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REVIEW ARTICLE

Rare Variants in Systemic Lupus Erythematosus: From Monogenic to Polygenic Disease

Ruth D. Rodríguez[1] and Marta E. Alarcón-Riquelme*[1,2]

[1]Center for Genomics and Oncological Research (GENyO). Pfizer/University of Granada/Andalusian Government
[2]Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

*Corresponding author: marta.alarcon@genyo.es

ABSTRACT
The clinical and genotypic characterization of autoimmune diseases, including systemic lupus erythematosus (SLE), has made great strides recently as a result of tremendous advancements in gene sequencing technologies. Systemic lupus erythematosus is a complex multisystem disease characterized by high clinical variability due to abnormalities in both the innate and adaptive immune systems. Several genetic variants as well as environmental and hormonal factors have been identified, but the etiology of lupus is not fully understood yet. The ability of genome-wide association studies to scan thousands of individuals has enabled researchers to associate thousands of common variants to lupus. Common polymorphisms may jointly predispose to lupus, but their individual impact on the disease is minimal. It's becoming progressively more evident that rare mutations have a far higher influence. The role of rare variation in lupus has been the subject of intense research. Several approaches including genotyped-based follow-up of the variants in families, hierarchical screening, and imputation, have been applied to elucidate their functional involvement. Nevertheless, due to their rarity and the absence of standardized methodology, rare variants are still challenging to study.
Most lupus patients present a polygenic form of the disease, which is defined by the complex interplay between genetic and environmental factors. Still, certain lupus patients and patients with lupus-like phenotypes might be affected by monogenic lupus, a group of disorders largely caused by individual gene mutation abnormalities. Although monogenic lupus is rare, it has been associated with a sizable number of genes in a range of pathways, mostly resulting in early-onset phenotypes. The study of rare variants causing monogenic lupus has resulted in incredibly useful breakthroughs in our understanding of the function of rare variants in the disease, nonetheless further research is still required.
Keywords: Systemic Erythematosus Lupus, SLE, monogenic lupus, polygenic lupus, rare variants

Introduction

Systemic Erythematosus Lupus (SLE) (OMIM 152,700) is a chronic systemic autoimmune disease with a complex etiopathogenesis that affects many different organs and systems. It has an extreme clinical heterogeneity as a result of defects in both the innate and adaptive immune systems[1] with significant differences between populations. Systemic lupus erythematosus is characterized by the formation of autoreactive B and T cells promoted by a breakdown in immune tolerance, abnormal cytokine production and the subsequent generation of autoantibodies against DNA- and RNA-based self-antigens[2].

Overall, the prevalence is higher in women of childbearing age, with a female predominance of 9:1, but male patients often present a severe disease with a high frequency of nephritis[3]. In addition, individuals of non-European ancestry experience the disease more severely and with an increased co-morbidity compared to European ancestry populations[4,5]. The overall heritability of SLE is estimated as ranging from 43% to 66% across populations[6,7].

Nowadays, more than 130 risk loci have been associated though genome-wide association studies (GWAS) explaining a significant proportion of SLEs' heritability[8,9]. GWAS studies were designed primarily to capture common variation (Minor allele frequency [MAF] > 5%) and thus have a limited ability to detect rare variants. Most GWAS-identified SLE-risk loci do not alter the amino acid sequence but instead they are either in non-coding regions such as introns, promoters, enhancers and other intergenic areas or they are coding but with minimal effects on protein function (i.e. synonymous)[2,10,11]. Currently, it is accepted that rare variants located in different genes may influence disease susceptibility more significantly than common variants [12,13]. Several rare variants have been identified as causal variants of monogenic disorders with an SLE-like phenotype with different inheritance patterns[10]. Although monogenic lupus is quite rare, exhaustive analysis of these patients has revealed valuable information about potentially relevant mechanisms in polygenic lupus. In this review we will focus on the most relevant genes altered in monogenic lupus as well as the advances in the study of new rare variants associated with the complex form of the disease.

