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SYSTEMIC LUPUS ERYTHEMATOSUS (M PETRI, SECTION EDITOR)

Genetics and Epigenetics of Systemic Lupus Erythematosus

Patrícia Costa-Reis · Kathleen E. Sullivan

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Abstract Genetics unquestionably contributes to systemic lupus erythematosus (SLE) predisposition, progression and outcome. Nevertheless, single-gene defects causing lupus-like phenotypes have been infrequently documented. The majority of the identified genetic SLE risk factors are, therefore, common variants, responsible for a small effect on the global risk. Recently, genome wide association studies led to the identification of a growing number of gene variants associated with SLE susceptibility, particular disease phenotypes, and antibody profiles. Further studies addressed the biological effects of these variants. In addition, the role of epigenetics has recently been revealed. These combined efforts contributed to a better understanding of SLE pathogenesis and to the characterization of clinically relevant pathways. In this review, we describe SLE-associated single-gene defects, common variants, and epigenetic changes. We also discuss the limitations of current methods and the challenges that we still have to face in order to incorporate genomic and epigenomic data into clinical practice.

Keywords Lupus · Systemic lupus erythematosus · SLE · Genetics · Epigenetics · Autoimmune diseases

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P. Costa-Reis (✉) · K. E. Sullivan
The Children's Hospital of Philadelphia, 3615 Civic Center Blvd. Abramson Research Center 1214, Philadelphia, PA 19104, USA
e-mail: pcr.patricia@gmail.com

K. E. Sullivan
e-mail: sullivak@mail.med.upenn.edu

P. Costa-Reis · K. E. Sullivan
The University of Pennsylvania Perelman School of Medicine, Philadelphia, USA

P. Costa-Reis
Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with a spectrum of clinical manifestations and outcomes. In spite of this variability, epidemiological data indicating a higher concordance ratio between monozygotic twins (24–69 %) compared to dizygotic twins or siblings (2–5 %) have made the role of genetics in SLE indubitable [1]. Nevertheless, single gene defects related to lupus-like phenotypes have infrequently been described and patients with monogenic causes of SLE are thought to comprise only about 1 % of most adult SLE cohorts. The majority of the identified genetic SLE risk factors are, therefore, common variants, with a modest magnitude of risk, which suggests that different mechanisms contribute to the pathogenesis of this disease, including epigenetic factors, which are just starting to be identified.

The proteins encoded by the SLE-associated genes participate in a multiplicity of mechanisms, including: monocyte, neutrophil, B and T-cell function; antigen presentation; type I interferon, toll-like receptor (TLR) and NFκB signaling; apoptosis, and clearance of cellular debris and immune complexes. Some SLE susceptibility variants are also associated with other autoimmune diseases, which may reflect common molecular pathways.

The human leucocyte antigen (HLA) region is the most gene-dense region in the human genome, including 120 functional genes, many of those with a role in immunity [2]. This region was identified as the strongest determinant of SLE predisposition in all the genome-wide association studies (GWAS) performed [3–6]. Furthermore, variants of *HLA-DRB1* were associated with SLE in multiple ethnic backgrounds and an *HLA-DR3* polymorphism (rs2187668) seemed to have an impact on the propensity to produce autoantibodies in SLE [7•].

In this review, we will focus on non-HLA genetic risk factors for lupus. Single-gene defects will be briefly described, followed by a summary of the variants and the broad epigenetic changes that have been associated with SLE.

Single Gene Defects and SLE

Single gene defects have been recognized as causing lupus since the 1970s. Specifically, complete deficiencies of C1q, C1r, C1s, C2, and C4 are strongly associated with SLE. A penetrance higher than 90 % occurs in *C1Q*, with lower penetrance for *C4* (75 %) and *C2* (10–30 %) [8, 9]. The role of complement on immune complexes and apoptotic body clearance is thought to be the underlying mechanism responsible for this association. Although partial deficiencies of C4 and Mannose-Binding Lectin (MBL) have been described as predisposing for SLE [10, 11], large-scale studies did not support this finding, so it seems unlikely that they markedly increase the susceptibility to lupus. They may, however, modify the disease phenotype [12].

