE or lupus, MIM 152700) is a potentially deadly, systemic illness, sometimes considered the prototype for systemic humoral autoimmune diseases. It is characterized by autoantibody production leading to tissue injury through the formation and deposition of autoantibody-autoantigen immune complexes. Severity, risk and clinical expression of SLE vary by race, geography and sex, with a prevalence that is higher in women and some non-European-derived populations (reviewed in ¹⁻³).

SLE is an unusually heterogeneous disease, with various combinations of four of eleven clinical criteria required for case classification (^{4,5}). A high sibling risk ratio ($8 < \lambda_s < 29$), high heritability (>66%) and higher concordance rates between monozygotic twins (20-40%) relative to dizygotic twins and other full siblings (2-5%), all predict that SLE has a complex genetic basis (^{6,7}).

Here we explore how innovations in genotyping have advanced our understanding of the genetic basis of SLE through their application to fine-mapping and genome-wide association studies, and how they are informing our understanding of disease pathophysiology. The number of convincingly established genetic associations with SLE has increased sharply over the last

few years. We now have both corroborating genetic evidence for existing theories and new insights about biological pathways that contribute to the pathophysiology of lupus. This increased genetic understanding provides the potential to investigate potential new therapeutic strategies and to improve diagnostic and prognostic tests for the disease

High Density Genotyping Accelerates Progress

In the 1990s, SLE risk genes were pursued using genome-wide family-based linkage studies and led to the identification of FCGR2A, FCGR3A and PDCD1 as candidates (⁸⁻¹⁰) (Table 1). However, linkage studies were limited in their ability to identify causal alleles because of a lack of dense marker sets, which hindered comprehensive fine-mapping efforts. In addition, these studies typically have low power to map variants of small phenotypic effect size. In recent years, increased knowledge of the structure of the human genome through efforts such as the International HapMap project, together with technological developments that allow efficient and relatively inexpensive high throughput genotyping, have resulted in the availability of custom designed dense marker sets (^{11,12}). Linkage marker sets used in the 1990s generally had average intermarker distances of 10 centiMorgans; in today's dense marker sets these distances are reduced to < 20 base pairs. Combined with the recruitment of large DNA collections from lupus patients and controls, these marker sets have allowed extensive fine mapping within candidate regions, which in several cases has led to the identification of causal variants (Table 1).

The last couple of years have also seen the application of the genome-wide association study (GWAS) design, with its ability to screen hundreds of thousands of SNPs across the genome without previous knowledge of candidate regions or genes. To date, results from five GWAS in SLE have been reported (¹³⁻¹⁷), which have identified and robustly replicated several novel loci (ITGAM, BLK, BANK1, KIAA1542, PXX, and TNFAIP3) (Table 1), confirmed association at a number of other previously implicated loci, and have generated a large second tier of candidate loci ($10^{-5} > P > 10^{-6}$) for further study. Before 2007, there were nine confirmed lupus susceptibility loci. With the progress made in the past two years by the utilization of high density genotyping capabilities, there are now more than 20 loci identified that show robust association to SLE.

Biological Pathways Involved in SLE

The genetic associations identified to date indicate that many different pathways, processes, and cell types are involved in generating the lupus phenotype (Figure 1). While this interpretation is biased by our prior beliefs and application of parsimony when assigning roles to the variants identified, these findings have reinforced our pre-existing understanding of lupus pathophysiology obtained from immunochemistry, animal studies and other diseases, and have refined our understanding to the molecular level. Most of these genes are involved in three types of biological process: 1) immune complex processing, 2) toll-like receptor function and type I interferon production, and 3) immune signal transduction in lymphocytes.

