Clinical Perspectives on Lupus Genetics

Advances and Opportunities

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KEYWORDS

• SLE • Lupus • Genetics • Clinical subphenotypes • GWAS • Nephritis • Autoantibodies

KEY POINTS

- Polymorphisms in genes important for ubiquitination, DNA degradation, innate immunity, cellular immunity, antigen presentation, and lymphocyte development are associated and confirmed in systemic lupus erythematosus (SLE).
- Select genetic associations are enriched in patients with SLE with certain autoantibodies, antiphospholipid syndrome, pericarditis, thrombosis, arthritis, or lupus nephritis.
- New lupus genetic studies are warranted, especially with large cohorts enriched for understudied races, and in patients with severe disease or poor prognosis.
- New lupus genetic studies are also warranted in large cohorts of patients with SLE with phenotype information about common lupus comorbidities and response to therapeutics.

INTRODUCTION

Systemic lupus erythematosus (SLE; lupus) is a complex clinical syndrome with a wide range of clinical symptoms and significant immune dysregulation including production of high concentrations of autoantibodies. Lupus cases have been found to cluster in families with 66% heritability and a lambda S between 8 and 29. Monozygotic twin studies have shown 24% to 69% twin concordance rates, compared with the dizygotic twin or sibling rates of 2% to 5%.[1–3] Since the first genome-wide association studies (GWAS) conducted in SLE were published in 2008,[4–6] the number of associated and confirmed genetic associations has increased greatly, as shown and referenced in **Table 1**, which summarizes these findings to December 2013.

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Pathways Implicated by Lupus Genetics

Genetic studies suggest, and mechanistic SLE studies support, the role of several different processes being implicated in lupus pathogenesis, such as altered cell signaling, impaired clearance of debris, and dysregulated immune cell development, function, and response.[3,7–9] Several of these pathways are discussed briefly in this article and in **Table 1**. Please see the reviews in Refs.[3,10–13] for additional information.

Ubiquitination (nuclear factor kappa beta signaling)

Polymorphisms within several genes involved in ubiquitination (a process of marking proteins for degradation) have been associated with SLE. Mutations in *TNFAIP3* (tumor necrosis factor alpha-induced protein 3) can alter ubiquitin patterns, resulting in improper degradation targeting and termination of proinflammatory responses through nuclear factor kappa beta (NFκB) signaling.[14] Mutations in *TNIP1* (transition protein-1), an adaptor protein whose expression is induced by NFκB,[3] can result in NFκB signaling pathway dysregulation.[15] *UBE2L3*, ubiquitin-conjugating enzyme E2 L3 is a ubiquitin-carrier enzyme, is expressed on all lymphocytes and is important for the ubiquitination of a NFκB precursor and cell development.[3,8] *IRAK1* (interleukin-1 receptor-associated kinase 1) encodes for a protein located downstream of NFκB signaling and genetic mutations in this gene can offer protection from or susceptibility to SLE.[8,16] Mutations in *SLC15A4* (solute carrier family 15 member 4), a peptide transporter in NFκB signaling pathway, and *PRKCB* (protein kinase C beta), a protein kinase involved in B-cell receptor–mediated NFκB activation, have also been implicated in SLE development in susceptible individuals.[8]

DNA degradation (apoptosis/clearance of debris)

In healthy individuals, apoptosis, or programmed cell death, is used to remove dead or dying cells into the surrounding environment without releasing the cellular components. However, in an individual with SLE, this process is defective, resulting in decreased removal and, thus, accumulation of apoptotic cells, release of apoptotic cellular materials into the surrounding environment, and activation of immune responses against self-antigens.[3,7–9] Genetic studies have suggested that variants in *FcγRIIB* (Fc gamma receptor II B), *ITGAM* (integrin alpha M), *ATG5* (autophagy protein 5), *ACP5* (acid phosphotase 5), *TREX1* (three prime repair exonuclease 1), *DNase 1*, and *DNase 1L3* (DNase 1-like 3) may play a role in the development of lupus through their roles in apoptosis or debris clearance.[8,9,17–19] Dysfunction in any of these processes leads to improper clearance of apoptotic cells and is associated with autoantibody production and SLE pathogenesis.

Innate immunity (Toll-like receptor pathways/interferon)

A large number of individuals with SLE have increased expression of interferon (IFN)-associated genes (IFN signatures) compared with healthy individuals. Because IFN signaling is important in protection against viral infection and in the development, activation, and proliferation of immune cells, dysregulation of IFN signaling pathways can have major consequences regarding the morbidity and mortality of patients with SLE. Genetic variants in Toll-like receptor (TLR) 7, TLR regulatory molecules (*UBE2L3*), IFN signaling transcription factors (*IRF5* [interferon regulatory factor 5], *IRF7/PHRF1* [interferon response factor 7/PHD and ring finger domains 1], *IRF8* [interferon regulatory factor 8], *ETS1*) are associated with increased SLE susceptibility.[8,9,20] Variants in molecules within or involved in the downstream signaling of the IFN pathway, such as *STAT4* (signal transducer and activator of transcription 4),