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REVIEW

Exploring the etiopathogenesis of systemic lupus erythematosus: a genetic perspective

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune multi-organ disorder that presents itself in a thousand ways. Its clinical course is extremely unpredictable, which makes diagnosis and treatment a challenge for clinicians. It appears that the clinical course of SLE is determined by genetic material in combination with environmental factors. In this article, we review recent findings on the pathogenesis of SLE from the perspective of genetics, focusing on defects in the clearance of apoptotic bodies and immune complexes, on alterations in the innate immune system response, and on impaired pathways in the adaptive immune system. Furthermore, the major histocompatibility complex (MHC) and non-MHC genes discovered during genome-wide association studies (GWASs) in SLE patients are also evaluated. In addition, the effect of these polymorphisms on the function of their related transcripts and their association with the clinical manifestations of SLE and its pathophysiology are explained. Finally, the association of genetic polymorphisms with clinical responses to common medications used in the treatment of SLE is also discussed.

Keywords Systemic lupus erythematosus · Autoimmunity · Medical genetics · Polymorphism · Physiopathology

Introduction

Systemic lupus erythematosus (SLE) is known in medicine as "the great imposter" because of its extremely diverse clinical presentations (Cojocaru et al. 2011). On the one hand, it can present as a butterfly, with mild cutaneous or articular involvements, in which the patients do not need medical attention, and the complication is controlled easily by a short period of low-dose steroids. On the other hand, in a postpartum mother, it can manifest as a werewolf, ending in the failure of almost all her organs in less than a week, and in death in approximately half of the patients, in spite of treatment with the multi-drug regimens of immunosuppressive medications and high-dose steroids (Bucciarelli et al. 2006). SLE is unique among other autoimmune disorders, because as well as having an unpredictable clinical course, it can directly affect any organ.

Over the past several years, considerable progress has been made in understanding the pathophysiology of SLE (Fathollahi et al. 2018; Foma et al. 2017), but there is still little evidence that can link the pathophysiology to the clinical course of the disease. Therefore, we cannot continue to use these immunological data to treat our patients. In general, epigenetics and certain miscellaneous environmental factors can expose certain nuclear autoantigens to the immune system, and the subsequent production of autoantibodies can develop into tissue damage in SLE patients (Aslani et al. 2016; Tsokos et al. 2016; Xiao and Zuo 2016). In most cases, the anti-nuclear antibodies (ANA) are identified years before the diagnosis of SLE, but confusingly, multiple cases have been reported with negative ANA and fulfilling the clinical presentation known as seronegative SLE (Ozdemir et al. 2005; Simmons et al. 2015).

According to a recent systematic review of epidemiologic studies, the incidence of SLE has been reported to be between 0.3 and 23.2 in 100,000 person-years (Rees et al. 2017). The highest estimate of SLE prevalence was 241 subjects per 100,000 population in North America, and the lowest was 0/847 in Northern Australia. Individuals of black ethnicity had the highest incidence and prevalence of SLE, followed by Asian and white persons (Lim et al. 2014). Differences in

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the prevalence of SLE among the different ethnicities support the crucial role of genetics in this disease. In line with this, a high prevalence of SLE among the siblings of affected individuals and monozygotic twins further supports this issue (Aslani et al. 2018). According to a population-based study among 23 million participants in Taiwan, the relative risk for SLE was 315.94 for twins and 23.68 for siblings of SLE patients (Kuo et al. 2015). Genetics, in addition to its role in susceptibility to SLE, also seems to be involved in the clinical course of the disease. Furthermore, Black, East Asian, South Asian, and Hispanic SLE patients appear to experience a more severe form of the disease and more rapidly develop irreversible damage to the involved organs (Lewis and Jawad 2017). In general, it appears that genetic factors not only influence the development of SLE but also affect the course of its clinical progression (Akhtari et al. 2016; Ebrahymian et al. 2018; Mahmoudi et al. 2015, 2017, 2018; Salmaninejad et al. 2017; Tahmasebi et al. 2013).

In this review article, we focus on exploring the influence of genetics on different aspects of SLE pathogenesis. In addition, more attention is given to the genetic polymorphisms of major histocompatibility complex (MHC) genes and certain other non-MHC genes, which have been identified during genome-wide association studies (GWASs) and by the whole exome sequencing of the familial SLE cases (Delgado-Vega et al. 2018). We also discuss the genetic polymorphisms and subsequent functional alteration of the proteins that might be related to the disease pathogenesis. Finally, the association of genetic variations with the treatment response to different common medications is also explained and shows the possible future link between these genetic findings and SLE treatment.

Pathogenesis of SLE

We have progressed considerably over the past several years in identifying the pathophysiology of SLE, but many questions about this mysterious disorder remain unanswered. It has been suggested that SLE is provoked by the recognition of nuclear antigens by the immune system. Several environmental factors like ultraviolet (UV) light, toxins, and infections lead to cellular apoptosis and impairment in the clearance of apoptotic bodies, causing their recognition by both the innate and the adaptive immune systems (Tsokos et al. 2016). The autoantibodies produced against these nuclear antigens result in the construction of immune complexes (IC), and a defective IC clearance mechanism in SLE patients eventuates in a deposition of the IC on susceptible organs, such as the glomerulus. The interaction of the immune cells with these ICs results in the appearance of clinical manifestations in an SLE patient and in further tissue damage.

It has been said that uncleared apoptotic bodies can trigger the next steps in SLE pathogenesis, and several important mechanisms have been proposed that contribute to the clearance of apoptotic bodies without eliciting an inflammatory response. Tyro-3, Axl, and Mer (TAM) receptors are tyrosine kinases expressed on the surface of phagocytes, macrophages, and immature natural killer (NK) cells, and they can bind indirectly to the apoptotic cells (Jung 2015). Protein S and Gas 6 are soluble proteins that connect the TAM receptors to the phosphatidylserines on the outer layer of the lipid membrane of apoptotic cells. Downstream activation of the TAM receptors promotes the phagocytosis of apoptotic cells and inhibits the signal transducer and activator of transcription 1 (STAT1) and the nuclear factor kappa-light-chain-enhancer of the activated B cell (NF-κB) pathway. Mice lacking TAM receptors have a severe lymphoproliferative disorder with multiple autoantibodies, including the anti-double strand DNA antibody (anti-dsDNA) and the anti-phospholipid antibody. Therefore, TAM knockout mice present SLE-like manifestations, such as arthritis, vasculitis, and the deposition of immunoglobulin G (IgG) on the glomeruli (Lu and Lemke 2001). Additionally, evidence suggests that genetic polymorphisms in the negative regulators of the NF-κB pathway have been associated with SLE susceptibility (Liu et al. 2018). *TNF alpha induced protein 3* (*TNFAIP3*) gene rs2230926 polymorphism (G allele) has been associated with an increased risk of SLE in Caucasians, Asians, and Africans, whereas *TNFAIP3 interacting protein 1* (*TNIP1*) gene rs7708392 polymorphism (C allele) is associated with an increased risk of SLE in Caucasians and Africans (Liu et al. 2018).

In addition to the TAM receptors, several other proteins also participate in the clearance pathway of the apoptotic debris linked to SLE pathogenesis. Pentraxins, including C-reactive protein (CRP) and serum amyloid P (SAP), are released from hepatocytes via stimulation by interleukin (IL)-6 (Jung 2015; Paul 1999). These proteins can bind to the nuclear antigens of apoptotic bodies and decrease their immunogenicity potential (Gershov et al. 2000). The association of several single nucleotide polymorphisms (SNPs) with SLE susceptibility has been reported in SLE families in the UK (Russell et al. 2004). The study also reported that homozygote individuals with the risk *CRP4* allele had a lower serum CRP level, which can explain the important role of CRP in the clearance of apoptotic bodies. In addition, DNase I contributes to the degradation of soluble chromatin released from apoptotic cells and, consequently, diminishes its accessibility by the immune system (Tsokos et al. 2016). Further evidence for the protective role of DNase I against autoimmunity has come from an observation in which a loss-of-function variant in the *DNASE1L3* gene caused a familial form of SLE (Al-Mayouf et al. 2011). Moreover, the diminished activity of poly(ADPribose) polymerase 1 (PARP1), which contributes to the apoptosis and repair of single-strand DNA (ssDNA) breaks, was reported among SLE patients (Martens et al. 2007). Nonetheless, the association of *PARP1* polymorphisms with SLE susceptibility was not supported by the studies on

patients of French Caucasian and African-American ethnicities (Tan et al. 2001).

In addition to the previously mentioned mechanisms involving the clearance of cellular debris, the complement system is another key actor in the pathogenesis of SLE. Similarly, a complement deficiency leads to disease development, since the complement system participates in impaired autoantigen clearance. The etiologic role of a complement deficiency is more pronounced in pediatric SLE patients with a more aggressive disease course (Afzali et al. 2018; Zoghi et al. 2018). A recent study has reported that a homozygous deficiency of the C4A isotype was identified as being the strongest risk factor for SLE (P value = 7.7×10^{-3} and odds ratio = 5.329) (Jüptner et al. 2018). It was also reported that a low *C4* gene copy number was associated with a more severe form of the disease, requiring cyclophosphamide therapy.

Complement proteins like C1q act as opsonins that facilitate IC clearance by phagocytes via the Scavenger receptor class F member 1 (SCARF1) without eliciting the inflammatory pathways (Benoit et al. 2012; Ramirez-Ortiz et al. 2013). Furthermore, the autoantigens opsonized by complement proteins are presented physiologically to immature B cells and contribute to the negative selection of autoreactive B cells (Leffler and Bengtsson 2014). In addition to the initiatory steps of disease development, the complement system can also influence the perpetuation and progression of the disease. The complement system components contribute to tissue damage by raising a destructive immune hyper-response against an organ in which IC deposits have been identified. However, mutations in the complement inhibitors, such as complement factor H, are also found in SLE patients (Zhao et al. 2011). In general, it appears that genetic factors affecting the complement proteins play a critical role in SLE pathogenesis and the progression of the disease (Douglas et al. 2009; Leffler and Bengtsson, 2014; Martens et al. 2009). It is also worth mentioning that the complement system members, including C1q, can significantly regulate CD8+ T cell metabolism and activation. It has recently been reported that C1q inhibits the CD8+ T cell response to self-antigens by modulating their mitochondrial metabolism (Ling et al. 2018). Moreover, a C1q deficiency can lead to exaggerated CD8+ T cell responses against viral infections and skew the immune system towards autoimmunity (Ling et al. 2018). These findings have ushered in a set of new questions regarding the role of environmental factor translators in relation to the body's autoimmunity.