Monogenic Systemic Lupus Erythematosus

The term monogenic lupus has been used to describe SLE individuals that have pathogenic mutations in a single gene that is either dominantly or recessively inherited. Monogenic autoimmunity only represents a small proportion of the total genetic burden of autoimmunity[11]. Nonetheless, it provides important insight into the mechanisms of autoimmune diseases. Monogenic SLE is an uncommon form of lupus that typically manifests as early-onset severe disease, mostly affecting the kidneys and central nervous system[14]. Mutations in genes encoding the complement system are the first and foremost described among these rare manifestations of the disease. Aside from complement deficits, the vast majority of single gene disorders that result in monogenic lupus fall under the heading of type I interferonopathies[15–17]. Currently there is no established categorization for genes causing monogenic diseases, however most authors establish these four main categories: (I) complement pathway, (II) nucleic acid sensing and degradation, (III) regulators of type I IFN pathway and (IV) B cell and T cell self-tolerance [15,16] (**Table 1**).

Table 1. List of main genes implicated in monogenic lupus or lupus-like diseases.

Category	Gene	Gene name	Protein	Gene Location	Inheritance
Complement pathway	C1QA	Complement C1q A chain	C1q	1p36.12	AR*
	C1QB	Complement C1q B chain			AR
	C1QC	Complement C1q C chain			AR
	C1R	Complement C1r	C1r	12p13.31	AR
	C1S	Complement C1s	C1s	12p13.31	AR
	C2	Complement C2	C2	6p21.33	AR
	C4A	complement C4A	C4	6p21.33	AR
	C4B	complement C4B			AR
Nucleic acid sensing and degradation	DNASE1	Deoxyribonuclease I	DNase1	16p13.3	AD
	DNASE1L3	Deoxyribonuclease 1 like 3	DNASE1L3	3p14.3	AR
	DNASE2	Lysosomal DNase II	DNase2	19p13.13	AR
	TREX1	Three-prime repair exonuclease 1	TREX1	3p21.31	AD/AR

Category	Gene	Gene name	Protein	Gene Location	Inheritance
	SAMHD1	SAM and HD domain containing	SAMHD1	20q11.23	AD
	ADAR1	Double-stranded RNA-specific adenosine deaminase	ADAR1	1q21.3	AR
	RNASEH2A	Ribonuclease H2 subunit A	RNaseH2 complex	19p13.13	AR
	RNASEH2B	Ribonuclease H2 subunit B		13q14.3	AR
	RNASEH2C	Ribonuclease H2 subunit C		11q13.1	AR
	IFIH1	Interferon induced with helicase C domain 1	MDA5	2q24.2	AD
Regulators of type I IFN pathway	ACP5	Tartrate-resistant acid phosphatase type 5	TRAP	19p13.2	AD/AR
	ISG15	SG15 ubiquitin-like modifier	ISG15	1p36.33	AR
	USP18	Ubiquitin Specific Peptidase 18	USP18	22q11.2	AR
	OTUD1	OTU Deubiquitinase 1	OTUD1	10p12.2	AR
B cell and T cell self-tolerance pathway	PRKCD	Protein kinase C delta type	PKC-δ	3p21.1	AR
	RAG1	Recombination activating 1	RAG1	11p12	AR
	RAG2	Recombination activating 2	RAG2	11p12	AD

Footnote: *AR: Autosomal recessive; AD: autosomal dominant

I. Complement pathway

The complement system (CS) is crucial for the innate and acquired immune responses against pathogens as well as for maintaining tissue homeostasis. Complement mediates in clearance of immune complexes and damaged self-cells or cell debris and mediates phagocytosis by neutrophils and monocytes[18]. Anaphylatoxins, which are strong proinflammatory chemicals, are also produced as a result of CS activation[19].

The complement system is composed of more than 30 proteins[20], most of those being plasma proteins or membrane-bound proteins that circulate in inactive forms. There are three pathways that can ultimately activate the complement system: the lectin (LP), alternative (AP) and classical (CP) pathways.

The CP is mainly initiated by the presence of immune complexes formed either by IgM or IgG. Other proteins, however, can bind to pathogens or other particles and directly activate CP even in the absence of specific antibodies, including C1q, pentraxins and C-reactive protein[21]. The LP is triggered once specific microbes' carbohydrates are bound by lectins, such as mannose-binding lectin (MBL) or the ficolins (ficolin-1, ficolin-2 and ficolin-3). The AP occurs by the spontaneous hydrolysis of an intramolecular thioester bond in C3, which is followed by an interaction with factors B and D, without needing a particular activator[22].

Regardless of the pathway activating the complement cascade, they all lead to the activation of C3, which activates a chain reaction resulting in a proteolytic process that cleaves C5 and forms the membrane attack complex (MAC, C5b-9)[23].