First, defects in antigen presenting cell-mediated apoptotic cell clearance, processing and presentation to lymphocytes have been implicated in the development of lupus. Alleles at certain loci for which association with lupus has been identified or confirmed (e.g. HLA-DR, C reactive protein (CRP), Fc receptors) might affect the way that the encoded proteins react with immune complexes, providing molecular support for immune complex processing as an important theme in lupus pathogenesis (Figure 2a). This suggestion is bolstered by the low levels of complement in the circulation of active lupus patients and by the association of lupus with the absence of complement as a consequence of homozygous null alleles at any one of a number of classic complement pathway loci. ITGAM, also known as CD11b or complement receptor 3 (CR3), is the newest member of this pathway to be convincingly associated with

lupus and was identified simultaneously in two GWAS studies and in an independent positional cloning study (^{14,15,18}). ITGAM, which encodes the $\alpha_M\beta_2$ -integrin, is an integrin adhesion molecule and binds not only the complement fragment, iC3b, but also a myriad of other possible SLE-relevant ligands. The fact that a strong candidate nonsynonymous polymorphism, H77R, has been identified that appears to explain the entire association effect (¹⁸) should help to differentiate between the possible ligands. H77R appears to cause significant structural changes to the ligand-binding domain of $\alpha_M\beta_2$ (¹⁸). In addition, alloantibodies reactive against this polymorphism block the $\alpha_M\beta_2$ -dependent adhesion of neutrophils to endothelial cells (¹⁹).

Second, interferon has been implicated in lupus pathophysiology since the 1970s (²⁰), supported by a range of more recent studies (for example, see ^{21,22}). Type I interferon production is induced by immune complexes with nucleic acid signaling through toll-like receptors (TLRs) 7 and 9 (Figure 2b). Several lupus genes recently identified through candidate gene and GWAS studies (e.g. IRAK1, TREX1, IRF5 and TNFAIP3, see ^{14,15,17,23-28}) encode components of several pathways up- and downstream of type I interferon production. Understanding how these genes are involved in lupus etiology will be critical since the overproduction of interferon can promote the expression of proinflammatory cytokines and chemokines, the maturation of dendritic cells, the activation of autoreactive B and T cells, the production of autoantibodies, and loss of self-tolerance (²⁹).

Third, signal transduction in immune cells, especially B and T cells, is another pathway that has been revealed to contain multiple lupus susceptibility genes (Figure 2c). The activation of B-cells via antigen-mediated cross-linking of the B-cell receptor (surface IgM) and subsequent interaction of autoreactive B-cell clones with Th2 cells leads to loss of self-tolerance and autoimmunity. B- and T-cells have long been known to be involved in lupus pathogenesis and signal transduction pathways have been previously implicated. For example, PTPN22 is a selective phosphatase that modulates signal transduction in T cells, and represents a case in which a causal variant has been identified that contributes to disease susceptibility. The known R620W (1858C→T) risk allele is a gain-of-function variant, with increased catalytic activity compared to the non-risk variant and is thought to be a more potent suppressor of T cell receptor signaling (^{30,31}). This polymorphism is more common in northern Europeans (8-15%) compared to southern Europeans (2-10%) and virtually absent in Asian and African populations (³²). In contrast to the R620W gain-of-function polymorphism, a loss-of-function mutation (R263Q) found in the promoter region that leads to reduced phosphatase activity has recently been identified (³³). Recent GWAS studies for lupus have also identified new associations with other genes in this pathway (e.g. BANK1 and BLK), producing renewed attention by investigators to the mediation of B- and T-cell responses. BANK1 is thought to alter B cell activation to increase lupus risk, while BLK is thought to influence B cell tolerance and may affect mature B-cell function (^{15,16}). Studies to uncover the exact function of BLK and BANK1 in SLE are currently underway and have the potential to provide new knowledge about the molecular pathways that affect B-cell responses when exposed to antigen.

Finally, the most potentially informative results of both candidate and GWAS studies concern those loci (e.g. PXX, XKR6, and KIAA1542) that have no obvious connection to pathways that have been previously implicated in SLE. Elucidating the pathophysiological mechanisms underlying the association at these loci will be difficult. A striking example of this is the case of *XKR6*, a member of a novel family of PDZCBM containing proteins sharing homology with the *C. elegans* gene *ced-8*, which has been implicated in regulating the timing of apoptosis (³⁴). *XKR6* contains an intronic microRNA, hsa-miR-598, which is highly expressed in human peripheral blood mononuclear cells, especially activated B-cells (³⁵). Dissecting the relative contribution of *XKR6* to SLE risk is likely to be a complicated undertaking, especially given that a polymorphic inversion under apparent selection pressure on 8p23 encompasses the

XKR6, *C8orf12*, *C8orf13*, and *BLK* genes, all of which have been implicated in SLE risk in GWAS studies (³⁶).