The non-specific inflammatory response of the innate immune system and the targeted autoreactive response of the adaptive immune system might stem from the signaling of toll-like receptors (TLRs) through recognizing uncleared apoptotic bodies and ICs (Tsokos et al. 2016; Wu and Tang 2015). Nuclear antigens are captured by plasmacytoid dendritic cells (pDC), resulting mainly in the triggered downstream pathway of TLR7 and TLR9, which recognize the single-strand RNA (ssRNA) and unmethylated CpG DNA, respectively. This downstream pathway leads to interferon (IFN)-I secretion by DCs, a key step in SLE pathogenesis. Furthermore, TLRs can stimulate DCs to secrete the B cell-activating factor (BAFF), and further activation of the autoreactive B cells occurs, thereby linking the innate and the adaptive immune system (Kim et al. 2009). Meta-analyses suggest that *TLR9* gene rs187084 polymorphism may increase the risk of SLE in the Asian population, whereas the other SNPs, including rs352139, rs352140, and rs5743836, did not show any association either in the Asian or the non-Asian population (Lee et al. 2016b; Wang et al. 2016). Moreover, the positive association of the *TLR8* gene rs3764879 SNP with SLE has been reported in the Caucasian population. Additionally, the minor alleles of the *TLR7* gene rs179008 and rs3853839 SNPs seem to be protective for SLE susceptibility in African and Asian patients, respectively (Lee et al. 2016b). Furthermore, genetic polymorphisms of different components of the downstream signaling TLR pathway have also been associated with SLE susceptibility. Interleukin-1R-associated kinases (IRAKs) are a family of serine/threonine kinases that transduce the signaling pathway of TLRs and the IL-1 receptors. It has been shown in a murine lupus model that the inhibition of IRAK4 significantly diminished the downstream activation of TLR2, TLR4, TLR7, and TLR9, with a significant effect on alleviation of the skin inflammation and on the steroid-sparing activity (Dudhgaonkar et al. 2017).

The cytosolic counterparts of TLRs, which are the membrane-bounded sensors of nuclear antigens, are cytosolic nucleic acid sensors (CNAS). Similarly, the downstream pathway of CNAS can also lead to IFN-I production in DCs but with a lower amount in comparison to TLRs (Shrivastav and Niewold 2013). In the same way, they can also contribute to SLE pathogenesis by way of genetic variations that hypothetically might influence the disease susceptibility and phenotype. A study was carried out on the genetic polymorphism of the *mitochondrial antiviral-signaling protein* (*MAVS*) gene, which encodes retinoic acid-inducible gene 1 (RIG-I), one of the key CNAS in SLE pathogenesis (Pothlichet et al. 2011). It was reported that a loss-of-function variant in the *MAVS* gene—rs11905552 (C79F)—was associated with both low IFN-I production and the absence of anti-RNA-binding protein autoantibodies in the African-American population. In contrast, evidence did not support the association of transmembrane protein 173 (TMEM173), another component of the CNAS, with SLE susceptibility (Balada et al. 2016).

Defects in the above-mentioned pathways lead to an accumulation of immunogenic mediators that can activate the innate and adaptive immune system, which in turn causes tissue damage and organ failure. DC is one of the leading members of the immune system in sensing the lupogenic mediators that can elicit non-specific inflammatory responses via cytokine

secretion and that can also initiate a targeted immune response by activating the adaptive immune system (Coutant 2016). It has been reported that DCs have a central role in SLE pathogenesis, and their number, composition, and function are altered in SLE patients (Klarquist et al. 2016). For instance, it has been reported that the migration of pDC to the injured kidney is one of the main steps in the development of lupus nephritis (LN). The chemokine gradients produced by the injured glomeruli can induce the migration of pDC via the IL-18 receptor, C-X-C chemokine receptor type 4 (CXCR4), and C-C chemokine receptor type 7 (CCR7) (Tucci et al. 2009). CXCR4 has been reported to be overexpressed on pDC, but evidence indicates that this overexpression is not due to a genetic variation but, on the contrary, is a result of the upstream stimulation of inflammatory mediators (Wang et al. 2009). Additionally, DCs can spread the inflammatory response by alerting members of the adaptive immune system via co-stimulatory molecules that their gene polymorphisms did not show any association with SLE susceptibility (Matsushita et al. 2000).

Although attention in recent years has focused more on the role of the innate immune system in SLE pathogenesis, the participation of the adaptive immune system in SLE has been known for some time. As discussed previously, one of the key steps in the onset of SLE is the secretion of autoantibodies from autoreactive B cells. One study reported the association of an intronic rs34933034 polymorphism of the *c-Src tyrosine kinase* (*Csk*) gene with SLE susceptibility (Manjarrez-Orduño et al. 2012). In patients with the risk allele, a higher level of B cell receptor (BCR)-mediated activation of B cells and a higher concentration of serum IgM levels were reported. The researchers also demonstrated an increased expansion rate of late transitional B cells, which could reflect the impaired tolerance checkpoint in subjects carrying the risk allele. An impairement of B cell tolerance can also occur by way of the activating signals from autoreactive T cells. As an example, activated antigen presenting cells (APCs) express the tumor necrosis factor ligand superfamily member 4 (TNFSF4), which binds to the tumor necrosis factor receptor superfamily member 4 (TNFRSF4) on naïve T cells and, consequently, these naïve cells are converted to follicular helper T (T_{FH}) cells (Tsokos et al. 2016). Afterwards, these T_{FH} cells can also activate autoreactive B cells in the lymphoid organ. Interestingly, genetic analyses showed that the SLE susceptibility alleles of the *TNFSF4* gene were associated with an increase in *TNFSF4* expression, which can participate in the overactivation of T_{FH} cells (Cunninghame Graham et al. 2008). As well as contributing to the development of SLE, *TNFSF4* gene polymorphisms are associated significantly with clinical and laboratory SLE phenotypes (Wang and Tu 2018). According to their logistic multivariate analysis, Wang et al. indicated that the rs3810936 (CT+TT) and rs4979462 (CC) variations were associated with SLE susceptibility (Wang and Tu 2018). Furthermore, the CC rs4979462 SNP genotype was associated with a higher rate of ANA positivity, supporting the probable role of T_{FH} cells in the activation of autoreactive B cells in SLE patients. In addition, the interaction between T_{FH} cells and B cells is further supported by co-stimulatory factors like CD40 and CD40L. It has been reported that the *CD40* gene rs1883832 T allele was associated with increased CD40 levels compared to the homozygous wild-type genotype in Chinese SLE patients, supporting the influence of genetic polymorphism in T cell/B cell interaction (Wu et al. 2016a). Furthermore, BAFF can also activate autoreactive B cells, and its critical role is supported by the promising effect of an anti-BAFF antibody (Belimumab) in SLE treatment (Guerreiro Castro and Isenberg 2017). Surprisingly, one group of researchers showed that the increased serum BAFF level did not result from its genetic polymorphism located in the promoter region (Eilertsen et al. 2011).

The independent intrinsic hyperactivation of T cells was also shown to be a contributing factor in SLE pathogenesis. Protein tyrosine phosphatase non-receptor type 22 (PTPN22), a negative regulator of T cell activation, may harbor certain polymorphisms, such as rs2476601 (R620W), resulting in a diminished inhibitory effect on T cell hyperactivation and SLE susceptibility (Chung and Criswell 2007). In addition, programmed death-1 (PD-1) is another crucial inhibitor of T cell proliferation that diminishes the cytolytic functions of these cells (Riley 2009). PD-1 is encoded by the *programmed cell death 1* (*PDCD1*) gene, and its PD1.3A/G polymorphism was strongly associated with SLE and LN susceptibility (Xiao et al. 2016). The gene expression profile of T cells can also be regulated differentially in SLE patients. Methyl-CpG-binding protein 2 (MECP2) is a key transcriptional regulator that can either activate or silence certain genes that are about to be transcribed through the nucleolar transcriptional system (Sawalha 2013). According to the reports, *MECP2* gene polymorphisms, including rs1734787 and rs1734791, have been associated with SLE susceptibility (Alesaeidi et al. 2015). It seems that the *MECP2* gene could further increase the expression of interferon-regulated genes in stimulated T cells of SLE patients who harbor the *MECP2* risk variant (Sawalha 2013). The association of *MHC* polymorphisms with SLE susceptibility is discussed further in a separate section.

MHC genes

Human leukocyte antigen (HLA) is involved in antigen presenting processes to T cells. HLA molecules are mainly categorized into two main classes: class I is expressed non-specifically on almost all of the cells and presents the cytosolic antigens to the immune system, whereas class II is predominantly expressed on APCs. As discussed previously, the

antigens—autoantigens in the case of SLE disease—are presented by APCs like DCs to CD4+ T cells, resulting in activation of the immune system. In general, structural variations of the HLAs, affected primarily by their gene polymorphisms, can influence the antigen processing pathway. Consequently, HLA polymorphisms have been associated with different autoimmune diseases, including SLE. Genetic analyses mainly support the association of HLA class II polymorphisms with SLE pathogenesis (Relle and Schwarting 2012).

A meta-analysis was performed on Latin American patients to elucidate the association of HLA-DRB1 and HLA-DQB1 polymorphisms with disease susceptibility. Results showed that the HLA-DRB1*0301 allele and HLA-DR3-DQ2 haplotypes were associated with disease susceptibility, while the HLA-DRB1*1101 allele had a protective effect (Castano-Rodriguez et al. 2008). A positive association with SLE susceptibility was indicated for the HLA-DR2 and HLA-DR3 groups, whereas a negative association was reported for the HLA-DR5 group. The results also demonstrated that the aforementioned polymorphisms influence the protein sequence of the protein binding groove, which can consequently affect the antigen presenting function of the HLA molecule. A second meta-analysis study gathered 25 case-control studies and reported the association of the HLA-DR genotype with SLE susceptibility and LN development (Niu and Zhang 2015). The results showed that the alleles HLA-DR4, DR11, and DR14 had protective effects, while HLA-DR3, DR9, and DR15 were potent risk factors for SLE susceptibility. In addition, HLA-DR4 and DR11 alleles were protective variations for LN, whereas HLA-DR3 and DR15 alleles were associated with renal involvement. Furthermore, another meta-analysis of 3701 independent SLE cases and 12,110 independent controls showed that HLA-DRB1*0301, HLA-DRB1*0801, and HLA-DQA1*0102 were associated with SLE susceptibility in Europeans (Morris et al. 2012).

The association of *MHC* gene polymorphisms with SLE susceptibility was also discovered previously during a GWAS. According to the study on Europeans, the association of the following alleles with SLE was reported: HLA-B*0801, HLA-DQA1*0501, HLA-DQB1*0201, HLA-DRB1*0301, HLA-DRB3*01, and HLA-DRB3*02. However, HLA-DQB1*0301 seemed to have a protective role (Armstrong et al. 2014). Moreover, the DR17 (broad antigen DR3) and B8 antigens were associated with disease susceptibility, while the DQ7 (broad antigen DQ3) had a protective effect. Another study performed on individuals with Asian ancestry from the Hong Kong Chinese population showed that the rs9271366 SNP, located between HLA-DRB1 and HLA-DQA1, increased the risk of SLE by approximately twofold. However, the rs9275328 SNP, located between HLA-DQB1 and HLA-DQA2, had a protective effect (Yang et al. 2010).

