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Clinical Perspectives on Lupus Genetics: Advances and Opportunities

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Synopsis

In recent years, genome wide association studies have led to an explosion in the identification of regions containing confirmed genetic risk variants within complex human diseases, for example in systemic lupus erythematosus (SLE). Many of these strongest SLE genetic associations can be divided into groups based upon their potential roles in different processes implicated in lupus pathogenesis, including ubiquitination (a process of marking proteins for degradation), DNA degradation, innate immunity, cellular immunity (B cell, T cell, neutrophil, monocytes), lymphocyte development, and antigen presentation. Recent advances have also demonstrated several genetic associations with SLE subphenotypes and subcriteria, such as autoantibody production, lupus nephritis, serositis, and arthritis. Despite the broad range of lupus genetic studies to date, many areas for further exploration remain to move lupus genetic studies toward clinically informative endpoints, such as identifying individuals at the greatest risk of end-organ damage, early mortality or poor response to a specific therapeutic regimen.

Keywords

SLE; lupus; genetics; clinical subphenotypes; GWAS; nephritis; autoantibodies

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

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with 66% heritability and a lambda S between 8 and 29. Monozygotic twin studies have demonstrating 24–69% twin concordance rates, compared to the dizygotic twin or sibling rates of 2–5%.[1–3] Since the first genome wide association studies (GWAS) conducted in SLE were published in 2008[4–6], an explosion in the number of associated and confirmed genetic associations has occurred as outlined and referenced in Table 1, which summarizes these findings through December 2013.

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 below and in Table 1. Please see the following reviews for additional information[3, 10–13].

Ubiquitination (NF-kB signaling)—Polymorphisms within several genes involved in ubiquitination (a process of marking proteins for degradation) have been associated with SLE. Mutations in *TNFAIP3* can alter ubiquitin patterns resulting in improper degradation targeting and termination of pro-inflammatory responses through NFκB signaling.[14] Mutations in *TNIP1*, an adaptor protein whose expression is induced by NFκB,[3] can result in NFκB signaling pathway dysregulation.[15] *UBE2L3*, 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* 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*, a peptide transporter in NFκB signaling pathway, and *PRKCB*, 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. In an individual with SLE, however, 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*, *ITGAM*, *ATG5*, *ACP5*, *TREX1*, *DNAse 1*, and *DNase 1L3* may play a role in the development of lupus through their roles in apoptosis or debris clearance.[8, 9, 17–19] Dysfunction at any of these processes leads to improper clearance of apoptotic cells and is associated with autoantibody production and SLE pathogenesis.

Innate immunity (TLR pathways/interferon)—A large number of individuals with SLE have increased expression of IFN associated genes (interferon signatures) compared to healthy individuals. As IFN signaling is important in the 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 SLE patients. Genetic variants in Toll-like receptor (TLR) 7, TLR regulatory molecules

(*UBE2L3*), IFN signaling transcription factors (*IRF5, IRF7/PHRF1, IRF8, ETS1*) associate with increased SLE susceptibility.[8, 9, 20] Variants in molecules within or involved in the downstream signaling of the IFN pathway, such as *STAT4, IFIH1*, and *PRDM1*, have also been associated with increased susceptibility of SLE.[8]

B cell immunity (function/signaling)—A hallmark of SLE is the presence of autoantibodies, which indicates improper function and signaling of B cells. *BLK, BANK1*, and *LYN* genetic variants increase SLE susceptibility, perhaps through altering B cell receptor signaling.[8, 9, 21] *IRF8, ETS1, IKZF1, AFF1, RasGRP3, PRDM1, FcγRIIB, PRKCB*, and *NCF2*, major players in the development, differentiation, proliferation, and activation of B cells, also contain polymorphisms associated with SLE susceptibility.[8, 9, 22–24] Polymorphisms in *HLA-DR2* & *DR3* (alter ability to produce antibodies), *IL-10* (inhibits T cells and antigen presenting cells, enhances B cell survival and activity) and *IL-21* (promotes antibody class switching and sustains autoantibody production) also contain associated and confirmed polymorphisms with SLE.[8, 9]

