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Review

# Roles of genetic variations in signalling/immunoregulatory molecules in susceptibility to systemic lupus erythematosus☆

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**Abstract**

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a complex genetic basis that includes many susceptibility genes on multiple chromosomes. As complex human diseases like SLE involve multiple, interacting genetic and environmental determinants, identifying genes for complex traits is challenging and has had limited success so far. However, recent advances in genetic resources and technology have been providing new tools to identify the novel pathways or the sequence variants that contribute to autoimmune diseases. During the past several years, several new candidate genes have been implicated in development of SLE though association studies. In this article we describe an overview of the latest findings in the genetics of SLE, especially focusing on the genetic variations in the signalling or immunoregulatory molecules including CD28 and IRF family members.


*Keywords:* Signalling; Immunoregulatory; SLE; Genetic variations

## 1. Introduction

Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease that is characterized by the production of multiple autoantibodies and immune complex formation. SLE in humans manifests a diverse array of clinical features, variably involving multiple organ systems such as the skin, kidneys, joints, and brain. Although the etiopathogenesis of SLE remains unclear, it appears to be a complex interplay of genetic and environmental factors. There is considerable evidence that the development of SLE has a strong genetic basis: indicated by an increased concordance rate in monozygotic twins (15–69%) as compared to dizygotic twins (2–5%) and the relative risk ratio for the siblings of affected individuals to disease incidence in the general population ($\lambda_s$), which range from 20 to 40 [1]. To date, multiple genome-wide linkage studies for SLE have been performed and have identified almost every chromosome. These and the complex pattern of inheritance of SLE suggest the contribution of multiple genes to the etiology, which means interaction of various combinations of contributing genes at multiple loci in individual patients. Moreover, some of these regions were also associated with other autoimmune diseases, suggesting that the same genes can be involved in multiple disorders. Candidate genes located within the linked regions have also been studied over the years, including *FCGR* genes at 1q23, poly(ADP-ribose) polymerase (*PARP*) at 1q41–42, and major histocompatibility complex (*MHC*) gene complex at 6p21. More recently, new attractive genes or pathways have been revealed through linkage and association studies as well as advanced techniques such as microarray technology. In this review, we summarize the recent advances in the identification of susceptibility genes and their related pathways for human SLE.

## 2. IFN and SLE

Studies of lupus patients and mouse models have strongly indicated important roles for both types I and II IFNs. Significantly increased levels of both IFNs in the sera of SLE patients are observed [2–5], and lupus-like symptoms occur in some individuals following IFN-α or IFN-γ treatment for various viral, autoimmune, or malignant diseases [6,7]. In addition, recent microarray expression studies with peripheral blood mononuclear cells (PBMCs) of SLE patients showed an "inter-

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feron gene signature", the up-regulation of IFN-α and IFN-γ-inducible genes, which correlated better with disease activity [8,9]. Another independent analysis of the above data suggested that genes preferentially regulated by IFN-α may predominate in early disease samples, while those regulated by IFN-γ may appear at later stages. Therefore, it is possible that IFN-α plays a role in the proximal events of disease pathogenesis bridging from pre-clinical stage to clinically apparent disease with altered immune function, and IFN-γ contributes to the later significant chronic inflammation and target organ damage [10,11].

## 3. Type I IFN pathway

For type II IFN called IFN-γ, it has been reported that IFN-γ plays a key regulatory role in the development of autoimmune kidney disease. In several spontaneous lupus-prone mice, similar to human SLE, elevated levels of IFN-γ are found [12–14]. NZB × NZW lupus mice treated with IFN-γ had accelerated development of glomerulonephritis [15], and treatment with IFN-γ-specific antibodies [16], soluble IFN-γ receptor [17], or c-DNA encoding IFN-γR/Fc caused a significant delay in disease progression [18]. Moreover, gene knockout of IFN-γ or the IFN-γR have significantly reduced disease [19–23]. Our group has reported an association of genetic polymorphisms within IFN-γ receptor 1 and 2 (*IFNGR1* and *IFNGR2*) with the risk of SLE [24]. We also showed evidence indicating an important pathogenic role of IFN-γ in human SLE, especially diffuse proliferative lupus nephritis [25,26]. Thus, until recently, the studies of cytokine activity in murine models of lupus had mainly focused on IFN-γ. However, several lines of evidence support a role for type I IFNs in the pathogenesis of SLE. Here we will focus on data implicating type I IFN, with an emphasis on data in humans.

