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Monogenic lupus

"It is increasingly evident that the clinical phenotype of systemic lupus erythematosus may represent a final common pathway resulting from multiple overlapping genetic conditions; although rare, monogenic forms of lupus offer important insight into pathogenesis as we continue to make these genotype/phenotype correlations."

Keywords: chilblain • complement • DNASE1L3 • immunodeficiency • lupus • Mendelian • monogenic • PRKCD • systemic lupus erythematosus • TREX1

Lupus has long been recognized to have a strong genetic component, although the degree of genetic contribution is as variable as the clinical heterogeneity with which this disease presents. While familial forms have been observed, the inheritance of systemic lupus erythematosus (SLE) is generally complex, suggestive of an oligogenic or multigenic origin. Many different genes have been implicated in the pathogenesis of SLE [1]. These genes have traditionally been identified by single nucleotide polymorphism studies, either linkage analysis or, more recently, genome-wide association studies (GWAS). Most of the associated genes play roles related to immune cell signaling (e.g., *PTPN22, STAT4, TYK2*) or apoptosis and antigen presentation (e.g., *CASP10, ITGAM*), although genes in other pathways have also been implicated.

The effect size of each individual gene variant is typically relatively small. In one cohort, examination of 22 SLE susceptibility polymorphisms identified by prior GWAS showed that the difference in risk allele frequency between cases and controls was small, with a mean of 15.1 risk alleles in cases, and 13.1 in controls [2]. Of the studied genes, HLA-DRB1 (DR3 allele) had the strongest association, with an odds ratio of 1.94 in cases over controls [2]. Susceptibility alleles identified through GWAS are also inadequate to explain the full heritability of SLE. The six strongest loci associations in one GWAS explained only 15% of SLE heritability, estimated using sibling recurrence risk [3]. There are multiple possible explanations for the missing heritability. These include either many small effect size variants yet to be identified, or rarer variants with larger effect size that are not captured well by GWAS-type analysis [4]. It is this latter possibility that is the most exciting, as these rarer variants are more likely to give insight into the pathogenesis of this disease, as well as present potential therapeutic targets.

Certainly, some rare gene variants with strong effect size have already been identified (Table 1). Perhaps the best characterized genetic defects associated with SLE are those related to members of the classical complement activation pathway. This relationship was noted as early as the 1970s [5]. Since then, inherited deficiencies of C1q, C1r, C1s, C2, C4A and C4B have all been described to predispose to SLE development [6]. The degree of risk varies depending on the deficiency but is overall high; in particular, patients with C1q deficiency have >90% risk for developing SLE [6]. In these patients, in whom SLE is inherited in a Mendelian fashion and who can thus be said to have a 'monogenic' form of SLE, lupus features present early in childhood. C1q-deficient patients also have a specific phenotype of prominent glomerulonephritis, although anti-DNA antibodies are commonly negative [7].

Recognition that complement activation plays a key physiologic role in SLE has yielded important insights into pathogenesis. Complement proteins mediate clearance of immune complexes, which can otherwise lead to tissue damage. Furthermore, inefficient processing of apoptotic cellular debris due

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Table 1. Gene deficiencies and variants with loss or gain of function that are strongly linked to systemic lupus erythematosus or systemic lupus erythematosus-like disease.

Gene	Ref.
C1q, C1r, C1s	[6,7]
C2	[8]
C4A, C4B	[9]
TREX1	[10]
Fas	[11,12]
FasL	[13]
DNase1	[14]
DNase1L3	[15]
SAMHD1	[16]
*TMEM17 (*STING*)*	[17]
*PRKCD (*PKCδ*)*	[18]
*ACP5 (*TRAP*)*	[19]
RAG2	[20]

to C1q deficiency may allow inappropriate presentation of self-antigens and breach of self-tolerance. Other defects of apoptosis may also contribute to SLE pathogenesis. For example, patients with homozygous Fas and FasL mutations develop a phenotype of lymphoproliferative disease with SLE-like autoimmune features, again most commonly presenting at an early age [11,13]. In non-Mendelian forms of SLE, single nucleotide polymorphisms in Fas are also described in higher frequency in cases as compared with controls [12].

With greater scrutiny of SLE genetics has come discovery of other monogenic conditions with lupus-like phenotypes. In 2006, familial chilblain lupus (FCL) was mapped to a locus on chromosome 3p. This autosomal dominant disease, which presents in early childhood with chilblain lesions, Raynaud symptoms and autoantibodies, evolves into SLE in 18% of cases. It was quickly recognized that Aicardi-Goutieres syndrome (AGS), a severe neurologic disease with some clinical features similar to those described in FCL, had previously been mapped to the same locus. Subsequent studies demonstrated that the relevant mutation for both conditions was in the gene encoding TREX1, a 3′–5′ DNA exonuclease [21,22]. Interestingly, IFN-α levels are elevated in FCL and AGS patients, as has been described in SLE. This, together with the clinical similarities, brought to mind the role of TREX1 in SLE pathogenesis. In a cohort of 417 patients with SLE, heterozygous *TREX1* mutations were found in nine (2%) [10]. Another study of *TREX1* polymorphisms in a larger cohort that included multiple ethnic groups found a lower frequency of mutations at 0.5% [23]. Further supporting the clinical overlap between AGS and SLE, the study also identified an association between the TREX1 SNP haplotype with neurologic manifestations in SLE patients.