Less commonly described are the associations of chronic granulomatous disease (CGD) and the carrier state for X-linked CGD with discoid and systemic lupus [13–16], presumely due to an inability to clear apoptotic cells.

The apoptotic pathway is also affected in autoimmune lymphoproliferative syndrome (ALPS). *FAS* and *FASL* are the genes related to classic ALPS, which have been associated with SLE predisposition [17–19]. Caspase 8 deficiency has similar features and is often categorized as an ALPS disorder, but the immunodeficiency dominates the phenotype. The mechanism of autoimmunity is not fully understood, but may relate to the excess of cytokines, like IL-10 and B-cell activating factor (BAFF), that can break B-cell tolerance.

Finally, approximately 10 % of the patients with prolidase deficiency develop lupus [20]. Cutaneous manifestations are common, but nearly all of the lupus end-organ effects can be seen. Prolidase participates in proline recycling, and its deficiency is thought to lead to apoptosis of cells where collagen synthesis is critical. The true mechanism, however, is not fully understood.

SLE Associated Variants Divided by Their Proposed Mechanisms

Apoptosis and Clearance of Nuclear Debris

In SLE, there is an imbalance of apoptosis and clearance of nuclear debris, which increases the availability of autoantigens, contributing to autoimmunity. Accordingly, several genes related to these mechanisms have been associated with SLE. One example is *ATG5* (autophagy related 5). Several variants of this gene, which encodes for a protein that participates in caspase-dependent apoptosis and autophagy, have been described in European SLE patients [5]. Another example is TREX1 (three prime repair exonuclease), which participates in DNA degradation, granzyme A activated apoptosis and oxidative stress response. *TREX1* null mutations are associated with Aicardi-Goutières syndrome, a disease with lupus-like features, and familial chilblain lupus. Certain *TREX1* variants were found to be related to SLE suceptibility [21] and, in a large case–control study, a *TREX1* haplotype was found to be associated with the risk of neurological manifestations in European SLE patients [22]. In addition, mutations in *ACP5* (acid phosphatase 5, tartrate resistant), which encodes a protein that participates in lysosomal digestion, were shown to cause bone dysplasia, as well as an increase on α-interferon and multiple autoimmune diseases, including SLE [23]. Although polymorphisms in *ACP5* have not been identified in GWAS, its major substrate, osteopontin, has been found in several studies as disease associated [24]. Finally, in a recent study of patients with African ancestry, several novel associations were found between variants of genes associated with the production of reactive oxygen species and SLE [25]. Collectively, these findings demonstrate the critical role of clearing nuclear debris in SLE pathogenesis.

Clearance of Immune Complexes

Genome-wide analysis and candidate gene association studies of diverse human populations showed a consistent linkage to 1q21.1-24, a region that includes the receptors that recognize the constant (Fc) portion of immunologlobulin (Ig) isotypes (FcγRs).

FcγRs can activate (FcγRI, FcγRIIA/C, FcγRIII) or inhibit (FcγRIIB) cellular functions, such as phagocytosis, antibody-dependent cellular cytotoxicity, degranulation, antigen presentation, B-cell activation, cytokine production and immune complex clearance. Numerous single nucleotide polymorphisms (SNP) and copy number variants have been characterized in the FcγR genes. Several of those variants have been associated with an increased risk for SLE. For instance, H131R of *FCGR2A* is a common variant that was shown to have lower affinity for the ligand, leading to a profound decrease on the phagocytosis of IgG2 opsonized particles [26]. The also lower IgG binding *FCGR2A* allele 158 F was associated with an increase risk for SLE in Caucasians [27], but not in an African-American population [28]. Another example is the single amino acid substitution that occurs on the I232T variant of *FCGR2B*, which was also associated with SLE in Asian populations [29, 30], but not in Caucasians [31]. Defective signaling by the risk *FCGR2B* variant increases the inflammatory response of macrophages to immune complexes, reduces the threshold for antigen presentation by dendritic cells and facilitates autoreactive B-cell activation [32], thus contributing for autoimmunity.