T cell immunity (function/signaling)—T cells play a role in both innate and adaptive immune responses. In SLE patients, altered T cells play a role in the activation of autoreactive B cells, production of antibodies, and the immune surveillance of regulatory cells. Mutations in *ETS1, IKZF1, PRDM1, AFF1* and *TNFS4* have been associated with altered differentiation, activation, and proliferation of SLE T cells.[8, 9, 25–28] Dysregulated T cell signaling has also been associated with *PTPN22, TYK2*, and *STAT4* mutations in SLE.[8, 9, 29–31] Genetic variations in *HLA-DR2* & *DR3, CD44, IL-10*, and *IL-21* are associated with altered lymphocyte activation by T cells in SLE patients.[8, 9, 21, 32]

Neutrophil/monocyte immunity (function/signaling)—Neutrophils and macrophages are important players in the innate and adaptive immune system. As a first line of defense, these cells migrate to areas of inflammation, are involved in the removal of dead cells and foreign antigens, and directly affect the activation of lymphocytes. ITGAM and ICAM polymorphisms lead to altered migration and adhesion of the neutrophils and monocytes in SLE patients.[8, 9] Genetic variants in *FcγRIIB* and *FcγIIIA/B, IL-10*, and *IRF8* can alter phagocytosis, monocyte signaling, and macrophage development, drastically changing SLE patient innate immune responses.[8, 9]

Lymphocyte development—In individuals with autoimmune disorders, impaired lymphocyte development leads to an increase in autoreactive lymphocytes, lymphocytes with altered tissue homing ability, and cells with inappropriate responses to external environmental stimuli. *ETS1* and *IKZF1* both play a role in the regulation of lymphocyte differentiation and development.[33, 34] Genetic variants of these genes result in abnormal differentiation of B cells into plasma cells, increased proliferation of Th17 cells, and loss of regulation of self-tolerance.[35–38]

Antigen presentation—In order to make a robust immune response to protect the host, foreign antigens must be taken up, processed, and presented to T and B cells. However, in

individuals with SLE, variations in the HLA-DRB1/MHC1 genes can lead to altered antigen presentation.[5, 39, 40]

Genetic associations with autoantibody production

Despite the many variations of clinical presentation, almost all individuals with SLE develop antibodies against self-antigens, particularly anti-nuclear antibodies against double stranded DNA (dsDNA), Ro, La, Sm, nRNP, ribosomal P, and antibodies against phospholipids.

Polymorphisms within the human leukocyte antigen (HLA) genes are one of the more well-known risk factors for the development of SLE. In addition to the increase of overall SLE risk, these HLA polymorphisms are also associated with increased risk of autoantibody development.[41] HLA haplotypes consisting of DRB1*1501/DQB1*0602 (DR2) are associated with anti-Sm responses, while HLA DRB1*0301/DQB1*0201 (DR3) haplotypes are associated with anti-Ro and anti-La responses.[41] Individuals with a mixture of DR2/DR3 haplotypes have an increased prevalence of anti-Ro, anti-La and Sm antibodies.[41]

Additional genetic polymorphisms are likely important in autoantibody development. Ramos and colleagues performed a linkage study for the presence of autoantibodies in a large collection of families multiplex for SLE and found regions on chromosome 3q21 linked with anti-La, chromosome 4q34 and 4q35 with anti-Ro and/or anti-La, and chromosome 3q27 with anti-nRNP.[42] IgM antiphospholipid antibody responses were enriched in individuals at chromosome 13q14.[42] Large scale genetic association studies of collections of SLE patients and controls with autoantibody detection by the same method, ideally at the same time, would be useful to help delineate genes and pathways further involved in the genetic susceptibility to SLE.