Complement activation is tightly regulated to prevent uncontrolled and persistent activation since it has a variety of outcomes that can either benefit or harm the host. CS regulators are classified as soluble regulators or membrane-bound regulators[24]. Soluble regulators are mostly pathway specific while membrane-bound regulators are relatively nonspecific and control all three of the complement activation pathways[25,26]. CS regulators primarily influence co-factors' activity decaying acceleration[24]. Most of them target the C3 and C5 convertases because of their critical roles in complement activation[20,26]. Although CS is necessary for infection prevention, it can also contribute to the inflammatory response in autoimmune disorders caused by immune complex binding and accumulation in tissues, activating complement[21].

The high frequency of deficit of the early components of the complement classical pathway (CP), is one of the most remarkable genetic associations in SLE, primarily C1q (90-93%), C1r/C1s (50-57%), C4 (75%), and C2 (10%)[21]. Paradoxically, excessive CS activation is a well-known contributor to tissue damage in lupus nephritis (LN), one of the most severe manifestations of SLE[27].

The CP starts with C1, of which C1q is the first subcomponent. C1q is directly responsible for apoptotic cell recognition and opsonization, which

accelerates phagocytosis and initiates the classical pathway[28]. Apoptosis produces cellular debris, which, if not cleaned properly, may expose autoantigens acting as a depot of immunogenic material, stimulating nucleic acid autoantibodies[26]. A variety of mutations, including nonsense, frameshift and splice defects has been associated with C1q deficiency in individuals with SLE-like phenotypes. C1q autoantibodies are present in 30-48% of SLE patients compared to the 2-8% of the healthy population[20]. These autoantibodies, that target a neoepitope of bound C1q that is not expressed in the intact C1 complex, are strongly associated with lupus nephritis[29].

When C1q binds to IgG or IgM forming an immune complex, a C1r/C1s binding site is exposed, allowing further activation of the complement pathway[30]. Deficiencies in subcomponents C1r and C1s were among the earliest reports linking complement deficiency with human glomerulonephritis or a lupus-like disease, with several deleterious mutations, resulting in no detectable protein in the serum, currently identified[30].

The most prevalent complement deficiency, C2, affects around 1 in 20,000 people of European ancestry; however, only about 10% of patients with C2 deficiency develop lupus[14]. There are two types of C2 deficiency currently known. Type I is caused by a 28-bp deletion in the C2 gene, which leads to the deletion of exon 6 and the absence of C2 protein translation. Type II deficiency is typically caused by a point mutation which impairs C2 secretion (Cys111Tyr, Ser189Phe and Gly144Arg), lowering plasma levels of this protein[30]. Given the relative high prevalence of homozygous C2 deficiency without or with mild clinical manifestation, it is possible that a compensating mechanism exists that enables complement activation without the strict necessity of C2. Laich et al (2022)[31] demonstrated that Factor B (FB), the C2 homologue of the alternative pathway (AP), can replace C2.

Finally, C4 is encoded by two genes closely located within the HLA class III region, C4A and C4B. It is a highly polymorphic locus with copy number variation (CNV), ranging from two to eight copies of each isoform. The association between C4 gene copy number and non-Mendelian SLE has been studied frequently, with the results consistently indicating that the lower the number of gene copies, the greater the risk of lupus. Increased C4 gene quantities, on the other hand, seem to be protective[32–34].

II. Nucleic acid sensing and degradation

One of the hallmarks of SLE is altered cytokine profiles, being interferon (IFN) signature the most characteristic and a reflection of this. Patients with SLE have higher serum levels of IFNα and an overexpression of interferon-stimulated genes (ISGs)[35]. Type I IFN family in humans consists of 13 IFNα species and a single species of IFNβ, IFNκ, IFNω and IFNε[36,37]. IFNα and IFNβ are the best-defined and most broadly expressed type I IFNs. Almost all cells in the body can produce IFNα/β, and this usually occurs in response to the stimulation of cytosolic receptors known as pattern recognition receptors (PRRs) by microbial products[38]. As well as foreign nucleic acids and self-DNA (generally not found in the cytosol), these receptors also identify a small number of other non-nucleic-acid pathogen-associated molecular patterns (PAMPs)[38]. Several Toll-like receptors (TLRs), e.g. TLR7 and TLR9, also activate diverse pathways that converge into IFNα/β production[29,39].