A functional study was designed to evaluate the response of mice with different HLA variations to the Smith D autoantigen (Jiang et al. 2010). According to the results, DR3 mice had the highest antibody response upon exposure to the Smith D antigen, followed by DQ8, DQ*0604, DQ*0601, and DR4 carriers. This finding was in line with previous genetic studies, strongly implying the association of *HLA-DR3* with SLE susceptibility. Interestingly, the probable protective role of HLA-DR4 in SLE pathogenesis had also been reported (Niu et al. 2015).

The association of MHC gene polymorphisms with clinical manifestations of SLE has not been investigated in detail, but the limited evidence indicates that these genetic variations can also influence progression of the disease. A study on a Chinese Han population showed that rs3077 and rs9277535 in the HLA-DP gene were associated with the risk of SLE (Zhang et al. 2017). In addition, rs3077 polymorphism was associated with cutaneous vasculitis as well as with serum IL-17 and INF-γ levels, but rs9277535 polymorphism was not associated with any cytokine or clinical manifestation. Another study on Hungarian SLE patients showed that the HLA-DRB1*03 and DRB1*07 alleles were associated with LN, whereas HLA-DRB1*1501 appeared to be a protective allele (Endreffy et al. 2003). Furthermore, HLA-DRB1*07 was positively associated with serositis, as well as with severe renal and cardiorespiratory involvement, and seems to be associated with fatal manifestations. In addition, the HLA-DRB1*04 and DRB1*1112 alleles were associated with resistant leukopenia and discoid lupus erythematosus (DLE), respectively. In another study performed on Arab SLE patients, it was shown that the HLA-DRB1*10, DRB1*11, DQB1*03, and DRB1*15 alleles were associated with hematologic, neurologic, cutaneous, and renal involvements, respectively (Wadi et al. 2014). Moreover, serositis was associated with the HLA-DRB3 and DRB1*11 alleles. Among Portuguese SLE patients, the HLA-DRB1*08 carriers faced a nearly four-fold higher risk of neurologic involvements, and the HLA-DRB1*03 allele was positively associated with LN (Vasconcelos et al. 2009). Additionally, it has been reported that the HLA-DRB1*01 allele had significant overexpression in SLE patients with neurologic disorders (*P* value of 0.013 and odds ratio of 20.25) (Hachicha et al. 2018). In general, the association of different MHC gene variations with SLE clinical presentations has been reported nearly worldwide, but it seems that these associations are extremely diverse among populations.

Non-MHC genes

IRF5

Interferon regulatory factor 5 (*IRF5*) is one the most important genes that has been widely investigated for its association with SLE (Niewold et al. 2008; Shin et al. 2007; Sigurdsson

et al. 2005; Siu et al. 2008). Since the increased blood levels of IFN-α and its gene transcripts in the blood cells have been associated with disease severity, the prominent role of the type I interferon pathway in the pathogenesis of SLE is worth reviewing (Baechler et al. 2003). The *IRF5* gene codes a transcription factor that induces the expression of IFN-related proteins as well as type I interferons (Rönnblom and Eloranta 2006). A study on the lupus murine model has indicated that IRF5 plays a crucial role in IFN-α production, which was induced by IgG from lupus patients (Yasuda et al. 2007). It is necessary to stress the pathogenic role of the *IRF5* risk alleles, which are highly lineage-specific and differ significantly among the different immune cell types (Calise et al. 2018).

A study was made of *IRF5* gene SNPs in four independent SLE case-control cohorts (Graham et al. 2006b), and it was reported that the T allele of the rs2004640 SNP generated a 5′ donor splice site in an alternate exon 1 of *IRF5*. The identified *IRF5* risk haplotype contributed to the expression of multiple IRF5 isoforms, elevated IRF5 expression, and the increased risk of SLE susceptibility (Graham et al. 2006b). Another study identified multiple over-transmitted haplotypes that might be responsible for the involvement of *IRF5* in SLE pathogenesis (Graham et al. 2006a). It was also proposed that the A allele of rs10954213 might generate a polyadenylation site, associated with the amplified expression of a transcript variant that contained a shorter 3′-UTR (Graham et al. 2006a). Another study identified a novel polymorphic insertion/deletion region that consists of four repeats in the sixth exon and that might define the pattern of expression of IRF5 isoforms (Kozyrev et al. 2012). Further case-control analyses showed that *IRF5* gene SNPs such as rs2070197 had a strong association with SLE risk, especially in Latin American populations (Reddy et al. 2007).

A few years later, a study was conducted on 3230 IRF5-TNPO3 common variants in over 8000 cases of SLE and 7000 healthy controls of different ethnicities (Kottyan et al. 2014). Four variants of the *IRF5* gene highlighted a genetic association in the promoter region. It was suggested that, in contrast to previously known functional variants, rs4728142, which is a SNP in the promoter region, could be associated with *IRF5* gene expression by altering the binding of transcription factor ZBTB3 (Kottyan et al. 2014). These findings still support the hypothesis that risk variants of the *IRF5* gene increase gene expression. However, a more recent study suggests that various functional SNPs contribute to the establishment of risk haplotypes and have a cumulative effect on the risk of developing SLE (Raj et al. 2016).

STAT4

The *signal transducer and activator of the transcription 4* (*STAT4*) gene was first proposed in 2007 to be associated with rheumatoid arthritis and SLE, suggesting a shared pathway in the pathogenesis of these diseases (Remmers et al. 2007). Further studies confirmed the association of *STAT4* and SLE, suggesting that rs3821236, rs3024866, and rs7574865 SNPs were associated with high levels of STAT4 expression (Abelson et al. 2009). Moreover, it was demonstrated that the rs3024896 polymorphism on the 3′ end of the *STAT4* gene was also strongly associated with SLE. Due to the 25-kb distance between *STAT1* and *STAT4*, the researchers suggested that the association between certain *STAT1* SNPs and SLE might reflect linkage disequilibrium (LD) with *STAT4* (Namjou et al. 2009). The *STAT4* association with SLE has been replicated in several populations (Mirkazemi et al. 2013; Piotrowski et al. 2012; Yang et al. 2009). A meta-analysis, involving 7381 patients and 11,431 controls, indicated an odds ratio of 1.65 for the minor T allele of the *STAT4* gene rs7574865 SNP in SLE. Subsequently, the major T allele of the *STAT4* gene rs7601754 polymorphism was proposed to be associated with the risk of SLE (Yuan et al. 2010). Moreover, the *STAT4* gene rs7582694 CC and CG genotypes were associated with juvenile SLE in the Egyptian population (Nageeb et al. 2018).

Another study on patients of European descent suggested that *STAT4* polymorphisms might be associated with LN (Chung et al. 2011), while another group examined the association of the *STAT4* gene and LN in two Swedish cohorts via a GWAS (Bolin et al. 2013). Four highly linked SNPs located within the *STAT4* gene were associated with LN. Additionally, in a case-only meta-analysis, the *STAT4* rs7582694 SNP was associated with worse outcomes, involving severe renal complications (Bolin et al. 2013). Moreover, it was shown that the *STAT4* susceptibility loci were strongly associated with the presence of anti-dsDNA in patients with SLE (Chung et al. 2011). In line with these findings, the association of the *STAT4* rs7582694 CC genotype with cutaneous manifestations, proteinuria, ANA, and anti-dsDNA positivity was reported among Egyptian juvenile onset SLE patients (Nageeb et al. 2018).

The role of STAT4 in autoimmune diseases was predominantly explained by its role in IL-12 signaling, which regulates Th1 cells and influences the shape of the immune system (Namjou et al. 2009). In fact, Th1-modified organisms that are STAT4-deficient seem to be protected against certain autoimmune diseases in which Th1 cells have a prominent role (Chitnis et al. 2001; Simpson et al. 1998). Studies on experimental autoimmune encephalomyelitis (EAE) models showed that a targeted deletion of the *STAT4* gene resulted in resistance to the induction of EAE (Chitnis et al. 2001). STAT4-deficient mice were also resistant to the induction of myocarditis and had a milder form of colitis (Afanasyeva et al. 2001; Simpson et al. 1998). However, several studies indicated that IFN-γ, as a proinflammatory cytokine, played a significant role in the pathogenesis of many autoimmune diseases such as SLE (Balomenos and Rumold 1998; Goropevšek and

Holcar 2017). Nevertheless, IFN-γ-deficient animal models are still susceptible to EAE, myocarditis, and colitis (Afanasyeva et al. 2001; Ferber et al. 1996; Simpson et al. 1998). These results suggest that, although IFN-γ is a prominent STAT4-induced cytokine, this transcription factor also regulates the expression of other genes that participate in the development of autoimmune diseases like SLE. Indeed, there are other known cytokines, such as IL-23 and IFN-α, that can potentially activate STAT4 (Kaplan 2005). These cytokines, in addition to those that are still unknown, could verify the phenotype of STAT4-deficient mice. However, future studies on animal models may shed light on the role of STAT4 and its signaling pathway in the pathogenesis of SLE.

ITGAM

Polymorphisms of *integrin alpha M* (*ITGAM*), a non-MHC gene, have been reported to have significant associations with SLE. GWASs on female SLE patients of European descent identified the minor alleles of rs1143678 and rs4548893 SNPs to be associated with disease susceptibility (Harley et al. 2008). Furthermore, a logistic regression model showed that rs9888739 made independent genetic contributions to a 1.7-fold higher genetic susceptibility to SLE. Moreover, a study performed on a European-American population revealed a strong association of the minor rs1143679 SNP allele with SLE susceptibility, a finding that was also replicated in an African-American and Gullah population (Nath et al. 2008). In line with the previous study, the association of rs1143679 with disease susceptibility was shown in GWASs on an Amerindian, Hong Kong, and Thai population (Alarcon-Riquelme et al. 2016; Yang et al. 2009). However, they also reported the significant positive association of the minor rs1143683 allele with disease susceptibility.