While only 40%–60% lupus patients develop antibodies to dsDNA,[43] anti-dsDNA responses are strongly associated with lupus nephritis and often indicate a poor survival outcome.[44, 45] Interestingly, Chung and colleagues have identified genetic variants in *STAT4*, *ITGAM*, *K1AA1542*, *BANK1*, and *UBE2L3* that associate with the presence of anti-dsDNA antibodies SLE patients.[43]

Several other genetic polymorphisms are associated with the presence of autoantibodies in lupus patients. In a Japanese SLE cohort, polymorphisms in PHRF1 are associated with the presence of anti-Sm antibodies.[46] PTPN22 polymorphisms are associated with the presence of anticardiolipin antibodies (a type of anti-phospholipid antibody) in European-American and anti-nRNP antibodies in Hispanic SLE patients.[47] An IRF8 variant is associated with the development of antibodies against dsDNA across European-American, African-American and Cretan lupus patients.[48] This topic is further reviewed in additional publications[49–51].

Association of genes within select lupus clinical subsets

In recent years, an emphasis has been placed on identifying individuals at the greatest risk of developing severe lupus to improve monitoring and identifying individuals for potential therapeutic clinical trials.

Studies have shown that the *PTPN22* risk allele is enriched in SLE patients with anti-phospholipid syndrome and in patients with concurrent autoimmune thyroid disease.[47] *TRAF3IP2* polymorphisms are associated with the development of pericarditis.[52] Genetic variants in *FGG*, *MTHFR*, and *FVL* have been shown to be associated with increased risk of thrombosis in European-Americans, while FGG is only associated with increased risk of thrombosis in Hispanic lupus patients.[53] *BANK1* variants are associated with hematological, immunological, and renal subphenotypes of SLE.[54] A recent study by Sanchez et al has examined the contribution of genetic risk alleles for SLE with clinical subphenotypes of the disease[55] and found that *TNFSF4* polymorphisms were significantly associated with renal disorder in individuals with European ancestry.[55] Polymorphisms in *ITGAM* are associated with arthritis[56], and nephritis[57].

Genetic polymorphisms that alter expression levels of the *MIF* gene affect both the overall risk for developing SLE and subphenotype susceptibility. The high expression MIF allele is associated with a lower risk of SLE and lower risk of ANA production. However, if the lower expression allele is present, and SLE develops, individuals then have an increased risk of serositis, double the risk for nephritis, and a nearly 9-fold risk increase in cerebritis.[58] For a more in-depth description of the genetic associations with clinical subphenotypes of SLE please refer to Rullo *et al*.[8] and to the genetics of nephritis section below.

Genetics of nephritis and renal outcomes

One of the most devastating clinical symptoms of SLE can be lupus nephritis (LN), especially when associated with end-stage renal disease. While many studies have identified genes associated with increased risk of developing SLE, genetic association with lupus nephritis or end stage-renal disease remains an understudied area. Polymorphisms in several genes (Table 2) have been associated with increased risk of lupus nephritis and vary based upon gender and race.[16, 59–61]

ABIN1/TNIP1—*ABIN1* [D485N] transgenic mice develop an SLE-like autoimmune disease[62], developing proliferative glomerulonephritis with histologic features similar to class III and IV human lupus nephritis.[16] SNPs within *TNIP1*, located within the *ABIN1* gene, have previously been associated with the development of SLE[63]. Caster and colleagues have examined the association of *TNIP1* with lupus nephritis in a large multi-racial cohort (n=16,999)[16], showing that SNP rs7708392 and rs495881 in *TNIP1* were significantly associated with lupus nephritis in individuals with European ($p=3.663\times10^{-24}$) or African ($p=8.473\times10^{-23}$) ancestry.[16]

APOL1—*APOL1* (apolipoprotein L1 gene) polymorphisms have been associated with progressive non-diabetic nephropathy in African-Americans.[64–70] Freedman and colleagues found that the G1 and G2 alleles of *APOL1* are significantly associated ($p=6.23\times10^{-6}$) with the risk of developing lupus nephritis end-stage renal disease in African-Americans (n=1389).[65, 66] However, a smaller study (n=407 AA) by Lin et al observed only a minimal association (p=0.023) of *APOL1* with LN in AA individuals with SLE.[71]