Associations with SLE in the MHC Region

The discovery that the major histocompatibility complex (MHC) region confers risk to SLE marked the inception of genetic studies of this disease. However, the unprecedented highly complex linkage disequilibrium structure of this locus, which extends an amazing 7.2 Mb (¹⁴) across >400 genes in European derived subjects, has hindered efforts to dissect the variants responsible for the considerable risk that this region confers in SLE. A recent meta-analysis of the results from the past 30 years of research found the most consistent HLA associations with SLE for class II alleles (HLA-DR3 and DR2) in European populations (³⁷). However, in the recently published GWAS results from European-derived women, greatest association with SLE was with the *MSH5* gene, a gene in the class III region (¹⁴). Further study is clearly required to determine whether *MSH5* or one of its close neighbors is a risk factor for SLE that is independent of the HLA-DR genes that have been so frequently associated with lupus. The structures of MHC haplotypes differ between populations and evaluation in non-Europeans has revealed that yet other alleles (e.g. HLA-DR4) confer susceptibility to lupus risk in these populations (³⁷).

Though this region is one of the most extensively studied regions of the human genome, the precise contribution attributable to the overall genetic risk in SLE remains to be determined. Therefore, studies performed in much larger cohorts that evaluate the entire MHC locus rather than specific regions, and that are inclusive of the non-Europeans have great potential increased our understanding of lupus pathogenesis.

Genetic Models of SLE Risk

Given the large number of lupus susceptibility loci now known, important questions can now be addressed: How many more loci are likely to be implicated in SLE pathogenesis? And what is their impact in terms of contribution to risk? Available evidence suggests that the genetic risk for lupus is derived from variation in many (perhaps as many as 100) genes, each of modest effect size (odds ratios 1.15 to 2.4) (see Table 1 for the 20 currently established lupus genes). The genetic architecture of SLE, therefore, more closely resembles that of Crohn's disease with > 30 susceptibility loci. This contrasts with rheumatoid arthritis, an autoimmune disease with which SLE shares common elements of pathophysiology and some susceptibility loci (*TNFAIP3*, *STAT4*, and *PTPN22*) where the GWAS has yielded relatively fewer genes (<10).

Interestingly, none of the identified associations in SLE exhibit evidence of epistasis. A stepwise multiple logistic regression analysis suggests that the variants in the *PXK*, HLA region, *IRF5*, *KIAA1542* and *ITGAM* genes act independently (¹⁴). When considered jointly, these variants explain ~15% of the lupus sibling risk ratio of 8 to 29 and are strongly predictive of lupus with significant sensitivity and specificity comparable to that used in some clinical tests (^{14,38}). This estimate needs independent replication; however, as it is biased upwards since it is based on the samples discovering the associations. As the number of robust genetic associations enlarges and their modes of inheritance are described, the practical utility of this new knowledge is likely to find application in new diagnostics and management strategies for lupus. In particular, the unusual clinical heterogeneity of lupus coupled with its clear genetic diversity argues for genetic tests that would classify the disease into subtypes, which might guide preventive and therapeutic strategies.

Challenges and Future Directions

The past few years have seen tremendous success in the identification of lupus susceptibility genes, with at least 20 robustly associated loci that contribute to disease risk. However, it is

likely that many more remain to be discovered. In terms of future studies, the GWAS design has its limitations. Because GWAS studies rely on tagging common haplotype blocks, association signals from these studies are more likely to identify a marker in strong linkage disequilibrium with a causal variant than they are to identify the actual causal variant. Second, they are unlikely to have the power to detect association in some lupus susceptibility loci - loci that have already been robustly replicated for association with SLE. For example, the FcγR gene cluster on 1q23.3 has multiple ancient (as well as modern) gene duplications and rearrangements. Consequently, marker coverage at these loci is relatively sparse. Similarly, because GWAS studies assay common variants, rare risk variants, such as those described in *TREX1* and variants of the complement component genes, C2, C4 and C1q, are unlikely to be detected by GWAS. Indeed, recessive modes of inheritance are generally underpowered in GWAS studies unless the risk allele is very common. Furthermore, to date, GWAS have only been carried out for SNPs. However, there is increasing evidence that other types of common genetic variation (e.g. copy number variants) contribute to complex disease, some of which have only recently been included in GWAS genotyping panels.