ITGAM encodes CD11, which binds to the common β2 subunit to form CD18 integrin. CD18 integrin (also known as complement receptor 3 [CR3] or macrophage receptor 1 [Mac-1]) is expressed on a variety of immune cells and orchestrates the proinflammatory and immunomodulatory pathways. Studies indicate that genetic polymorphisms can affect the CD18 function in different ways, but all of these effects lead to an impairment of the normal functioning of the immune system. CD18 contributes to the leukocyte recruitment pathway by directly binding to the receptors of activated endothelial cells, including intercellular adhesion molecule 1 (ICAM-1). In vitro studies indicated that the CD18 integrin protein harboring the R77H variant of the CD11 subunit had a diminished tendency to bind to ICAM-1 under shear stress (MacPherson et al. 2011; Rosetti and Mayadas 2016). Similarly, it was shown that neutrophils from SLE patients, carrying the *CD11* gene rs1143678 and rs1143683 polymorphisms, have reduced CD18 ligand-binding properties (Zhou et al. 2013). Additionally, CD18 integrin participates in leukocyte recruitment via another pathway, modulated by the binding of the FCγ receptor (FCγR) to IC. Studies on the animal model of anti-glomerular basement membrane (anti-GBM) glomerulonephritis (GN) indicated that the leukocyte retention time in the injured glomerulus was lower in the Mac-1-deficient animal (Devi et al. 2013). This pathway is a key factor in SLE pathogenesis and seems to be affected by *ITGAM* gene polymorphisms in these patients. Moreover, the previously mentioned processes can be mediated via the complement components covering the antigens or ICs. It has been shown that the rs1143678 SNP (P1146S substitution) promoted the Mac-1-mediated adhesion of immune cells to the iC3b component (Ong et al. 2017).

In addition to its crucial IC-mediated role in leukocyte migration to the injured tissue, Mac-1 is also a major contributor in the proinflammatory processes. A recently published study showed that SLE patients carrying the minor alleles of rs1143678, rs1143679, and rs1143683 polymorphisms had a higher level of IFN-I activity, a dominant cytokine in SLE pathogenesis (Faridi et al. 2017). However, individuals carrying the haplotype rs1143679(G)-rs1143683(T) also had a higher level of IFN-I. This association was independent of the disease activity, which could also significantly influence the IFN-I level. It was shown that $CD11b^{-/-}$ macrophages secrete higher levels of IFN-β upon exposure to lipopolysaccharide (LPS) as the TLR4 agonist (Faridi et al. 2017). In line with the previously mentioned findings, the group also reported that the CD11b agonist (LA1) could significantly decrease IFN-β secretion in LPS-activated wild-type macrophages but fail to affect $CD11b^{-/-}$ cells. LA1-mediated CD11b activation suppresses the proinflammatory TLR and IFN-I downstream pathways via the MyD88/NF-κB and AKT/FOXO3/IRF3/7 axes. Interestingly, the group found that the minor alleles of *ITGAM* polymorphisms failed to maintain the forkhead box O3 (FOXO3) nuclear level, which led to a diminished suppressive effect on IRF7 and to an increase in IFN-I gene expression.

However, Mac-1 also participates in IC phagocytosis and clearance, and its impairment has been highlighted in SLE pathogenesis. One study demonstrated that the neutrophils of SLE patients harboring the homozygous minor alleles for rs1143678/rs1143683/rs1143679 (TT/TT/AA) had significantly less phagocytic activity for complement-opsonized particles compared to common polymorphisms (Zhou et al. 2013). Furthermore, neutrophils with the TT/TT/GG genotype, respectively, also had a statistically significant reduction in phagocytic activity compared to neutrophils with the CC/CC/GG genotype. Notably, rs1143678 and rs1143683 polymorphisms are located in the regions encoding the cytoplasmic tail and calf-1, respectively. Interestingly, the phagocytic activity of neutrophils carrying minor variants did not alter for particles that are able to bind to domains that are different from the complement binding site. It was also reported that

neutrophils with the TT/TT/AA and TT/TT/GG genotypes demonstrated reduced phagocytic activity for the IgG-coated particles compared to their counterparts harboring the CC/CC/GG genotype. This finding indicated that *ITGAM* polymorphisms could also have a significant influence on the FCγR-mediated phagocytic function. These findings were not compatible with other studies, however, which showed that the R77H (rs1143679) substitution was associated with the reduced phagocytic activity of neutrophils and monocytes in SLE cases (MacPherson et al. 2011; Rhodes et al. 2012). Moreover, an association of the rare variants of *ITGAM* with reduced phagocytic activity in SLE has also been reported in a study describing how the F941V and G1145S variations were associated with reduced complement-mediated phagocytosis (Roberts et al. 2014). The F941V and G1145S variations are located in the calf-2 and cytoplasmic domain, respectively, indicating the influential role of these domains in the phagocytic action of Mac-1. However, in contrast, the group reported that the minor alleles of rs1143683 and rs11861251 SNPs did not alter the phagocytic action of neutrophils.

Limited data exist as regards the association of *ITGAM* polymorphism with the clinical manifestations of SLE. One of the studies conducted on the patients of European descent showed that the minor allele of the rs1143679 polymorphism was positively correlated with LN, discoid rash, and immunologic manifestations, including anti-dsDNA and anti-ribonucleoprotein antibody (anti-nRNP) (Kim-Howard et al. 2010). In another study undertaken on Asian patients, 13 SNPs including rs1143679 were identified to be associated with LN. In contrast, however, they were negatively associated with the discoid rashes but there was a positive trend regarding the anti-Sm antibody. It should be noted that the studied SNPs were mostly located in the *ITGAM* gene regulatory regions that affect Mac-1 expression and cellular concentration. This finding is not fully compatible with previous research, which mostly studied SNPs in the genes coding the structural part of Mac-1 without any influence on its expression level (Rhodes et al. 2012; Roberts et al. 2014; Zhou et al. 2013). Among the Hong Kong Chinese and Thai SLE patients, it was shown that minor alleles of the rs1143679 and rs1143683 polymorphisms are linked to LN, and minor alleles of the rs1143683 and rs1143678 SNPs are positively associated with neurologic involvement (Yang et al. 2009). Consequently, it appears that despite discrepancies among the GWASs dealing with the association of *ITGAM* polymorphisms with disease manifestations, a consensus still exists that these polymorphisms have a significant influence on the development of LN.

BANK1

The association of *B cell scaffold protein with ankyrin repeats 1* (*BANK1*) polymorphisms with SLE susceptibility was investigated in several populations. Nine different SNPs were identified among Swedish SLE patients: namely, rs4522865 (A), rs4572885 (T), rs10516487 (G), rs10516486 (C), rs17200824 (A), rs6849308 (C), rs10516482 (C), rs10516483 (C), and rs2631271 (G) (Kozyrev et al. 2008). The association of rs10516487, rs17266594, and rs3733197 was replicated in Argentina, Germany, Italy, and Spain, which showed pooled odds ratios of 1.38, 1.42, and 1.23, respectively. The association of rs10028805 with SLE was also reported previously in another GWAS performed on European patients (Bentham et al. 2015).

The potential role of the BANK1 protein in SLE pathogenesis was addressed recently in a publication showing that B cells harboring risk variants of the rs17266594, rs10516487, and rs3733197 SNPs had a decrease in AKT protein activation following BCR or CD40 stimulation (Dam et al. 2016). Due to the inhibitory effect of AKT on FOXO1, the nuclear levels of FOXO1 and its target genes were increased simultaneously. Consequently, B cells tend to develop into memory cell subtypes. The authors concluded that this altered pathway might play a role in the perpetuation of the disease (Dam et al. 2016).

In another recently published paper, the potential role of BANK1 in the innate immune system has also been elucidated (Wu et al. 2016b). The study was performed on the B6.Sle1.yaa mouse model, which develops the disease as a result of TLR7 overexpression. According to the results, a BANK1 deficiency led to the impaired production of IL-6 and IgG2c upon exposure to the TLR7 agonist. In line with this finding, the serum BAFF levels and anti-dsDNA IgG were lower in the BANK1-deficient mice, but the IgM level was unaffected. Interestingly, the cumulative glomerulonephritis score, serum urea level, and histological nephritis were not affected by the BANK1 deficiency. Furthermore, a BANK1 deficiency reduced the expression—by TLR7 agonist signaling—of signaling-dependent genes, such as STAT1 and IRF7. Consequently, it was concluded that BANK1 might participate in the development of SLE by contributing to the TLR7 signaling pathway and to the autoantibody production mechanism.

BANK1 is expressed in two different ways: as a full-length variant and a Δ2 variant, which lacks exon 2 and codes for the inositol trisphosphate receptor (IP3R) binding domain. Previous studies demonstrated that the risk allele of rs17266594 led to an increase in the expression ratio of the full-length variant/Δ2 variant in SLE (Kozyrev et al. 2008). This SNP is in strong LD with rs10516487. In opposition to the above-mentioned work, the group later reported that the non-synonymous rs10516487 SNP located in exon 2 influenced splicing efficiency by creating an exonic splicing enhancer site for the serine-rich protein 40 (SRp40) factor, but rs17266594 did not significantly affect the splicing process (Kozyrev et al. 2012). The study showed that the minor allele of rs10516487 (G) lacked any site for splicing enhancer

protein SRp40 and, consequently, there was a higher full-length variant/Δ2 variant ratio in the cells harboring this allele. In line with these findings, it has been shown that the mice overexpressing the full-length variant of BANK1 had increased levels of the total IgM and anti-dsDNA IgG antibodies, increased transcript levels of several class-switched IgG antibodies, and an increased level of activation-induced deaminase (AID) in comparison to mice overexpressing the Δ2 variant (Pathak et al. 2015). Moreover, the study indicated that these different levels of expression could strongly influence the homing of B cells to the follicles and spleen.

The clinical significance of *BANK1* polymorphisms was not investigated in detail, but the limited amount of evidence that exists indicates that *BANK1* SNPs can influence the disease subtype. A European SLE cohort study reported that different *BANK1* SNPs were associated with diverse SLE-specific autoantibodies and clinical disease manifestations (Guo et al. 2009). Among the previously mentioned SNPs, rs17266594 and rs10516487 were negatively associated with immunological disorders and renal involvement. Furthermore, it has also been described that risk variants of *BANK1* are associated with anti-dsDNA positive SLE cases but not with their anti-dsDNA negative counterparts (Chung et al. 2011).

The potential clinical value of genetic risk: implications for personalized medicine

It is still a long way to the era of using personalized medicine for the treatment of SLE patients. Nonetheless, certain cases have been reported that show promising progress in this approach. For instance, one recent study reported on a 4-year-old SLE patient who—when she was 3 years old—had presented with malar rash, arthritis, a high ANA titer, anti-dsDNA, anti-cardiolipin antibody, leucopenia, and Coombs positive anemia (Ellyard et al. 2016). At 4 years old, she presented with right-side hemiparesis, upon which—on the basis of the irregular medium-size vessels in her magnetic resonance angiography (MRA)—a diagnosis of SLE vasculitis/cerebritis was made. Whole exome sequencing (WES) identified an R97H homozygous mutation in the *three prime repair exonuclease 1* (*TREX1*) gene. TREX1 is an intracellular exonuclease that cleaves the ssDNA and the non-functional variant of R97H in the coding gene, leading to an increased serum IFN-α level, as observed in this SLE case. It was finally concluded that this patient was a suitable fit for treatment with the anti-IFN-α antibody, and the benefit of WES in finding the appropriate treatment target was demonstrated.