FcγRIIB, Fc gamma receptors (FcγR) play a large role in the clearance of immune complexes and are major players in SLE pathogenesis. Impaired clearance and removal of immune complexes may result in immune complex deposition in organs which could then lead to organ damage. Genome wide association studies have implicated FcγR polymorphisms as genetic risk factors for SLE.[72] However, these studies were in SLE as a whole and did not assess the association of these receptors with clinical phenotypes. A small study from Zidan and colleagues (n=90) identified the *FcγRIIB* 232 ILE/Thr polymorphism as increasing the risk of the development of LN in Egyptian SLE patients.[73]

STAT4—*STAT4* polymorphisms have been associated with a number of different autoimmune diseases, including SLE. *STAT4* polymorphisms have been associated with LN in individuals of European decent and with severe LN.[74, 75] Bolin and colleagues utilized GWAS to examine genetic association with LN in two Swedish cohorts[76], showing genome wide significant association ($p<5\times10^{-8}$) in four SNPs located within the *STAT4* gene. Additionally, *STAT4* association was found in SLE patients with severe renal insufficiency ($p=7.6\times10^{-6}$).[76]

TNFSF4—Previous reports have linked TNFSF4 with susceptibility to SLE in Chinese and European individuals.[10, 23, 77] Zhou et al found a significant additive association between *TNFSF4* alleles rs2205960 (p=0.014) and rs10489265 (p=0.005) and LN.[78]

SLE genetic studies on the horizon

With all of the studies which have been performed to help decipher genetic contributions to lupus, many areas for further exploration remain. SLE is oftentimes more severe with poorer outcomes in some racial subpopulations, including African American, American Indian and some Asian subpopulations.[79–83] Unfortunately, to date, the major GWAS have focused on individuals of European descent or select Asian populations, but GWAS are currently underway in populations from additional racial demographics.[84] These studies may identify genetic associations that are unique to select populations and may also serve to help narrow associated regions by allowing trans-racial mapping across common genetic areas of association.

Larger GWAS have already been published for other autoimmune diseases, such as multiple sclerosis[85] and rheumatoid arthritis[86]. These studies of greater than 72,000 subjects, in each, have nearly doubled the number of confirmed genetic associations for these complex human diseases with somewhat lower heritability compared to SLE. Therefore, extremely large SLE studies may help to identify additional confirmed genetic associations that help to address the still unexplained heritability in SLE. These findings may, in turn, help focus or expand pathways important to lupus pathogenesis. Once more causal variants are identified and a greater amount of the genetic heritability of SLE has been described, then another large opportunity will evolve to further explore gene-gene, gene-environment and other types of pathway analyses with SLE.

Studies are also ongoing to perform directed deep sequencing, exome sequencing and whole genome sequencing in SLE patients compared to healthy controls and family members to identify rare variants that are missed on the GWAS arrays and may be important in lupus

pathogenesis or within smaller homogenous subsets of this disease. With the decreasing cost of exome and whole genome sequencing, new data will likely be accruing quickly, allowing for broader studies of rare variants.

Copy number variations (CNVs) are also beginning to be explored in lupus pathogenesis. Work by Yu and colleagues[87] have demonstrated that CNVs of IL-17F, IL-22, and IL-21 are associated with SLE. Additional CNV studies are warranted to examine other potential SLE genetic associations.

Of course, for many, many of these confirmed SLE genetic associations, functional consequences of putative causal variants have yet to be elucidated. Novel methods and analytic approaches to help speed throughput, prioritize candidates, and select the highest likelihood variants for functional impact and potential causation are needed to help make the next monumental leap in deciphering the impact of genetic risk on lupus pathogenesis. Although time consuming, these necessary next steps are crucial to help move toward more directed therapies or better selections of patients for specific therapeutic interventions.

Future Considerations

Opportunities for additional clinically important genetic studies

Although significant advances have been made in identifying and confirming genetic associations in SLE, opportunities abound to move lupus genetic studies toward even more clinically informative endpoints (Box 1).