FCγR variants are not only associated with disease susceptibility, but also with disease progression and phenotypic features. Variants of *FCGR3A*, for example, were associated with end-stage renal disease in patients with lupus nephritis [33, 34].

Finally, copy number variation is common in regions of the genome coding for immune related genes and it is also associated with SLE predisposition, namely a low copy number variation at the *FCGR3B* locus was associated with SLE and it affected the immune complex uptake by neutrophils [35].

Complement has a dual role in SLE. On the one hand, there is clear evidence that complement activation contributes to the pathogenesis of the glomerular injury that occurs in lupus nephritis. On the other hand, complement participates in the clearance of immune complexes and apoptotic bodies. As previously discussed, complete deficiencies of complement are among the strongest known genetic risk factors for SLE. Moreover, genes associated with the regulation of the alternative complement pathway have also been recently found to contribute to SLE risk, namely genes encoding complement factor H regulator (CFHR) and five-related CFHR-proteins [36].

Toll Like Receptors and α- Interferon Pathway

Type I interferons (α and β interferon) participate in anti-viral immune responses as key regulators of the proliferation, differentiation, survival and activity of the majority of the immune cells [37]. Increased expression of α-interferon and its regulated genes has been described in SLE [38–42] and propelled the development of α-interferon inhibitors for the control of this disease. A number of variants in the receptors that recognize nucleic acids (TLRs), their regulatory molecules (UBE2L3), downstream transcription factors (IRFs, ETS1) and the interferon signaling pathway itself (TLK2) have been described in association with SLE. This large family of variants is a testament of the importance of this pathway in SLE etiopathogenesis.

TLR activation contributes to the production of type I interferons, which may explain the solid evidence connecting TLRs to SLE pathogenesis. One of the possible examples is the association between a functional variant of *TLR7* and SLE in an Asian population [43]. Other robust SLE associations were found with variations in genes coding for the interferon regulatory factors (IRFs): IRF5, IRF7 and IRF8 [44], the transcription factors downstream of TLRs. IRF5 is a transcription factor that induces the expression of multiple pro-inflammatory cytokines, including α-interferon, tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-17, IL-23, MCP1 (monocyte chemotactic protein-1), and RANTES (regulated on activation, normal T cell expressed and secreted) [45]. IRF5 is associated with SLE, as well as other autoimmune diseases, including rheumatoid arthritis, Sjogren's syndrome, systemic sclerosis, multiple sclerosis, and inflammatory bowel disease [46]. The IRF5 locus was implicated in SLE through candidate gene analysis [47] and later confirmed by multiple independent case–control cohorts [48–51] and GWAS [4–6, 7•]. Several IRF5 insertion and deletion polymorphisms and SNPs have been described in association with increased or decreased levels of IRF5, α-interferon and, consequently, SLE susceptibility [52, 53]. Interestingly, IRF5 is necessary for the development of lupus-like disease in mice, which demonstrates the importance of this transcription factor in SLE pathogenesis [54]. *IRF7* variants also contribute for SLE predisposition. An *IRF7* SNP (Q412R) is associated with an increase in IRF7 levels and SLE risk in several ancestral populations [55] and additional *IRF7* risk alleles have been associated with anti-double stranded DNA antibodies and anti-Sm antibodies [56, 57]. UBE2L3 (Ubiquitin-conjugating enzyme E2 L3) is known to participate in the degradation of TLRs and genetic variations in *UBE2L3* were also identified as predisposing for SLE and other autoimmune diseases [5, 6, 7•, 58, 59]. ETS1 (v-ets erythroblastosis virus E26 oncogene homolog 1 avian) is a transcription factor that binds the interferon-stimulated response elements, controlling type I interferon-induced transcription. It also participates in the inhibition of Th17 and B-cell differentiation. Evidence of animal models supports the role of ETS1 in SLE, since *Ets1*-deficient mice develop a lupus-like phenotype, characterized by the production of autoantibodies, glomerulonephritis and local activation of complement [60]. In humans, *ETS1* was identified as one of the loci associated with SLE predisposition [6, 61, 62]. Finally, *TYK2* (tyrosine kinase 2) variants were also associated with higher interferon production, SLE and discoid and subacute lupus [47, 63].