There is recent sound evidence suggesting that genetic polymorphisms can highly predict the clinical course of SLE (McGlasson et al. 2018). According to a meta-analysis, the polymorphisms of genes involved in the immune complex clearance pathway are significantly associated with neuropsychiatric SLE (NPSLE) (Ho et al. 2016). It also appears that individuals carrying the *FCGR3A* 158FF, *FCGR3B* NA1/2, and *ITGAM* rs1143679 HH genotypes are at greater risk of experiencing the neuropsychiatric manifestations of their disease (Ho et al. 2016). Moreover, the association of the *TREX1* risk haplotype with NPSLE has recently been demonstrated in a multi-ancestral lupus cohort (McGlasson et al. 2018). Furthermore, patients carrying the wild-type rs7925662 TT genotype in the *Transient receptor potential cation channel, subfamily C, member 6* (*TRCP6*) gene had a greater risk of developing NPSLE (Ramirez et al. 2015). TRCP6 is a membrane-bound protein that increases the intracellular level of calcineurin in the neurons, which further inhibit activation of the *N*-methyl-D-aspartate (NMDA) receptor (Ramirez et al. 2015). In vivo and in vitro studies have documented that anti-NMDA antibodies cause neuronal apoptosis and remodeling in SLE patients, which further lead to neuropsychiatric manifestations (Arinuma 2018). It appears that this pathway can be a promising candidate for novel therapeutic strategies.

Genetic polymorphisms can also predict the outcome of treatment in SLE patients. An investigation was made involving the association of *HSP90AA1* gene polymorphisms with the clinical response of SLE patients to glucocorticoid therapy (Zou et al. 2016). *HSP90AA1* encodes heat shock protein 90 (HSP90), which is considered to be a crucial protein in regulating the glucocorticoid receptor effects by mediating its translocation and further activation. The study demonstrated that rs7160651, rs10873531, and rs2298877 polymorphisms were associated with the treatment response to glucocorticoid, which was assessed by the SLE disease activity index (SLEDAI). However, a more recent study did not find any association between *HSP90AA2* gene polymorphisms and glucocorticoid efficacy among Chinese SLE patients (Zhang et al. 2018). Moreover, an investigation regarding the association of *HSP90B1* gene polymorphisms with treatment response to glucocorticoid among Anhui SLE patients showed that the CCCGAACATCCC haplotype of the *HSP90B1* gene was associated with glucocorticoid efficacy (Sun et al. 2018). Furthermore, it had been reported earlier that polymorphisms of the glucocorticoid receptor (rs4912905, rs17100234, and rs7701443) by themselves could greatly influence the clinical improvement of SLE patients (Zou et al. 2013).

Antimalarials are one of the cornerstones of SLE treatment and have been studied for their clinical efficacy with regard to genetic polymorphisms. It had been demonstrated that the serum TNF-α level was lower in patients treated with antimalarials, and the study also showed that patients with a combination of the AA/AG genotype in the −1082 position of the *IL10* gene and the AA/GA genotype in the −308 position of the *TNFA* gene had the best treatment response to antimalarials, which was measured by the serum TNF-α level (López et al. 2006). The aforementioned SNPs are located in the

promoter regulating regions of the related genes, and they further regulate the basal concentration of IL-10 and TNF-α. Additionally, the association of the genetic polymorphism of cytochrome P450 isoforms with the serum hydroxychloroquine (HCQ) level has been studied among Korean SLE cases. The *N*-desethyl HCQ/HCQ ratio was seen to be higher in carriers of the GG genotype of the *CYP2D6*10* (rs1065852) polymorphism and the C/C genotype of the *CYP2D6*10* (rs1135840) polymorphism (Lee et al. 2016a). *CYP3A5*3* and *CYP3A4*18B* polymorphisms did not display any significant association with the serum medication level. Consequently, it seems that the serum drug level is highly influenced by genetic variations in these patients.

The association of genetic polymorphisms with the treatment outcome of LN has also been investigated. In one study, it was shown that the CT genotype of the *glutathione S transferase* (*GST*) *A1* gene had a lower LN remission rate compared with the CC carriers during treatment with cyclophosphamide (Wang et al. 2015). Cyclophosphamide is a prodrug activated by multiple cytochrome P450 enzymes, and its active metabolite is further inactivated by glutathione *S* transferase. It appears that genetic polymorphisms are involved in the inactivation process and, consequently, alter the efficacy of cyclophosphamide. In line with the previous study, the *GSTP1* gene Ile105Val genotype was an independent factor in the poor renal results in LN patients treated with cyclophosphamide, and the null genotype of *GSTM1* gene was associated with an adverse drug reaction (Audemard-Verger et al. 2016). Unlike the previously mentioned study on HCQ, no association was detected between *cytochrome P450s* gene polymorphism and the efficacy or adverse drug reaction to cyclophosphamide. In addition, another study showed the influence of genetic polymorphisms in the *Fc fragment of the IgG receptor* (*FCGR*) gene cluster in the renal outcome following cyclophosphamide treatment. It was shown that carriers of the minor alleles of rs6697139, rs10917686, and rs10917688, located between the *FCGR2B* and *Fc receptor-like A* (*FCRLA*) genes, had a lower response to treatment (Kim et al. 2016). Therefore, medications might be influenced by genetic variations, which ultimately determine the degree of renal amelioration or exacerbation in SLE subjects.

Future perspectives and concluding remarks

In the years since the first description of SLE, we have been able to clarify a great deal regarding the physiopathology of this disease. In general, it seems that certain environmental factors such as ultraviolet light can induce cell apoptosis and the subsequent exposure of the nuclear autoantigen to the immune system. The impaired clearance mechanisms of apoptotic bodies lead to their accumulation and, consequently, the autoantibodies secreted from the autoreactive B cells break the tolerance. The IC formation and poor clearance pathways lead to their deposition in the organs of anatomically susceptible persons. ICs can further activate the adaptive and innate immune pathways, which later results in tissue damage and organ failure. Pieces of evidence demonstrate that the footprints of genetic polymorphisms are evident in all of the previously mentioned pathways. In addition, with the aid of GWASs, several SNPs with a higher contributing impression in SLE pathogenesis have been identified. Studies support the fact that each of these polymorphisms causes structural and functional changes in its related protein, which leads further to an impairment of one of the pathways.

SLE has an extremely unpredictable clinical course, and every expert physician is frequently faced with life-threatening, treatment-resistant cases, although not every patient presents with this type of aggressive manifestation. In addition, all of the investigated genetic variants and pathways are often demonstrated theoretically, and the conclusions drawn have little practical application at the patient's bedside. However, recent studies have contributed to a clearer elucidation of the role of these SNPs in the clinical course of the disease and the treatment of SLE patients. As was discussed, several SNPs have been detected that can predict the treatment response to certain traditional and essential SLE medications. Furthermore, the association of these polymorphisms with particular clinical and serologic manifestations has also been reported. We hope that genetic studies in the future will eventuate in a tool designed to better discriminate between those patients presenting with either a werewolf-like or a butterfly-like manifestation of SLE. This will enable us to accurately select the patients best suited for more aggressive follow-up and to make more effective and better-informed choices from among the treatment options.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

References

Abelson A-K, Delgado-Vega AM, Kozyrev SV, Sanchez E, Velazquez-Cruz R, Eriksson N, Wojcik J, Linga Reddy MVP, Lima G, D'Alfonso S, Migliaresi S, Baca V, Orozco L, Witte T, Ortego-Centeno N, the AADEA group, Abderrahim H, Pons-Estel BA, Gutierrez C, Suarez A, Gonzalez-Escribano MF, Martin J, Alarcon-Riquelme ME (2009) STAT4 associates with systemic lupus erythematosus through two independent effects that correlate