Many lupus consortia are performing studies to help identify early in the course of disease the patients at the highest risk of damage or early mortality. For example, work from the University of Toronto Lupus Clinic has shown that 25% of SLE patients with early damage (defined as Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index [SDI] score ≥ 1at initial assessment) died within 10 years of their initial assessment compared to only 7.3% without early damage (log rank P-value=0.0002)[88]. Work from the LUMINA (Lupus in Minority Populations, Nature versus Nurture) consortia assessed five year follow-up data from 288 patients to identify potential predictors of early mortality. They demonstrated that living below the poverty level (OR=4.06, CI [1.50–11.01), SDI at initial visit (as above) (OR=1.45, CI [119-1.91]) and a disease activity measure at baseline – SLAM or Systemic Lupus Activity Measure (OR=1.09, CI [1.01–1.17]) were each associated with early mortality in 34 individuals who died during the first five years of study.[89] If lupus cohorts of sufficient size and with SDI measurements near lupus onset can be assembled, assessing genetic risk of those SLE patients at increased risk of early mortality and/or increased morbidity would be useful in guiding therapeutic selection and potential pathway directed therapies.

Alternately, some SLE patients followed in longitudinal cohorts are found to have persistently elevated disease activity and, therefore, may have increased risk of disease damage as measured by SDI.[90] Genetic analysis of these patients may be useful in better understanding patients who are candidates for more aggressive immunosuppression or, conversely, better understanding the genetic susceptibility of patients with persistently

quiescent or suppressed disease may help lead to pathways which may help temper or control lupus inflammation and damage.

Definitions of “severe” lupus have been difficult to adapt and are usually focused on specific individual clinical manifestations of lupus, such as nephritis or major central nervous system involvement. Alternate approaches have explored the total number of ACR classification criteria[91, 92]. Another approach that may be useful would be to use therapeutic use as a surrogate for severe disease. Most rheumatologists and other lupus care providers would not give major immunosuppressive drugs, such as cyclophosphamide, cyclosporine, or rituximab, to patients with mild or moderate lupus. Although patients with nephritis might dominate this category, patients with other less common serious manifestations of lupus, such as cerebritis, systemic vasculitis, or pulmonary hemorrhage, would not be eliminated from this analysis. As the field evolves and can help clinically define those patients with the most severe forms of SLE, genetic, as well as partnered genomic, epigenetic, and immunologic measurements, may help provide critical insights to the most appropriate pathways to target in these highest risk individuals.

Many opportunities remain in further assessing the genetic architecture of SLE clinical subphenotypes. Expansion of sample sizes of the lupus phenotype genetic association studies, partnered with detailed clinical phenotype for ACR classification criteria and subcriteria in needed. Detailed phenotype data might also provide opportunities to look for genetic associations with atypical presentations, such as anti-nuclear antibody negative, or uncommon clinical subtypes, such as thrombocytopenia at diagnosis, that are enriched within select large multiplex families or are found often enough to be studied in very large case-control association studies. Novel analytic methods that allow for more sophisticated bioinformatic assessments of clinical subgroups are also intriguing options to provide more insight to clinical subtypes identified by machine learning or other methods (please see review by Vyse and colleagues[93]). Alternate options for further genetic dissection would allow testing of markers of genetic risk with co-morbidities that are enriched in lupus patients, such as accelerated atherosclerosis, osteonecrosis, or others. Genetic associations of response to therapy would help with selection of medications, optimization of treatment or potentially identification of individuals at increased risk of select toxicities.

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Key points

- Polymorphisms in genes important for ubiquitination, DNA degradation, innate immunity, cellular immunity, antigen presentation, and lymphocyte development are associated and confirmed in SLE.
- Select genetic associations are enriched in SLE patients 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 SLE patients with phenotype information about common lupus co-morbidities and response to therapeutics.