NFκB Pathway

The NFκB pathway is triggered by multiple stimuli, including TLR activation. Several genes that participate in NFκB signaling were associated with SLE risk, namely *IRAK1* (interleukin-1 receptor associated kinase 1) [64, 65], *TNFAIP3 (*Tumor necrosis factor, alpha-induced protein 3) [3, 6, 66], *TNIP1* (TNFAIP3 Interacting Protein 1) [6, 58], *SLC15A4* (Solute Carrier Family 15 Member 4) [6] and *PRKCB* (Protein Kinase C, Beta) [67].

IRAK1 is involved in α-interferon and γ-interferon induction and is a central regulator of NFκB pathway. Five SNPs spanning *IRAK1*, an X chromosome-encoded gene, were associated with both adult- and childhood-onset SLE, in four different ethnic groups [64].

TNFAIP3 encodes A20, an ubiquitin-editing enzyme, which participates in the termination of NFκB signaling. *TNFAIP3* is an established susceptibility locus for SLE [68, 69]. Recently, a novel TT>A polymorphic dinucleotide was found to be associated with SLE in subjects of European and Korean ancestry [66]. This haplotype resulted in reduced *TNFAIP3* mRNA and A20 protein expression and the enzyme variant bound a nuclear protein complex, which included NFκB subunits, with reduced avidity [66]. This haplotype is, thus, associated with a decreased inhibitory activity of A20, which consequently causes an activation of the NFκB

pathway. The role of A20 in NFκB inhibition has been demonstrated in animal models by the development of systemic organ inflammation and death within six weeks of birth in A20 deficient mice [70], and by the existence of a lupus-like phenotype in mice with B lymphocyte specific A20 deletion [71].

Function of Monocytes and Neutrophils

The role of innate immunity in SLE has been increasingly appreciated. Monocytes play essential roles in SLE pathogenesis, since they participate in lupus nephritis and atherosclerosis, processes responsible for considerable morbidity and mortality in SLE. Increased interest in neutrophils also arose with the description of NETosis, the process by which neutrophils extrude fibrillary networks composed of DNA, histones and granular antimicrobial proteins. These NETs trap microorganisms, decreasing their ability to spread, facilitate the interaction with neutrophil-derived effector molecules and induce the production of cytokines, such as α-interferon. A positive feedback loop occurs, since this cytokine increases NETosis. In SLE, circulating immune complexes activate neutrophils and lead to an increase in the production of NETs. The DNA present in the NETs is protected from nuclease degradation, functioning as autoantigen and potentiating autoimmunity and chronic inflammation.

Genes coding for proteins related to adhesion and migration of both monocytes and neutrophils have been associated with SLE. ITGAM (CD11b), a protein mainly expressed by macrophages, monocytes and neutrophils, encodes a leucocyte-specific integrin, important in the adherence of neutrophils and monocytes to stimulated endothelium. This receptor also participates in the phagocytosis of complement coated particles and immune complexes, since it is a receptor for iC3b. An association between *ITGAM* variants and SLE susceptibility has been documented in multiple populations [4, 5, 7•, 72, 73].