Previous studies demonstrated increased serum levels of IFN-α in SLE, and the IFN-α levels correlate with both disease activity and severity. Blood leukocytes of SLE patients display increased amounts of the IFN-α-inducible protein MxA, even when serum IFN-α cannot be detected [27]. Furthermore, several clinical signs and symptoms in SLE resemble those during influenza infection or IFN-α therapy, for instance, fever, fatigue, myalgia, arthralgia and leukopenia. Another evidence supporting a causal role for IFN-α in SLE pathogenesis is the development of autoantibodies including anti-DNA antibodies and an SLE-like syndrome in a proportion of patients who receive IFN therapy. These indicate that an abnormal ongoing IFN-α production in SLE, which is further supported by the finding that deficiency of the IFN-α/β receptor results in attenuation of autoantibody production and disease in the NZB murine model of SLE [28]. In addition, glucocorticoids (GCs), a standard treatment of SLE, shuts down the IFN signature, which suggest that GCs may act in disease treatment through the blocking of IFN activity [9]. Recently, several gene variants have been reported to be associated with SLE by analyzing candidate genes from the type I IFN pathway. We here review recent findings regarding the genetic variants in the type I IFN signalling and their correlation with SLE.

### 3.1. TYK2 and IRF5

By analyzing 44 single-nucleotide polymorphisms (SNPs) in 13 genes from the type I IFN pathway, Sigurdsson et al. recently identified in the *TYK2* and *IRF5* genes that displayed strong signals of joint linkage and association with SLE in the Swedish and Finnish population [29]. In this study, combination of the *P* values from both population increased significance further, with adjusted *P* values of $1.1 \times 10^{-5}$ for *TYK2* and $7.9 \times 10^{-6}$ for *IRF5*. The type I IFNs act on the IFN-α/β receptor, which consists of IFNAR1 and IFNAR2 subunits that are associated with cytoplasmic protein tyrosine kinases TyK2 and Jak1, respectively [30]. Therefore, the fact that minor allele frequencies of the associated allele of *TYK2* were lower in the affected individuals than in the corresponding controls suggests that the missense variants in *TYK2* may reduce the function of TYK2, resulting in a decreased susceptibility to SLE. Of note, the *TYK2* gene is located on chromosome 19p13.2, and this locus has been linked to SLE in white pedigrees stratified by the presence of anti-dsDNA antibodies [31]. IRF5 is one of the IRF family members that play an important role in the innate immune response during viral infection [32]. Expression of IRF-5 was detected primarily in B cells and dendritic cells and further enhanced by type I IFN, suggesting its participation in the IFN system [33]. IRF5 is phosphorylated in cells upon viral infections and translocates to the nucleus, which results in activation of expression of IFN-α subtypes that differ from those activated by IRF7 [34,35]. In addition, recent study indicate that IRF-5 is involved downstream of the TLR-MyD88 signalling pathway as a master transcription factor in the activation of genes for inflammatory cytokines [36]. The intronic polymorphism within the *IRF5* gene may have a functional role by altering the splicing of the IRF5, leading to affect several cellular functions related to the development of SLE. Moreover, an essential role of many IRF family members in the differentiation of T helper ($T_H$) cells implies that IRF polymorphisms could underlie either inherited diseases or the bias in an individual towards $T_H1$-cell-mediated autoimmunity or $T_H2$-cell-mediated allergy (NaReImmunol. Lohoff M, 2005).

### 3.2. Interferon-inducible gene IFI202

Further evidence for a role of IFN in mouse lupus was the identification of interferon-inducible protein 202 (Ifi202) as a lupus susceptibility gene at the Nba2/Lbw7 locus on chromosome 1 of the NZB genome [37]. In this report, the Nba locus, predisposing to autoantibody production, splenomegaly, and glomerulonephritis, was linked to a polymorphism in the promoter region of Ifi202, leading to increased p202 expression in B cells and other non-B, non-T cells. The p202 phosphoprotein is thought to affect cell-signalling pathways by modulating the function of transcription factors involved in cell proliferation, differentiation, and apoptosis [38,39]. However, the exact mechanism by which it predispose to systemic autoimmune remains to be elucidated.