with gene expression and act additively with IRF5 to increase risk. Ann Rheum Dis 68:1746–1753
Afanasyeva M, Wang Y, Kaya Z, Stafford EA, Dohmen KM, Sadighi Akha AA, Rose NR (2001) Interleukin-12 receptor/STAT4 signaling is required for the development of autoimmune myocarditis in mice by an interferon-γ-independent pathway. Circulation 104: 3145–3151
Afzali P, Isaeian A, Sadeghi P, Moazzami B, Parvaneh N, Robatjazi M, Ziaee V (2018) Complement deficiency in pediatric-onset systemic lupus erythematosus. J Lab Physicians 10:232
Akhtari M et al (2016) Analysis of killer cell immunoglobulin-like receptors and their human leukocyte antigen-ligands gene polymorphisms in Iranian patients with systemic lupus erythematosus. Lupus 25: 1244–1253
Alarcon-Riquelme ME et al (2016) Genome-wide association study in an Amerindian ancestry population reveals novel systemic lupus erythematosus risk loci and the role of European admixture. Arthritis Rheum 68:932–943. https://doi.org/10.1002/art.39504
Alesaeidi S et al (2015) Methyl-CpG-binding protein 2 (MECP2) polymorphism in Iranian patients with systemic lupus erythematosus. Inflammation 38:2185–2190. https://doi.org/10.1007/s10753-015-0201-6
Al-Mayouf SM et al (2011) Loss-of-function variant in DNASE1L3 causes a familial form of systemic lupus erythematosus. Nat Genet 43:1186–1188. https://doi.org/10.1038/ng.975
Arinuma Y (2018) Antibodies and the brain: anti-N-methyl-D-aspartate receptor antibody and the clinical effects in patients with systemic lupus erythematosus. Curr Opin Neurol 31:294–299. https://doi.org/10.1097/wco.0000000000000554
Armstrong DL et al (2014) GWAS identifies novel SLE susceptibility genes and explains the association of the HLA region. Genes Immun 15:347–354. https://doi.org/10.1038/gene.2014.23
Aslani S, Mahmoudi M, Karami J, Jamshidi AR, Malekshahi Z, Nicknam MH (2016) Epigenetic alterations underlying autoimmune diseases. Autoimmunity 49:69–83
Aslani S, Rezaei R, Jamshidi A, Mahmoudi M (2018) Genetic and epigenetic etiology of autoimmune diseases: lessons from twin studies. Rheumatol Res 3:45–57
Audemard-Verger A et al (2016) Glutathione S transferases polymorphisms are independent prognostic factors in lupus nephritis treated with cyclophosphamide. PLoS One 11:e0151696
Baechler EC et al (2003) Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci 100:2610–2615
Balada E, Selva-O'Callaghan A, Felip L, Ordi-Ros J, Simeon-Aznar CP, Solans-Laque R, Vilardell-Tarres M (2016) Sequence analysis of TMEM173 exon 5 in patients with systemic autoimmune diseases. Autoimmunity 49:12–16. https://doi.org/10.3109/08916934.2015.1113404
Balomenos D, Rumold R, Theofilopoulos AN (1998) Interferon-gamma is required for lupus-like disease and lymphoaccumulation in MRL-lpr mice. J Clin Invest 101:364–371
Benoit ME, Clarke EV, Morgado P, Fraser DA, Tenner AJ (2012) Complement protein C1q directs macrophage polarization and limits inflammasome activity during the uptake of apoptotic cells. J Immunol 188:5682–5693. https://doi.org/10.4049/jimmunol.1103760
Bentham J et al (2015) Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. Nat Genet 47:1457–1464. https://doi.org/10.1038/ng.3434
Bolin K, Sandling JK, Zickert A, Jönsen A, Sjöwall C, Svenungsson E, Bengtsson AA, Eloranta ML, Rönnblom L, Syvänen AC, Gunnarsson I, Nordmark G (2013) Association of STAT4 polymorphism with severe renal insufficiency in lupus nephritis. PLoS One 8:e84450
Bucciarelli S et al (2006) Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum 54:2568–2576. https://doi.org/10.1002/art.22018
Calise J, Marquez Renteria S, Gregersen PK, Diamond B (2018) Lineage-specific functionality of an interferon regulatory factor 5 lupus risk haplotype: lack of B cell intrinsic effects. Front Immunol 9:996–996. https://doi.org/10.3389/fimmu.2018.00996
Castano-Rodriguez N, Diaz-Gallo LM, Pineda-Tamayo R, Rojas-Villarraga A, Anaya JM (2008) Meta-analysis of HLA-DRB1 and HLA-DQB1 polymorphisms in Latin American patients with systemic lupus erythematosus. Autoimmun Rev 7:322–330. https://doi.org/10.1016/j.autrev.2007.12.002
Chitnis T, Najafian N, Benou C, Salama AD, Grusby MJ, Sayegh MH, Khoury SJ (2001) Effect of targeted disruption of STAT4 and STAT6 on the induction of experimental autoimmune encephalomyelitis. J Clin Invest 108:739–747
Chung SA, Criswell LA (2007) PTPN22: its role in SLE and autoimmunity. Autoimmunity 40:582–590. https://doi.org/10.1080/08916930701510848
Chung SA et al (2011) Differential genetic associations for systemic lupus erythematosus based on anti-dsDNA autoantibody production. PLoS Genet 7:e1001323
Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD (2011) Manifestations of systemic lupus erythematosus. Maedica (Buchar) 6:330–336
Coutant F, Miossec P (2016) Altered dendritic cell functions in autoimmune diseases: distinct and overlapping profiles. Nat Rev Rheumatol 12:703–715. https://doi.org/10.1038/nrrheum.2016.147
Cunninghame Graham DS et al (2008) Polymorphism at the TNF superfamily gene TNFSF4 confers susceptibility to systemic lupus erythematosus. Nat Genet 40:83–89. https://doi.org/10.1038/ng.2007.47
Dam EM et al (2016) The BANK1 SLE-risk variants are associated with alterations in peripheral B cell signaling and development in humans. Clin Immunol 173:171–180. https://doi.org/10.1016/j.clim.2016.10.018
Delgado-Vega AM, Martínez-Bueno M, Oparina NY, López Herráez D, Kristjansdottir H, Steinsson K, Kozyrev SV, Alarcón-Riquelme ME (2018) Whole exome sequencing of patients from multicase families with systemic lupus erythematosus identifies multiple rare variants. Sci Rep 8:8775. https://doi.org/10.1038/s41598-018-26274-y
Devi S et al (2013) Multiphoton imaging reveals a new leukocyte recruitment paradigm in the glomerulus. Nat Med 19:107–112. https://doi.org/10.1038/nm.3024
Douglas KB et al (2009) Complement receptor 2 polymorphisms associated with systemic lupus erythematosus modulate alternative splicing. Genes Immun 10:457–469. https://doi.org/10.1038/gene.2009.27
Dudhgaonkar S et al (2017) Selective IRAK4 inhibition attenuates disease in murine lupus models and demonstrates steroid sparing activity. J Immunol (Baltimore, md : 1950) 198:1308–1319. https://doi.org/10.4049/jimmunol.1600583
Ebrahymian H, Rezaei R, Mostafaei S, Aslani S, Goulielmos GN, Jamshidi A, Mahmoudi M (2018) Association study between STAT4 polymorphisms and susceptibility to systemic lupus erythematosus disease: systematic review and meta-analysis. Meta gene 16:241–247. https://doi.org/10.1016/j.mgene.2018.03.010
Eilertsen GO, Van Ghelue M, Strand H, Nossent JC (2011) Increased levels of BAFF in patients with systemic lupus erythematosus are associated with acute-phase reactants, independent of BAFF genetics: a case-control study. Rheumatology (Oxford) 50:2197–2205. https://doi.org/10.1093/rheumatology/ker282
Ellyard JI, Jerjen R, Martin JL, Lee A, Field MA, Jiang SH, Cappello J, Naumann SK, Andrews TD, Scott HS, Casarotto MG, Goodnow CC, Chaitow J, Pascual V, Hertzog P, Alexander SI, Cook MC, Vinuesa CG (2016) Identification of a pathogenic variant in

TREX1 in early-onset cerebral SLE by whole-exome sequencing. Pathology 48:S47

Endreffy E, Kovacs A, Kovacs L, Pokorny G (2003) HLA class II allele polymorphism in Hungarian patients with systemic lupus erythematosus. Ann Rheum Dis 62:1017–1018

Faridi MH, Khan SQ, Zhao W, Lee HW, Altintas MM, Zhang K, Kumar V, Armstrong AR, Carmona-Rivera C, Dorschner JM, Schnaith AM, Li X, Ghodke-Puranik Y, Moore E, Purmalek M, Irizarry-Caro J, Zhang T, Day R, Stoub D, Hoffmann V, Khaliqdina SJ, Bhargava P, Santander AM, Torroella-Kouri M, Issac B, Cimbaluk DJ, Zloza A, Prabhakar R, Deep S, Jolly M, Koh KH, Reichner JS, Bradshaw EM, Chen JF, Moita LF, Yuen PS, Li Tsai W, Singh B, Reiser J, Nath SK, Niewold TB, Vazquez-Padron RI, Kaplan MJ, Gupta V (2017) CD11b activation suppresses TLR-dependent inflammation and autoimmunity in systemic lupus erythematosus. J Clin Invest 127:1271–1283. https://doi.org/10.1172/jci88442

Fathollahi A, Gabalou N, Aslani S (2018) Mesenchymal stem cell transplantation in systemic lupus erythematous, a mesenchymal stem cell disorder. Lupus 27:1053–1064

Ferber IA et al (1996) Mice with a disrupted IFN-gamma gene are susceptible to the induction of experimental autoimmune encephalomyelitis (EAE). J Immunol 156:5–7

Foma AM, Aslani S, Karami J, Jamshidi A, Mahmoudi M (2017) Epigenetic involvement in etiopathogenesis and implications in treatment of systemic lupus erythematous. Inflamm Res 66:1057–1073

Gershov D, Kim S, Brot N, Elkon KB (2000) C-reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity. J Exp Med 192:1353–1364

Goropevšek A, Holcar M, Avčin T (2017) The role of STAT signaling pathways in the pathogenesis of systemic lupus erythematosus. Clin Rev Allergy Immunol 52:164–181

Graham DSC et al (2006a) Association of IRF5 in UK SLE families identifies a variant involved in polyadenylation. Hum Mol Genet 16:579–591

Graham RR et al (2006b) A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. Nat Genet 38:550

Guerreiro Castro S, Isenberg DA (2017) Belimumab in systemic lupus erythematosus (SLE): evidence-to-date and clinical usefulness. Ther Adv Musculoskelet Dis 9:75–85. https://doi.org/10.1177/1759720x17690474

Guo L et al (2009) Replication of the BANK1 genetic association with systemic lupus erythematosus in a European-derived population. Genes Immun 10:531

Hachicha H et al (2018) Human leukocyte antigens-DRB1*03 is associated with systemic lupus erythematosus and anti-SSB production in South Tunisia. Int J Health Sci 12:21–27

Harley JB et al (2008) Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet 40:204–210. https://doi.org/10.1038/ng.81

Ho RC, Ong H, Thiaghu C, Lu Y, Ho CS, Zhang MW (2016) Genetic variants that are associated with neuropsychiatric systemic lupus erythematosus. J Rheumatol 43:541–551. https://doi.org/10.3899/jrheum.150884

Jiang C, Deshmukh US, Gaskin F, Bagavant H, Hanson J, David CS, Fu SM (2010) Differential responses to Smith D autoantigen by mice with HLA-DR and HLA-DQ transgenes: dominant responses by HLA-DR3 transgenic mice with diversification of autoantibodies to small nuclear ribonucleoprotein, double-stranded DNA, and nuclear antigens. J Immunol 184:1085–1091. https://doi.org/10.4049/jimmunol.0902670

Jung JY, Suh CH (2015) Incomplete clearance of apoptotic cells in systemic lupus erythematosus: pathogenic role and potential biomarker. Int J Rheum Dis 18:294–303. https://doi.org/10.1111/1756-185x.12568

Jüptner M et al (2018) Low copy numbers of complement C4 and homozygous deficiency of C4A may predispose to severe disease and earlier disease onset in patients with systemic lupus erythematosus. Lupus 27:600–609. https://doi.org/10.1177/0961203317735187

Kaplan MH (2005) STAT4: a critical regulator of inflammation in vivo. Immunol Res 31:231–242. https://doi.org/10.1385/ir:31:3:231

Kim WU, Sreih A, Bucala R (2009) Toll-like receptors in systemic lupus erythematosus; prospects for therapeutic intervention. Autoimmun Rev 8:204–208. https://doi.org/10.1016/j.autrev.2008.07.046

Kim K, Bang S-Y, Joo YB, Kim T, Lee H-S, Kang C, Bae S-C (2016) Response to intravenous cyclophosphamide treatment for lupus nephritis associated with polymorphisms in the FCGR2B-FCRLA locus. J Rheumatol 43:1045–1049. https://doi.org/10.3899/jrheum.150665

Kim-Howard X et al (2010) ITGAM coding variant (rs1143679) influences the risk of renal disease, discoid rash and immunological manifestations in patients with systemic lupus erythematosus with European ancestry. Ann Rheum Dis 69:1329–1332. https://doi.org/10.1136/ard.2009.120543

Klarquist J, Zhou Z, Shen N, Janssen EM (2016) Dendritic cells in systemic lupus erythematosus: from pathogenic players to therapeutic tools. Mediat Inflamm 2016:5045248–5045212. https://doi.org/10.1155/2016/5045248