B-cell Function

One of the hallmarks of SLE is the production of autoantibodies and the formation of immune complexes that drive the systemic inflammatory response. B-cells are thus key players in the pathogenesis of this disease and the existence of effective drugs that target their function, as anti-BLyS (B lymphocyte stimulator) and rituximab (anti CD-20), further supports their role in SLE. Numerous genes associated with B-cell function and signaling have been found to predispose to SLE [74•], including *BLK* (B lymphoid tyrosine kinase) [4–6], *BANK1* (B-cell scaffold protein with ankyrin repeats gene) [7•, 75] and *LYN* (tyrosine protein kinase Lyn) [5, 76], whose proteins participate in B-cell receptor signaling. The SLE-risk variants found for *BANK1* affect the regulatory sites and functional domains of the protein and contribute to sustained B-cell activation through a change in the intracellular calcium levels [75]. LYN, a src-tyrosine kinase, is a binding partner of BANK1, whose variants were also associated with SLE in European-derived individuals, with rs6983130 described as a SLE protective factor [76]. The complement receptor 2 (CR2/CD21) is a membrane glycoprotein, mainly expressed on B-cells and follicular dendritic cells, that has also been implicated in the tolerance to nuclear self-antigens such as single and double stranded DNA, chromatin and histones [77]. Reduced levels of CR2 have been described in SLE and family-based analysis provided evidence for an association of SNPs in *CR2* and SLE in Caucasian and Chinese populations [78]. This association was later confirmed in a case–control study of a European-derived population [79]. NCF2, a cytosolic subunit of the NADPH oxidase, was found to participate in B-cell activation and recently it was also implicated in SLE susceptibility [44, 58]. IL-10 is a pivotal cytokine, responsible for globally down-regulating the immune response. Interestingly, IL-10 production by monocytes and B-cells has been shown to correlate with disease activity in SLE. IL-10 polymorphisms were found to be associated with SLE in multiple populations, including European and Asian [80, 81]. IKZF1 (IKAROS family zinc finger 1) is a transcription factor involved in the regulation of lymphocyte differentiation and proliferation, and B-cell receptor signaling. It also participates in the control of *STAT4* (Signal Transducer And Activator Of Transcription 4) gene expression. Interestingly, the levels of IKZF1 were found to be decreased in the serum of SLE patients and, recently, a GWAS identified variants of *IKZF1* associated with SLE in an Asian population [6] .

T-cell Function

The role of T-cells in the orchestration of the immune response cannot be overstated, so, as expected, several genes implicated in T-cell function have also been associated with SLE, including *PTPN22* (Protein phosphatase nonreceptor type 22), *TNFSF4* (Tumor Necrosis Factor (Ligand) Superfamily, Member 4), *STAT4* and *CD247*.

PTPN22 participates in the T-cell receptor signaling pathway. A *PTPN22* SNP (rs2476601) was associated with multiple autoimmune diseases, including SLE [82]. This association was shown in a GWAS [5] and verified in a replication study [58].

TNFSF4 is a co-stimulatory molecule found on the surface of antigen-presenting cells. It binds to the T-cell receptor OX40, contributing to the global activation of T-cells, with the exception of regulatory T-cells, whose generation and function is inhibited by this signal. Protective and risk haplotypes of *TNFSF4* have been reported for SLE [83].

STAT4 is a key regulator of IL-12, IL-17, IL-23 and α-interferon signaling, having, therefore, a critical role in the development of Th1 and Th17 immune responses. Associations with SLE and multiple SNPs located within *STAT4* gene have

been found in different ethnicities, including African Americans, Hispanics and Asians [4–6, 7•, 84, 85]. There is also evidence of an association with other autoimmune diseases [85].

CD247 is a component of the T-cell receptor—CD3 complex, which was found to be decreased in SLE. Aberrant *CD247* transcript variants were detected in SLE T-cells and an association between a *CD247* SNP and SLE was detected on a recent GWAS [86].

Table 1 provides a comprehensive list of variants associated with SLE susceptibility, according to the proposed mechanism of action.