Box 1

Opportunities for Clinically Important genetic Studies

1. Markers of early damage (poor prognosis)
2. Markers of persistently elevated diseases (other SLE subsets)
3. Markers of “severe” disease
4. Expanded studies of genetic architecture of clinical subphenotypes
5. Larger sample size (allow subsetting
6. Better phenotype data for ACR criteria/subcriteria
7. Opportunities to look for genetic associations with:
    a. Atypical disease presentations
    b. Uncommon clinical subtypes
    c. Phenotypes enriched within select large multiplex families
8. Novel analytic methods
9. Markers of common SLE co-morbidities
10. Pharmacogenetics
    a. Markers of early flare off medication
    b. Selection of medication
    c. Response to medication

Table 1

Loci associated with SLE through GWAS, meta-analysis studies, candidate gene studies, or replication studies from 1992 to December 2013.

Gene	Pathway	Location	Variant	Population	References
IKBKE	NFkB signaling	1q32.1	rs1539241/rs12142086	EU	(94)
TNIP1	Ubiquitination in NFκB signaling	5q32	rs10036748	EU, AA, AS	(4, 15, 23, 77, 95, 96)
TNFAIP3	Ubiquitination in NFκB signaling	6q23	rs2230926	EU, AA, AS	(4, 23, 77, 97) (14, 98, 99)
SLC15A4	Ubiquitination in NFκB signaling	12q24.32	rs1385374	AS	(15, 23)
UBASH3A	Ubiquitination	21q22.3	rs9976767	EU	(100)
UBE2L3, HIC2	Ubiquitination in NFκB signaling	22q11.21	rs463426	EU, AS	(5, 23, 101, 102)
IRAK1/MECP2	Ubiquitination in NFκB signaling	Xq37	rs1734787	EU, HA, AS	(4, 77, 103–105)
Complement genes	Apoptosis/clearance of debris; Neutrophil/monocyte immunity	1q36	multiple	EU	(106–110)
IL-2/IL-21	Apoptosis/clearance of debris; Neutrophil/monocyte immunity	4q26	rs907715	EU, AA, AS	(111, 112)
ATG5	Apoptosis/clearance of debris	6q21	rs548234	EU, AS	(4, 5, 23, 77)
ITGAM	Apoptosis/clearance of debris	16p11.2	rs9888739	EU, HA, AS	(4–6, 77, 103, 113–115)
DNAse 1	Apoptosis/clearance of debris	16p13.3	rs8176927	AS, A	(116, 117)
ACP5/TRAP	Apoptosis/clearance of debris	19p13.2	rs79525531	EU, AS, H	(118)
Mir146a	mRNA stability/translation	6q5	rs57095329	EU, AA, AS	(119, 120)
ZBP2	mRNA stability/translation	17q12	rs1453560	EU, AA	(22)
IFIH1	TLR/Interferon pathways; T cell immunity	2q24	rs1990760	EU	(22)
STAT4	TLR/Interferon pathways; T cell immunity	2q23.2	rs7582694	EU, HA, AA, AS	(4, 5, 31, 97, 103, 113, 121–123)
RASGRP3	TLR/Interferon pathways	2p24.1	rs13385731	AS	(23)
PRDM1	TLR/Interferon pathways; B cell immunity; T cell immunity	6p21	rs6568431	EU	(77)
IRF5/TNPO3	TLR/Interferon pathways	7q32	rs12537284	EU, HA, AA, AS	(4, 5, 77, 101, 124–126)
PHRF1/IRF7/KIAA1542	TLR/Interferon pathways	11p15.5	rs4963128	EU, AA	(4, 5, 23, 77)
IRF8	TLR/Interferon pathways; Neutrophil/monocyte immunity	16q24.1	rs116440334	EU	(22, 127)
TLR7	TLR/Interferon pathways	Xp22.3	rs3853839	EU, AS	(128, 129)
UHRF1BP1	Cellular growth	6p21	rs11755393	EU	(77)