Each newly identified association presents new challenges. Finding the causal variants, understanding how they affect disease pathophysiology and dissecting their contribution to SLE risk remain major undertakings. For some genes, the effect sizes or risk allele frequencies may be so small that still larger collections of lupus patients are needed to identify a sufficient number of patients with the responsible risk allele for subsequent functional studies. Studies to evaluate the molecular differences in the gene regulation or function due to the supposed causative genetic risk variants (e.g. protein expression level and cellular function differences between cases and controls) are needed to explore the possible mechanisms through which the causal variant generates disease risk. Still, even when the gene has an obvious potential to explain pathogenesis and to be a component of the mechanism of disease, some inferences concerning function may be flawed because of hidden and cryptic relationships that are still unknown.

It is important to note that many of the associations detected to date have been in European populations. Though some of these genes also associate with SLE in non-European populations (e.g. FcGR2A, IRF5, ITGAM), SLE associations have been mostly left unexplored in African, Asian and Hispanic ancestries, mainly due to previously underpowered sample collections. Furthermore, meta-analyses are needed to improve power and capitalize on existing results. Finally, understanding how the implicated genes interact with the environment (e.g. Epstein-Barr virus antigens, smoking, etc) will be an important goal that has so far not been tackled.

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John B. Harley, MD, PhD, a Member and Chair of the Arthritis and Immunology Program at the Oklahoma Medical Research Foundation (OMRF), is a rheumatologist with expertise in systemic lupus erythematosus and related conditions. He has led the OMRF lupus genetics effort for over 25 years and leads the OMRF Lupus Family Registry and Repository (LFRR). Dr. Harley leads a department of 13 independent investigators and 200 employees. He is a current NIH Merit Award recipient in lupus genetics and has been the Director of the International Consortium on the Genetics of Systemic Lupus Erythematosus (SLEGEN) since 2006.

Jennifer Kelly, MPH, a Research Project Director in the Arthritis and Immunology Program at the Oklahoma Medical Research Foundation (OMRF), has more than 12 years experience working in lupus genetics and has earned a well-deserved reputation for the quality of her work. She is currently the Assistant Director of the Lupus Family Registry and Repository (LFRR) (<http://lupus.omrf.org>), where she helps oversee the overall direction of the project. Her educational background is in microbiology and biostatistics, and she is the central depot for organization and analysis of the human genetics data generated from the Lupus Genetics Studies at the OMRF.

Figure 1. Pathways that contain established candidate SLE susceptibility loci
 Genes involved in each pathway are indicated.

Figure 2. Pathways in which identified SLE risk alleles operate

Note that these are proposed models and it is possible, even likely, that the mechanism(s) by which these genes confer risk for SLE involve not only the pathways presented, but also other pathways.

a | Phagocytosis. A presumed environmental trigger (for example, UV irradiation, viral infection or dysregulated apoptosis) leads to activation of antigen presenting cells which phagocytose self-antigen coated by opsonins (e.g. C3b), which are bound by their respective receptors (e.g. ITGAM). This leads to subsequent APC activation and presentation of self-antigen to host lymphocytes. This pathway potentially plays a role in disease initiation and perpetuation. In terms of initiation, a tendency towards antigen-presenting cell hyperactivation

is a path toward loss of self-tolerance. In terms of perpetuation, when immune complexes are not cleared, this leads to the production of autoantibodies. [C1q: Complement component 1, subcomponent q; C2: Complement component 2; C3: Complement component 3; C3a: C3 cleavage product a; C3b: C3 cleavage product b; C4: Complement component 4; CRP: C-reactive protein; ITGAM: Intergrin α_M ; Fc γ R: Fc fragment of IgG receptor; HLA-DR: major histocompatibility complex, class II, DR]