Kottyan LC et al (2014) The IRF5–TNPO3 association with systemic lupus erythematosus has two components that other autoimmune disorders variably share. Hum Mol Genet 24:582–596

Kozyrev SV et al (2008) Functional variants in the B-cell gene BANK1 are associated with systemic lupus erythematosus. Nat Genet 40:211–216. https://doi.org/10.1038/ng.79

Kozyrev SV, Bernal-Quiros M, Alarcon-Riquelme ME, Castillejo-Lopez C (2012) The dual effect of the lupus-associated polymorphism rs10516487 on BANK1 gene expression and protein localization. Genes Immun 13:129–138. https://doi.org/10.1038/gene.2011.62

Kuo CF, Grainge MJ, Valdes AM, See LC, Luo SF, Yu KH, Zhang W, Doherty M (2015) Familial aggregation of systemic lupus erythematosus and coaggregation of autoimmune diseases in affected families. JAMA Intern Med 175:1518–1526. https://doi.org/10.1001/jamainternmed.2015.3528

Lee JY et al (2016a) Association of polymorphisms of cytochrome P450 2D6 with blood hydroxychloroquine levels in patients with systemic lupus erythematosus. Arthritis Rheumatol 68:184–190

Lee YH, Choi SJ, Ji JD, Song GG (2016b) Association between toll-like receptor polymorphisms and systemic lupus erythematosus: a meta-analysis update. Lupus 25:593–601. https://doi.org/10.1177/0961203315622823

Leffler J, Bengtsson AA, Blom AM (2014) The complement system in systemic lupus erythematosus: an update. Ann Rheum Dis 73:1601–1606. https://doi.org/10.1136/annrheumdis-2014-205287

Lewis MJ, Jawad AS (2017) The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus. Rheumatology (Oxford) 56:i67–i77. https://doi.org/10.1093/rheumatology/kew399

Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley K, Drenkard C (2014) The incidence and prevalence of systemic lupus erythematosus, 2002–2004: The Georgia Lupus Registry. Arthritis Rheumatol (Hoboken, NJ) 66:357–368. https://doi.org/10.1002/art.38239

Ling GS et al (2018) C1q restrains autoimmunity and viral infection by regulating CD8(+) T cell metabolism. Science 360:558–563. https://doi.org/10.1126/science.aao4555

Liu X, Qin H, Wu J, Xu J (2018) Association of TNFAIP3 and TNIP1 polymorphisms with systemic lupus erythematosus risk: a meta-analysis. Gene 668:155–165

López P, Gómez J, Mozo L, Gutiérrez C, Suárez A (2006) Cytokine polymorphisms influence treatment outcomes in SLE patients treated with antimalarial drugs. Arthritis Res Ther 8:R42

Lu Q, Lemke G (2001) Homeostatic regulation of the immune system by receptor tyrosine kinases of the Tyro 3 family. Science 293:306–311. https://doi.org/10.1126/science.1061663

MacPherson M, Lek HS, Prescott A, Fagerholm SC (2011) A systemic lupus erythematosus-associated R77H substitution in the CD11b chain of the Mac-1 integrin compromises leukocyte adhesion and phagocytosis. J Biol Chem 286:17303–17310. https://doi.org/10.1074/jbc.M110.182998

Mahmoudi M, Rezaiemanesh A, Salmaninejad A, Harsini S, Poursani S, Bahrami T, Tahghighi F, Ziaee V, Rezaei N (2015) PDCD1 single nucleotide genes polymorphisms confer susceptibility to juvenile-onset systemic lupus erythematosus. Autoimmunity 48:488–493

Mahmoudi M, Aslani S, Hamzeh E, Ziaee V, Poursani S, Nicknam MH, Rezaei N (2017) Association study of MECP2 gene single nucleotide polymorphisms in juvenile-onset systemic lupus erythematosus patients from Iran. Fetal Pediatr Pathol 36:423–431

Mahmoudi M et al. (2018) Association of TYK2 rs34536443 polymorphism with Susceptibility to Systemic Lupus Erythematosus in Iranian Population. Rheumatology Research 3:151–159. https://doi.org/10.22631/rr.2018.69997.1057

Manjarrez-Orduño N et al (2012) CSK regulatory polymorphism is associated with systemic lupus erythematosus and influences B-cell signaling and activation. Nat Genet 44:1227

Martens HA, Nolte IM, van der Steege G, Schipper M, Kallenberg CGM, te Meerman GJ, Bijl M (2007) Association of poly(ADP-ribose) polymerase 1 and a novel candidate locus, LOC127086, with systemic lupus erythematosus. Ann Rheum Dis 66:424–425. https://doi.org/10.1136/ard.2006.065102

Martens HA et al (2009) Analysis of C1q polymorphisms suggests association with systemic lupus erythematosus, serum C1q and CH50 levels and disease severity. Ann Rheum Dis 68:715–720. https://doi.org/10.1136/ard.2007.085688

Matsushita M, Tsuchiya N, Oka T, Yamane A, Tokunaga K (2000) New polymorphisms of human CD80 and CD86: lack of association with rheumatoid arthritis and systemic lupus erythematosus. Genes Immun 1:428–434. https://doi.org/10.1038/sj.gene.6363704

McGlasson S, Wiseman S, Wardlaw J, Dhaun N, DPJ H (2018) Neurological disease in lupus: toward a personalized medicine approach. Front Immunol 9:1146–1146. https://doi.org/10.3389/fimmu.2018.01146

Mirkazemi S, Akbarian M, Jamshidi AR, Mansouri R, Ghoroghi S, Salimi Y, Tahmasebi Z, Mahmoudi M (2013) Association of STAT4 rs7574865 with susceptibility to systemic lupus erythematosus in Iranian population. Inflammation 36:1548–1552

Morris DL et al (2012) Unraveling multiple MHC gene associations with systemic lupus erythematosus: model choice indicates a role for HLA alleles and non-HLA genes in Europeans. Am J Hum Genet 91:778–793. https://doi.org/10.1016/j.ajhg.2012.08.026

Nageeb RS, Omran AA, Nageeb GS, Yousef MA, Mohammad YAA, Fawzy A (2018) STAT4 gene polymorphism in two major autoimmune diseases (multiple sclerosis and juvenile onset systemic lupus erythematosus) and its relation to disease severity. Egypt J Neurol Psychiatry Neurosurg 54:16. https://doi.org/10.1186/s41983-018-0011-5

Namjou B et al (2009) High-density genotyping of STAT4 reveals multiple haplotypic associations with systemic lupus erythematosus in different racial groups. Arthritis Rheum 60:1085–1095

Nath SK et al (2008) A nonsynonymous functional variant in integrin-alpha(M) (encoded by ITGAM) is associated with systemic lupus erythematosus. Nat Genet 40:152–154. https://doi.org/10.1038/ng.71

Niewold TB, Kelly JA, Flesch MH, Espinoza LR, Harley JB, Crow MK (2008) Association of the IRF5 risk haplotype with high serum interferon-α activity in systemic lupus erythematosus patients. Arthritis Rheum 58:2481–2487

Niu Z, Zhang P, Tong Y (2015) Value of HLA-DR genotype in systemic lupus erythematosus and lupus nephritis: a meta-analysis. Int J Rheum Dis 18:17–28. https://doi.org/10.1111/1756-185x.12528

Ong LT, Tan HF, Feng C, Qu J, Loh SC, Bhattacharyya S, Tan SM (2017) The systemic lupus erythematosus-associated single nucleotide polymorphism rs1143678 in integrin alphaM cytoplasmic tail generates a 14-3-3zeta binding site that is proinflammatory. J Immunol 198:883–894. https://doi.org/10.4049/jimmunol.1601447

Ozdemir FN, Elsurer R, Akcay A, Ozdemir BH, Sezer S, Kuscu E, Haberal M (2005) Seronegative systemic lupus erythematosus: etiology of nephrotic syndrome and acute renal failure in early postpartum period. Lupus 14:629–631. https://doi.org/10.1191/0961203305lu2148cr

Pathak S et al (2015) BANK1 transgenic mice exhibit lupus-associated B cell phenotypes (BA3P.105). J Immunol 194:46.42

Paul E, Carroll MC (1999) SAP-less chromatin triggers systemic lupus erythematosus. Nat Med 5:607–608. https://doi.org/10.1038/9450

Piotrowski P, Lianeri M, Wudarski M, Olesińska M, Jagodziński PP (2012) Contribution of STAT4 gene single-nucleotide polymorphism to systemic lupus erythematosus in the Polish population. Mol Biol Rep 39:8861–8866

Pothlichet J, Niewold TB, Vitour D, Solhonne B, Crow MK, Si-Tahar M (2011) A loss-of-function variant of the antiviral molecule MAVS is associated with a subset of systemic lupus patients. EMBO Mol Med 3:142–152. https://doi.org/10.1002/emmm.201000120

Raj P et al (2016) Regulatory polymorphisms modulate the expression of HLA class II molecules and promote autoimmunity. Elife 5:e12089

Ramirez GA et al (2015) TRPC6 gene variants and neuropsychiatric lupus. J Neuroimmunol 288:21–24. https://doi.org/10.1016/j.jneuroim.2015.08.015

Ramirez-Ortiz ZG et al (2013) The scavenger receptor SCARF1 mediates the clearance of apoptotic cells and prevents autoimmunity. Nat Immunol 14:917–926. https://doi.org/10.1038/ni.2670

Reddy MPL, Velázquez-Cruz R, Baca V, Lima G, Granados J, Orozco L, Alarcón-Riquelme ME (2007) Genetic association of IRF5 with SLE in Mexicans: higher frequency of the risk haplotype and its homozygozity than Europeans. Hum Genet 121:721–727

Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W (2017) The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology (Oxford) 56:1945–1961. https://doi.org/10.1093/rheumatology/kex260

Relle M, Schwarting A (2012) Role of MHC-linked susceptibility genes in the pathogenesis of human and murine lupus. Clin Dev Immunol 2012:584374–584315. https://doi.org/10.1155/2012/584374

Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, de Bakker PIW, le JM, Lee HS, Batliwalla F, Li W, Masters SL, Booty MG, Carulli JP, Padyukov L, Alfredsson L, Klareskog L, Chen WV, Amos CI, Criswell LA, Seldin MF, Kastner DL, Gregersen PK (2007) STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. N Engl J Med 357:977–986

Rhodes B, Furnrohr BG, Roberts AL, Tzircotis G, Schett G, Spector TD, Vyse TJ (2012) The rs1143679 (R77H) lupus associated variant of ITGAM (CD11b) impairs complement receptor 3 mediated functions in human monocytes. Ann Rheum Dis 71:2028–2034. https://doi.org/10.1136/annrheumdis-2012-201390