The normal role of TREX1 appears to be the degradation of genomic DNA in granzyme A-mediated cell death. In the case of either TREX1 deficiency, or resistance to TREX1 exonuclease activity (as with oxidized or UV-damaged DNA), self-DNA is immunogenic and stimulates type I IFN production. This IFN response, which is part of the normal intracellular DNA-sensing pathway critical for antiviral immunity, is mediated by the stimulator of interferon genes (STING). STING deficiency ablates the autoimmune phenotype of TREX1-deficient mice; by contrast, increased STING activity may thus lead to overproduction of IFN and chronic inflammation [24]. Confirming this concept, gain-of-function mutations in *TMEM173*, the gene encoding STING, were recently described in a cohort of children with high IFN levels and severe vasculitic disease presenting in infancy [17].

Autoimmunity stemming from the abnormal clearance of DNA in apoptosis is a recurring theme in SLE. Decreased DNase activity has been observed in humans with SLE, and two different mouse models of lupus carry missense mutations in *DNase1L3*, although DNase mutations were not previously seen in human disease. Recently, however, examination of seven consanguineous families with multiple affected children by linkage analysis and exome sequencing identified loss-of-function mutations in *DNase1L3* [15]. The mutation correlated with disease in a strictly Mendelian, autosomal recessive pattern. Age of disease onset in all of these children was quite young, ranging from 2 to 11 years, and clinically the children showed near universal presence of anti-dsDNA antibodies and hypocomplementemia [15].

> "A strong pattern of familial inheritance, especially in a family with known consanguinity, easily justifies the search for a monogenic causative mutation."

Linkage analysis and whole-exome sequencing was also used to study another consanguineous family with three siblings affected by SLE [18]. The children were found to have homozygous inactivating mutations in *PRKCD*, which encodes PKCδ. PKCδ has been implicated in apoptotic pathways, but also participates in B-cell signaling. B cells from the patients carrying *PRKCD* mutations were more susceptible to spontaneous cell death, but also demonstrated hyperproliferative responses to stimulation through the BCR, CD40 and TLR9 signaling pathways [18]. Phenotypically, the

affected siblings had anti-dsDNA antibodies, nephritis and hypocomplementemia without hypergammaglobulinemia. Two of the siblings had severe disease with skin and nervous system involvement [18].

> "Monogenic forms of systemic lupus erythematosus may thus illustrate the blurred distinction between primary immunodeficiency and autoimmunity."

A strong pattern of familial inheritance, especially in a family with known consanguinity, easily justifies the search for a monogenic causative mutation. With the continued drop in cost, whole-exome sequencing has rapidly become the approach of choice for studying such families. Limitations include the inability to detect mutations in noncoding regions or mitochondrial genomes, copy number and structural variants, and some exons that are not well covered by current sequencing technology [25]. However, in individual cases of SLE without obvious family history, the indication to search for a genetic cause is less clear. For example, recently, whole-exome sequencing was used to study a 4-year-old girl with severe SLE and cerebral vasculitis [26]. There was consanguinity in the family, although no family history of autoimmunity. Using a stepwise approach to narrow the number of candidate gene variants, a homozygous mutation in the gene encoding TREX1 was identified. Although TREX1 mutations had not previously been considered for this patient, they have been associated with cerebral vasculopathy in FCL [27]. Furthermore, the TREX1 risk allele haplotype has also been associated with neurologic manifestations in SLE patients, again demonstrating the overlap between FCL, AGS and SLE [23]. As seen in FCL and AGS, the patient showed significantly elevated levels of IFN-α, raising the possibility that she might be a candidate for anti-IFN-α therapies currently in development [26]. This study thus demonstrates the potential for personalized approaches to therapy based on individual genetic analysis.

As a final example of rare gene variants in lupus, a patient with SLE and erosive arthritis was recently found to have a heterozygous mutation in *RAG2* [20]. Homozygous *RAG2* deficiency typically leads to severe immunodeficiency, but hypomorphic mutations are associated with both increased infections, as well as autoimmune disease. Monogenic forms of SLE may thus illustrate the blurred distinction between primary immunodeficiency and autoimmunity.

Going forward, it is clear that more monogenic causes of SLE will continue to be discovered. We propose that the following clinical observations in patient should prompt consideration for further genetic study:

- Early onset disease, particularly prepubertal children in whom hormonal influences presumably play little role;
- Evidence of Mendelian inheritance or other strong family history;
- Less typical manifestations, such as severe skin, neurologic or joint disease;
- Disease that is refractory to standard therapy;
- Male gender;
- Consanguinity even in the absence of family history.

It is increasingly evident that the clinical phenotype of SLE may represent a final common pathway resulting from multiple overlapping genetic conditions; although rare, monogenic forms of lupus offer important insight into pathogenesis as we continue to make these genotype/phenotype correlations. Better understanding of these subtypes within SLE will also allow more individualized approaches to targeted therapy.

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