b | Type I interferon production: Recent data ⁽⁴⁸⁾ suggest that *TREX1* digests cytosolic DNA and prevents activation of a cell-intrinsic type I interferon (notably, interferon- α) response pathway (see ⁴⁸). Similarly, activation of Toll-like receptors (TLRs – notably *TLR7*, *TLR8*, and *TLR9*) on ligand recognition (CpG DNA or ssRNA) leads to production of type I interferon by immune cells, notably plasmacytoid dendritic cells and the interferon responsive gene expression signature observed in lupus serum. [CpG DNA: DNA containing CpG dinucleotides; ssRNA: single-stranded RNA; TLR: toll-like receptor; IRAK1: Interleukin-1 receptor associated kinase-1; TNFAIP: Tumor necrosis factor- α induced protein 3 (aka A20); IRF5: interferon regulatory factor 5; IRF7: interferon regulatory factor 7; TREX1: three prime repair exonuclease 1; STAT4: signal transducer and activator of transcription 4; STAT1: signal transducer and activator of transcription 1]

c | Immune Signal Transduction: Various stages in the life-cycle of lymphocytes are important for the development of the autoreactive B-cell clones, which produce the pathological autoantibodies observed in SLE. Here we focus on activation events. Self-antigen recognition by B-cells starts at the B-cell receptor (membrane IgM), where the balance of positive (B-cell receptor cross-linking) and negative signals (FCGR2B ligation) are transduced via intracellular kinases, such as BLK and BANK1, leading to B-cell activation. A similar process, leading to T cell activation occurs after uptake of the self-antigen and presentation on a class II MHC molecule, such as HLA-DR to a CD4+ T lymphocyte, which subsequently provides “Help” to B lymphocytes. It should be noted that autoreactive clones must avoid deletion before activation events can lead to florid autoimmunity. [BCR: B cell receptor; FCGR2B: Fc fragment of IgG receptor, low affinity 2B; BLK: B lymphoid tyrosine kinase; BANK1: B-cell scaffold protein with ankyrin repeats 1; TNFRSF4: tumor necrosis factor receptor superfamily, member 4; TNFSF4: tumor necrosis factor superfamily, member 4; PTPN22: protein tyrosine phosphatase, non-receptor type 22; TCR: T cell receptor; PDCD1: programmed cell death 1; CD274: programmed cell death 1 ligand 1 precursor; PDCD1LG2: programmed cell death 1 ligand 2 precursor].

Table 1
SLE candidate genes identified or confirmed in recent studies

Gene(s)	Odds Ratio	Study Design ^a	Comments ^b	Ref.
TREX1 ^d	25	Candidate	Rare; found in 12/417 cases and 2/1712 controls	23
Clq	~10	Candidate	Rare; >90% -/- affected	39
C4A & C4B	6.5 & 2.02	Candidate	Rare; >70% -/- affected; associated with a CNV	40-41
C2	~5	Candidate		42
TNFAIP3 ^c	2.3	GWAS		17-24
HLA-DR2 and 3 ^{c,d}	2	Candidate, confirmed in GWAS	Region of high linkage disequilibrium	14'15'37
IRF5 ^{c,d}	1.8	Candidate, confirmed in GWAS	Three identified causal variants	14'15'25'27
ITGAM ^{c,d}	1.6	Simultaneous GWAS and Candidate	H77R causal variant	14'15'18
FcGR3A ^f	1.6	Linkage Candidate	F176V causal variant	9
STAT4/STAT1 ^{c,d}	1.5	Candidate, confirmed in GWAS		14'15'43
BLK/C8orf13/XKR6 ^c	1.5	GWAS	Included in a polymorphic inversion on Chr. 8	14'15'17
BANK1 ^c	1.38	GWAS		16
FcGR2A ^{c,e}	1.35	Linkage Candidate, confirmed in GWAS	H131R causal variant	8'9'14
PTPN22 ^{c,d}	1.3	Candidate, confirmed in GWAS	N. European; familial lupus; RA susceptibility	14'44
CRP ^f	1.3	Candidate		45
OX40/TNFSF4 ^d	1.3	Candidate		46
KIAA1542 ^c	1.28	GWAS	Near IRF7	14
PXK ^c	1.25	GWAS		14
MECP2/IRAK1 ^d	1.2	Candidate	Located on X chromosome	28'47
PDCD1 ^e	1.2	Linkage Candidate		10

^a Candidate: candidate gene association study
^b -/-: homozygous for the null allele
^c GWAS p<5×10⁻⁸ and confirmed
^d Candidate gene p<1×10⁻⁵ and confirmed
^e LOD>3.2 and confirmed

f_{gene} may have not yet reached stringent thresholds of c - e , but observed in multiple independent studies and sufficient biological evidence to conclude is real.