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Gene	Pathway	Location	Variant	Population	References
TNXB	Cellular adhesion	6p21.32–33	rs310342	AS	(130)
PXK	Synaptic transmission	3p14.3	rs6445975	EU	(4, 5, 102, 113)
HIP1	Endocytosis and protein trafficking	7q11	rs6964720	AS	(97)
NCF2	B cell immunity	1q25	rs17849502	EU, AS	(4, 77, 111, 131)
IL-10	B cell immunity; Lymphocyte activation; Neutrophil/monocyte immunity	1q31-q32	rs3024505	EU, AA, AS	(4, 77, 101, 103, 132)
BANK1	B cell immunity	4q24	rs10513487	EU, HA, AA, AS	(4, 103, 133, 134)
BLK	B cell immunity	8p3	rs7812879	EU, HA, AA, AS	(5, 6, 23, 97, 135, 136)
LYN	B cell immunity	8q13	rs7829816	EU, AA, AS	(5, 137)
ELF1	B cell immunity; T cell immunity	13q13	rs7329174	AS	(138)
PRKCB	B cell immunity	16p11.2	rs16972959	AS	(139)
IKZF3	B cell immunity; T cell immunity; lymphocyte development	17q21	rs8079075	EU, HA, AA	(22)
CD40	B cell immunity; Antigen presentation	20q12	rs4810485	EU	(140)
PTPN22	T cell immunity	1p13.2	rs2476601	EU, HA	(5, 77, 101, 141)
TNFSF4	T cell immunity	1q25	rs2205960	EU, HA, AS	(4, 5, 23, 77, 102)
AFF1	T cell immunity	4q21	rs340630	AS	(97)
IKZF1	T cell immunity; Lymphocyte development	7p13	rs4917014	EU, AS	(4, 23, 96)
ETS1	T cell immunity; B cell immunity; TLR/Interferon pathways; Lymphocyte development	11q24.3	rs6590330	AS	(23, 95–97, 114)
CSK	T cell immunity	15q24.1	rs3433034	EU	(142)
TYK2	T cell immunity	19p13.2	rs280519	EU	(22, 113)
SH2D1A	T cell immunity; B cell immunity; Lymphocyte development	Xq25	rs2049995	AS	(143)
CRP	Neutrophil/monocyte immunity	1q21	rs3093061	EU, AA	(144)
HLA Genes	Lymphocyte activation, antigen presentation	6p21.32–33	rs1270942 rs2647012 rs2187668 rs2301271 rs9271100 rs3135394 rs3131379	EU, HA, AA, AS	(4–6, 15, 23, 39, 43, 77, 95, 97, 101, 119, 145, 146)
CD44, PDHX	Lymphocyte activation	11p13	rs507230	EU, AA, AS	(32)

Gene	Pathway	Location	Variant	Population	References
TMEM39A	Unknown	3q13.33	rs1132200	EU, AS	(22)
TREX1	Unknown	3p21.31	rs3135945	EU	(147, 148)
PITG1	Unknown	5q33.3	rs2431697	EU	(5)
JAZF1	Unknown	7p15.2	rs849142	EU	(4, 77)
XKR6	Unknown	8p23.1	rs6985109	EU	(5, 101)
C8orf12	Unknown	8p23.1	rs7836059	EU	(5)
LRRC18, WDFY4	Unknown	10q11.23	rs1913517	AS	(4, 23, 114, 149)
VKORCI	Unknown	16p11.2	rs9934438	AS	(150)
CLEC16A	Unknown	16p13 17q21	rs12599402 rs1453560	AS EU, AA	(22, 127)

EU=European, AA= African-American; AS= Asian; A= Arab; HA= Hispanic American; H=Hispanic

Table 2

Genetic variants associated with lupus nephritis.

Gene	Location	Variant	Population	References
ABIN1/TNIP1	5q32	rs7708392 rs495881	EU AA	(16, 62, 63)
APOL1	22q13.1	rs2157257 rs5750250 rs2413396 rs4820232 rs73885319; rs60910145/rs71785313	EU AA	(64, 65, 67–71)
FcyRIIB	1q23	rs1050501	EU	(72, 73)
STAT4	2q32.2–32.3	rs11889341 rs7582694	EU	(74–76)
TNFSF4	1q25	rs2205960 rs10489265	AS	(10, 23, 77, 78)

EU= European; AA= African-American; AS=Asian