Genetic Susceptibility for SLE and other Autoimmune Diseases

The clustering of multiple autoimmune disorders in families, in addition to the identification of variants associated with increased susceptibility for different diseases, created the notion of a common autoimmunity-related genetic background. *PTPN2* is one of those examples, since variants of this gene have been associated with juvenile idiopathic arthritis, rheumatoid arthritis, systemic sclerosis, generalized vitiligo, alopecia areata, type 1 diabetes, Graves disease, Hashimoto thyroiditis, myasthenia gravis and Addison disease [2]. PS Ramos and collaborators, however, showed that only a partial pleiotropy exists among autoimmune diseases [87]. For instance, genes like *ITGAM* and *TNFSF4*, which have been clearly associated with SLE, were not found to be associated with other autoimmune diseases, and the opposite was found for *IL23R*, one of the loci found to be shared among the highest number of autoimmune diseases, but not SLE. Thus, SLE seems to have a distinct pattern of genetic susceptibility.

Table 1 List of genes whose variants were associated with SLE susceptibility

Pathway	Genes
Function of Immune Cells	
Monocytes and Neutrophils	*FCGR2B, FCGR3A/B, ICAMs, IL10, IRF8, ITGAM.*
B-cells	*AFF1, BANK1, BLK, ETS1, FCGR2B, HLA-DR2, HLA-DR3, IKZF1, IL10, IL21, IRF8, LYN, MSH5, NCF2, PRDM1, PRKCB, RASGRP3.*
T-cells	*AFF1, CD44, CD247, ETS1, FYB, HLA-DR2, HLA-DR3, IKZF1, IL10, IL21, PRDM1, PTPN22, STAT4, TNFSF4, TYK2, UBASH3A.*
Signaling	
Toll-like receptor and α-Interferon signaling	*ACP5, ELF1, ETS1, IFIH1, IRAK1, IRF5, IRF7/PHRF1, IRF8, PRDM1, STAT4, TLR7, TREX1, TYK2, UBE2L3.*
NFkB signaling	*IRAK1, PRKCB, SLC15A4, TNFAIP3, TNIP1, UBE2L3.*
Other pathways	
Clearance of immune complexes	*C1Q, C1R/C1S, C2, C4A/B, FCGR2A/B, FCGR3A/B, ITGAM.*
Apoptosis and clearance of cellular debris	*ACP5, ATG5, DNASE1, DNASE1L3, FCGR2B, TREX1.*
Production or regulation of reactive oxygen and nitrogen intermediates	*GSR, NDUFS4, NOS1.*
Loci with unknown function	*CLEC16A, JAZF1, PTTG1, PXK, TMEM39A, TNXB, UHRF1BP1, WDFY4, XKR6.*

Adapted from Rullo and Tsao [100]

The Role of Epigenetics in SLE

The phenotype of a cell is broadly determined by the epigenomic landscape, which modulates gene expression and may serve to perpetuate pathologic mechanisms. The epigenetic changes, including histone modifications, DNA methylation, and the microRNA pattern, globally determine the set of transcribed and repressed genes. DNA methylation and histone modifications change the chromatin structure to allow or prevent the access of the transcription machinery to DNA. microRNAs are non-coding RNAs responsible for post-transcriptional gene silencing, by blocking the translation or causing mRNA degradation. These regulatory molecules are involved in essential cell mechanisms, including proliferation, differentiation and apoptosis. microRNAs also exert control on the immune system, particularly on the maintenance of immunological tolerance, participating in the regulation of T-cell selection in the thymus, B-cell selection in germinal centers, and development of regulatory T-cells.

Epigenetic mechanisms are particularly important for autoimmunity, since the expression of pro-inflammatory genes, like TNF-α, is regulated at the level of the chromatin [88].

A very well characterized epigenetic change seen in SLE is the hypomethylation of DNA in T-cells, causing a state of euchromatin and, consequently, a global activation of transcription, which correlates with disease activity [89•]. Interestingly, procainamide and hydralazine, which induce lupus-like syndromes, were both found to inhibit DNA methyltransferase 1, the former directly and the latter through the inhibition of the ERK (extracellular-signal, regulated kinase) pathway [90]. Recently, a genome-wide DNA methylation study of naïve CD4+ T-cells from SLE patients and controls found significant hypomethylation in interferon-regulated genes [91]. Hypomethylation is, therefore, another mechanism responsible for the characteristic type-I interferon hyper-responsiveness seen in lupus T-cells.