Riley JL (2009) PD-1 signaling in primary T cells. Immunol Rev 229:114–125. https://doi.org/10.1111/j.1600-065X.2009.00767.x

Roberts AL, Thomas ERA, Bhosle S, Game L, Obraztsova O, Aitman TJ, Vyse TJ, Rhodes B (2014) Resequencing the susceptibility gene, ITGAM, identifies two functionally deleterious rare variants in systemic lupus erythematosus cases. Arthritis Res Ther 16:R114. https://doi.org/10.1186/ar4566

Rönnblom L, Eloranta ML, Alm GV (2006) The type I interferon system in systemic lupus erythematosus. Arthritis Rheum 54:408–420

Rosetti F, Mayadas TN (2016) The many faces of Mac-1 in autoimmune disease. Immunol Rev 269:175–193. https://doi.org/10.1111/imr.12373

Russell AI et al (2004) Polymorphism at the C-reactive protein locus influences gene expression and predisposes to systemic lupus erythematosus. Hum Mol Genet 13:137–147. https://doi.org/10.1093/hmg/ddh021

Salmaninejad A, Mahmoudi M, Aslani S, Poursani S, Ziaee V, Rezae N (2017) Association of STAT4 gene single nucleotide polymorphisms with Iranian juvenile-onset systemic lupus erythematosus patients. Turk J Pediatr 59:144–149

Sawalha AH (2013) Overexpression of methyl-CpG-binding protein 2 and autoimmunity: evidence from MECP2 duplication syndrome, lupus, MECP2 transgenic and Mecp2 deficient mice. Lupus 22:870–872. https://doi.org/10.1177/0961203313497119

Shin HD, Sung Y-K, Choi C-B, Lee SO, Lee HW, Bae S-C (2007) Replication of the genetic effects of IFN regulatory factor 5 (IRF5) on systemic lupus erythematosus in a Korean population. Arthritis Res Ther 9:R32

Shrivastav M, Niewold TB (2013) Nucleic acid sensors and type I interferon production in systemic lupus erythematosus. Front Immunol 4:319. https://doi.org/10.3389/fimmu.2013.00319

Sigurdsson S et al (2005) Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. Am J Hum Genet 76:528–537

Simmons SC, Smith ML, Chang-Miller A, Keddis MT (2015) Antinuclear antibody-negative lupus nephritis with full house nephropathy: a case report and review of the literature. Am J Nephrol 42:451–459. https://doi.org/10.1159/000443747

Simpson SJ et al (1998) T cell-mediated pathology in two models of experimental colitis depends predominantly on the interleukin 12/Signal transducer and activator of transcription (Stat)-4 pathway, but is not conditional on interferon γ expression by T cells. J Exp Med 187:1225–1234

Siu H-O, Yang W, Lau CS, Chan TM, Wong RW, Wong WH, Lau YL, Alarcon-Riquelme ME (2008) Association of a haplotype of IRF5 gene with systemic lupus erythematosus in Chinese. J Rheumatol 35:360–362

Sun X-X et al (2018) Association of HSP90B1 genetic polymorphisms with efficacy of glucocorticoids and improvement of HRQoL in systemic lupus erythematosus patients from Anhui Province American Journal of. Clin Exp Immunol 7:27–39

Tahmasebi Z et al (2013) Interleukin-1 gene cluster and IL-1 receptor polymorphisms in Iranian patients with systemic lupus erythematosus. Rheumatol Int 33:2591–2596

Tan FK, Reveille JD, Arnett FC, Stivers DN, Tsao BP (2001) Poly(ADP)-ribose polymerase and susceptibility to systemic lupus erythematosus and primary antiphospholipid syndrome: comment on the article by Delrieu et al. Arthritis Rheum 43:1421–1422. https://doi.org/10.1002/1529-0131(200006)43:6<1421::AID-ANR29>3.0.CO;2-K

Tsokos GC, Lo MS, Costa Reis P, Sullivan KE (2016) New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol 12:716–730. https://doi.org/10.1038/nrrheum.2016.186

Tucci M, Ciavarella S, Strippoli S, Dammacco F, Silvestris F (2009) Oversecretion of cytokines and chemokines in lupus nephritis is regulated by intraparenchymal dendritic cells: a review. Ann N Y Acad Sci 1173:449–457. https://doi.org/10.1111/j.1749-6632.2009.04805.x

Vasconcelos C et al (2009) HLA in Portuguese systemic lupus erythematosus patients and their relation to clinical features. Ann N Y Acad Sci 1173:575–580. https://doi.org/10.1111/j.1749-6632.2009.04873.x

Wadi W, Elhefny NE, Mahgoub EH, Almogren A, Hamam KD, Al-Hamed HA, Gasim GI (2014) Relation between HLA typing and clinical presentations in systemic lupus erythematosus patients in Al-Qassim region. Saudi Arabia Int J Health Sci (Qassim) 8:159–165

Wang X-M, Tu J-C (2018) TNFSF15 is likely a susceptibility gene for systemic lupus erythematosus. Gene 670:106–113. https://doi.org/10.1016/j.gene.2018.05.098

Wang A et al (2009) CXCR4/CXCL12 hyperexpression plays a pivotal role in the pathogenesis of lupus J Immunol 182:4448-4458. J Immunol 182:4448–4458. https://doi.org/10.4049/jimmunol.0801920

Wang HN et al (2015) The GSTA1 polymorphism and cyclophosphamide therapy outcomes in lupus nephritis patients. Clin Immunol 160:342–348. https://doi.org/10.1016/j.clim.2015.07.010

Wang D, Zhang C, Zhou Z, Pei F (2016) TLR9 polymorphisms and systemic lupus erythematosus risk: an update meta-analysis study. Rheumatol Int 36:585–595. https://doi.org/10.1007/s00296-015-3404-0

Wu YW, Tang W, Zuo JP (2015) Toll-like receptors: potential targets for lupus treatment. Acta Pharmacol Sin 36:1395–1407. https://doi.org/10.1038/aps.2015.91

Wu CJ, Guo J, Luo HC, Wei CD, Wang CF, Lan Y, Wei YS (2016a) Association of CD40 polymorphisms and haplotype with risk of systemic lupus erythematosus. Rheumatol Int 36:45–52. https://doi.org/10.1007/s00296-015-3345-7

Wu YY, Kumar R, Iida R, Bagavant H, Alarcon-Riquelme ME (2016b) BANK1 regulates IgG production in a lupus model by controlling TLR7-dependent STAT1 activation. PLoS One 11:e0156302. https://doi.org/10.1371/journal.pone.0156302

Xiao G, Zuo X (2016) Epigenetics in systemic lupus erythematosus. Biomed Rep 4:135–139. https://doi.org/10.3892/br.2015.556

Xiao J-P, He W-T, Wang X-R, Wang J, Wang J, Pan H-F, Wang D-G (2016) Association of PDCD1 gene polymorphisms with systemic lupus erythematosus and lupus nephritis: an up-date meta-analysis. Int J Clin Exp Med 9:20571–20582

Yang W et al (2009) ITGAM is associated with disease susceptibility and renal nephritis of systemic lupus erythematosus in Hong Kong Chinese and Thai. Hum Mol Genet 18:2063–2070. https://doi.org/10.1093/hmg/ddp118

Yang W et al (2010) Genome-wide association study in Asian populations identifies variants in ETS1 and WDFY4 associated with systemic lupus erythematosus. PLoS Genet 6:e1000841. https://doi.org/10.1371/journal.pgen.1000841

Yasuda K, Richez C, Maciaszek JW, Agrawal N, Akira S, Marshak-Rothstein A, Rifkin IR (2007) Murine dendritic cell type I IFN production induced by human IgG-RNA immune complexes is IFN regulatory factor (IRF) 5 and IRF7 dependent and is required for IL-6 production. J Immunol 178:6876–6885

Yuan H, Feng J-B, Pan H-F, Qiu L-X, Li L-H, Zhang N, Ye D-Q (2010) A meta-analysis of the association of STAT4 polymorphism with systemic lupus erythematosus. Mod Rheumatol 20:257–262

Zhang J et al (2017) Genetic polymorphisms of rs3077 and rs9277535 in HLA-DP associated with systemic lupus erythematosus in a Chinese population. Sci Rep 7:39757. https://doi.org/10.1038/srep39757

Zhang M et al (2018) Associations of HSP90AA2 gene polymorphisms with disease susceptibility, glucocorticoids efficacy and health-related quality of life in Chinese systemic lupus erythematosus patients. Genes Genomics 40:1069–1079. https://doi.org/10.1007/s13258-018-0714-0

Zhao J, Wu H, Khosravi M, Cui H, Qian X, Kelly JA, Kaufman KM, Langefeld CD, Williams AH, Comeau ME, Ziegler JT, Marion MC, Adler A, Glenn SB, Alarcón-Riquelme ME, BIOLUPUS Network, GENLES Network, Pons-Estel BA, Harley JB, Bae SC, Bang SY, Cho SK, Jacob CO, Vyse TJ, Niewold TB, Gaffney PM, Moser KL, Kimberly RP, Edberg JC, Brown EE, Alarcon GS, Petri MA, Ramsey-Goldman R, Vilá LM, Reveille JD, James JA, Gilkeson GS, Kamen DL, Freedman BI, Anaya JM, Merrill JT, Criswell

LA, Scofield RH, Stevens AM, Guthridge JM, Chang DM, Song YW, Park JA, Lee EY, Boackle SA, Grossman JM, Hahn BH, Goodship THJ, Cantor RM, Yu CY, Shen N, Tsao BP (2011) Association of genetic variants in complement factor H and factor H-related genes with systemic lupus erythematosus susceptibility. PLoS Genet 7:e1002079. https://doi.org/10.1371/journal.pgen.1002079

Zhou Y et al (2013) Multiple lupus-associated ITGAM variants alter Mac-1 functions on neutrophils. Arthritis Rheum 65:2907–2916. https://doi.org/10.1002/art.38117

Zoghi S, Ziaee V, Hirschmugl T, Jimenez-Heredia R, Krolo A, Boztug K, Rezaei N (2018) Exome sequencing revealed C1Q homozygous mutation in pediatric systemic lupus erythematosus. Allergol Immunopathol 46:594–598

Zou Y-F, Xu JH, Wang F, Liu S, Tao JH, Cai J, Lian L, Xiao H, Chen PL, Tian G, Wu M, Wang DG, Liu SX, Liang CM, Pan FM, Su H, Pan HF, Ye DQ (2013) Association study of glucocorticoid receptor genetic polymorphisms with efficacy of glucocorticoids in systemic lupus erythematosus: a prospective cohort study. Autoimmunity 46:531–536

Zou Y-F et al (2016) Single nucleotide polymorphisms of HSP90AA1 gene influence response of SLE patients to glucocorticoids treatment. Springerplus 5:222