Genomics of Systemic Lupus Erythematosus

Insights Gained by Studying Monogenic Young-Onset Systemic Lupus Erythematosus

Linda T. Hiraki, MD, FRCPC, ScD[a,b,c], Earl D. Silverman, MD, FRCPC[a,b,d,*]

KEYWORDS

• Genetics • Systemic lupus erythematosus • Monogenic diseases
• Interferonopathies • DNA sensing • RNA sensing • Complement deficiency

KEY POINTS

- Monogenic systemic lupus erythematosus (SLE) should be considered in patients with very young onset SLE (<5 years of age), children of consanguineous parents' marriages, and in patients with severe or resistant skin disease.
- Genetic defects of the complement system are the main cause of monogenic SLE and are frequently associated with an increased risk of infection.
- Genetic defects in RNA and DNA sensing molecules, and RNases and DNases can lead to the production of autoantibodies and autoimmunity via the abnormal production of type 1 interferons.
- Mutations in DNA endonucleases can lead to a failure to clear self-DNA, resulting in a breaking of tolerance with the production of autoantibodies and autoimmunity, including SLE.

Genetics play an important role in systemic lupus erythematosus (SLE) susceptibility. There is a 10-fold increased concordance for SLE in monozygotic compared with dizygotic twins as well as familial aggregation of SLE, with heritability estimates up to 66%.[1–3] Genome-wide association studies (GWASs) have identified more than 50 SLE-associated risk loci, suggesting that SLE is a complex phenotype.[4,5] However, aside from genetic variants in the human leukocyte antigen (HLA) region, the SLE risk attributed to an individual single nucleotide polymorphism (SNP) is often less than 2-fold. These GWAS-significant loci, collectively, explain less than 30% of the heritability of SLE.[5]

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[a] Division of Rheumatology, SickKids Hospital, SickKids Research Institute, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; [b] Department of Paediatrics, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; [c] Epidemiology, Dalla Lana School of Public Health, 155 College Street, Toronto, Ontario M5T 3M7, Canada; [d] Department of Medicine, University of Toronto, Toronto, Ontario, Canada
* Corresponding author. 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.
E-mail address: Earl.silverman@sickkids.ca

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It has been suggested that, because of the earlier onset of SLE in childhood-onset SLE (cSLE) with a generally more severe disease phenotype, it is likely that there is a higher genetic contribution to its development compared with adult-onset SLE (aSLE). Targeted SNP studies have not identified any unique genes associated with cSLE, although it has been shown that a higher genetic load was associated with young age of onset and cSLE (Dominez, unpublished data, 2017 and Ref.[6]) Few studies have estimated heritability or the proportion of variance explained in susceptibility to cSLE. A study of 252 cSLE subjects had a heritability estimate of 21% from autosomal SNPs.[7] This is much lower than the anticipated heritability estimate derived from epidemiologic studies. This small fraction of explained heritability may be because SLE is not a single, complex disease but a heterogeneous phenotype comprised of genetically distinct, monogenic diseases with overlapping clinical features, autoantibodies, and shared inflammatory pathways. It is increasingly recognized that these monogenic forms of SLE are generally enriched in the pediatric population due to young onset, and in families with multiple affected members (multiplex families).[8] This article focuses on the monogenic forms of SLE and their insights into the pathogenesis of SLE (**Table 1**).

COMPLEMENT DEFICIENCIES

The complement system comprises more than 30 proteins and is an important component of the innate and adaptive immune systems' defense against foreign pathogens. Genetic defects in the complement system can lead to increased susceptibility to infection, autoimmunity, and SLE. Genetic defects in the complement system are the most common cause of monogenic SLE. Complement is important in host defense and maintaining tolerance (see later discussion).

Removal of Apoptotic Cells and Immune Complexes

Complement components, in particular C1q, C4b, and C3b, are important in opsonization of apoptotic cells. Therefore, any defect in these complement components might prevent or hinder the removal or clearance of apoptotic cells or immune complexes, thus allowing these potential autoantigens to activate the immune system and lead to a loss of tolerance and SLE.

Complement Receptors are Important in Immune Tolerance

The interaction of the innate and adaptive immune systems is important to maintain self-tolerance. Complement receptors 1 (CR1/CD35) and 2 (CR2/CD21) on follicular dendritic cells are important in presenting complement-coated self-antigens to maintain autoreactive B cells in a state of anergy. Experimental evidence for this theory includes the demonstration that mice deficient in CD21/CD35 or C4 exhibit lupus-like disease.[9]

Control of Dendritic Cell Cytokine Production

C1q is important in toll-like receptor–induced cytokine production and immune complex–induced IFN-1 production by dendritic cells.[10] Therefore, abnormalities of C1q can lead to abnormal cytokine production, including type 1 interferon (IFN-1) and production of autoantibodies.

Monogenic defects in the complement activation proteins C1q, C1s, C1r, C2, and C4 have been described in patients with SLE and this is the focus instead of complement receptors.