Histone acetyltransferases and deacetytransferases also control gene expression by adding or removing acetyl groups on histone lysine residues. H4 acetylation is a histone modification associated with activation of transcription. This epigenomic mechanism was found to be overall increased in monocytes from SLE patients [92]. Notably, 63 % of the genes with a higher H4 acetylation had the potential of IRF1 regulation. IRF1 is an interferon-induced weak transcription factor, which regulates the transcription of genes involved in immune modulation. Interestingly, IRF1 can interact with p300 to acetylate histones, which could explain the globally increased H4 acetylation pattern seen in SLE.

MicroRNAs are also dysregulated in SLE [93•]. miR-146a, which inhibits type I interferon expression by targeting *IRF5* and *STAT-1* mRNA [94], was found to be decreased in SLE [94], contributing, therefore, for the high levels of type I interferon characteristic of this disease. Another example is miR-3148, which was found to modulate the allelic expression of a *TLR7* variant associated with SLE [95]. Finally, in a recent study a four-miRNA SLE signature was identified in plasma [96].

The interactions and consequences of these mechanisms are under intense study. Histone modifications and DNA methylation can regulate the expression of microRNAs in SLE, as is the case of miR-142 expression on T-cells from lupus patients [97], while microRNAs, like miR-21 and miR-148, which are increased in T-cells from SLE patients, decrease the expression of DNA methyltransferase 1 [98]. These findings suggest that the epigenome is globally affected in SLE and that the persistence of the epigenomic changes could lead to a durably aberrant gene expression, contributing to the perpetuation of the disease mechanisms.

Limitations of the Current Methodologies

GWAS use a high throughput technology to analyze hundreds of SNPs and capture genome common variants. Through this approach, the joint effect of many weakly contributing variants across different loci can be studied and gene variants associated with different complex diseases can be identified. This type of study is particularly tailored for complex polygenic associations, being drastically more sensitive than family studies. In comparison to linkage analysis and sequencing, however, GWAS have less power in cases of allelic heterogeneity and may be affected by the occurrence of epistasis. The majority of the variants associated with SLE susceptibility only cause a modest increase on the risk, so large sample sizes are necessary to find significant variations. Futhermore, since the loci found by this kind of study have a weak additive predictive power for a specific phenotype, their clinic relevance may be small. Finally, occasionally results from GWAS are not replicated across studies and in different populations.

Meta-analyses are an important tool to increase the statistical power and analyze the effect of gene variations across groups of different ancestries. Predictive mathematical models integrating the weakly contributing loci may also be helpful. In addition, it is necessary to understand how specific genetic variants are responsible for the association and the biological effect. Finally, fine mapping and resequencing studies are under way, as well as new tools for the analysis of transcriptomics, proteomics and metabolomics [99•], with the final goal of being able to risk-stratify patents to truly develop a personalized approach to care.

Conclusions

For most patients the pattern of SLE heritability is not characterized by a single gene with a causal Mendelian effect, but by a multigenic mode of inheritance. Further studies are necessary to understand how the identified susceptibility variants contribute to SLE manifestations. Moreover, the majority of the large-scale studies on SLE genetics were performed in European and Asian populations. Since SLE is more frequent and more severe in other groups, namely Hispanic and African-American, new studies focusing on these populations are essential. The trajectory of our understanding of the disease pathogenesis has been extraordinarily rapid since the introduction of arrays, genomic approaches and epigenetic strategies. Next generation sequencing efforts and other new technologies are also likely to rapidly advance our knowledge. The era of personalized medicine with genomic data incorporated into diagnosis, prognosis, treatment, and adverse event prevention may truly be beginning.

Compliance with Ethics Guidelines

Conflict of Interest Kathleen E. Sullivan has received gifts from CSL Behring, has received grant support from Baxter, has received honoraria from Boston Children's Hospital, and has received royalties from UpToDate.

Patrícia Costa-Reis declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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