Although type I IFN production limits viral assembly and replication during a viral infection, it can have adverse outcomes with persistent overexpression[29]. Also, endogenous nucleic acids not metabolized, can potentially promote the overexpression of type I IFNs through binding to PAMPs. ISG overexpression has been extensively confirmed through bulk and single-cell transcriptional profiles in SLE-patients' blood and tissues such as skin and kidney[40–49].

Deoxyribonucleases (DNase) are enzymes that catalyze the destruction of DNA molecules, hence preventing self-DNA recognition. So far, four DNAses have been associated with monogenic lupus: DNase1, DNase1L3, DNase2 and TREX1.

Since the 1950s, many authors have highlighted the connection between low DNase1 activity in serum and the development of autoantibodies, particularly anti-nucleosomal autoantibodies, and active SLE disease in both humans and mice[50–54]. An A → G mutation in exon 2 of the human DNASE1 gene, was found in 2 Japanese SLE patients causing a reduction in enzymatic activity[54].

The sequencing of seven consanguineous families revealed a fully penetrant, autosomal recessive form of pediatric-onset SLE. It was caused by mutations in the DNASE1L3 gene, a homolog of DNASE1. Deoxyribonuclease 1 like 3 (DNase1L3) is thought to fulfill a role in clearance of neutrophil extracellular traps (NETs)[16,55]. Mutations in DNASE1L3 reduce its functional activity causing accumulation of DNA in microparticles and DNA with high molecular weight in plasma[56]. These

higher order structures are significantly more capable of stabilizing interactions between several B cell receptors (BCRs)[57] and may therefore be effective stimulators of B cells with DNA-reactive BCRs[56].

DNase2 is a major lysosomal endonuclease that cleaves endocytosed apoptotic cell-derived DNA[56]. Homozygous mutations were identified in three children presenting severe autoimmune features[58]. TREX1 (also called DNase 3) is a major mammalian 3′-5′ DNA exonuclease that cleaves either single or double-stranded cytosolic DNA. Heterozygous or recessive loss-of-function mutations in the TREX1 gene lead to dysfunctional exonuclease activity in Aicardi-Goutières syndrome (AGS), a rare pediatric neurological condition that phenotypically overlaps with SLE[16]. The relationship of TREX1 mutations to SLE is yet unclear, although the presence of lupus-like disease in AGS patients suggests a clinical association[59,60]. TREX1-associated familial chilblain lupus, a rare chronic form of cutaneous lupus erythematosus has been associated almost exclusively with Asp18Asn dominant mutation[60–62]. Similarly, SAMHD1 disease-causing variants are present in AGS, SLE, and chilblain lupus[14].

SAMHD1 (SAM domain and HD domain-containing protein 1) is a triphosphohydrolase that regulates intracellular levels of deoxynucleoside triphosphates (dNTPs), preventing reverse transcription of retroviral genomes[63]. The dysregulation of dNTPs pools leads to loss of DNA repair and replication, DNA damage and apoptosis; leading to upregulation in IFN-stimulated genes.

Not only mutations in DNAses, but also in ribonuclease RNASEH2 and RNA-specific adenosine deaminase 1 (ADAR1) cause interferonopathies associated with SLE[64–66]. RNaseH2 (Ribonuclease H2) is an endoribonuclease that binds to RNA-DNA duplexes and cleaves the RNA strand. The three proteins that constitute RNaseH2 are encoded in RNASEH2A, RNASEH2B and RNASEH2C genes. Systemic lupus Erythematosus and AGS have been associated with mutations in all three genes, causing an accumulation of RNA/DNA hybrids or RNA molecules that ultimately induce an excessive type I IFN signaling[64]. ADAR1 catalyzes post-transcriptional deamination of adenosines in dsRNA, converting them to inosines, A-to-I, the most common type of RNA editing in humans[66]. Patients with SLE showed higher levels of A-to-I editing compared to controls together with patients with higher ISGs expression levels having the highest level of RNA editing, as well as elevated ADAR1 expression but lowered ADAR2 expression[65]. All things considered, these results suggest ADAR1 as a contributing factor to SLE.

The IFIH1 gene encodes MDA5 (melanoma differentiation-associated protein 5), a cytoplasmic receptor that binds cytoplasmic double stranded RNA. The gain of function mutation in IFIH1 gene causes constitutive activation of MD5, resulting in activation of macrophages and plasmacytoid dendritic cells (pDCs), the primary producers of IFN-alpha in response to nucleic acid [14,67].

III. Regulators of type I IFN pathway

Osteopontin (OPN) is a cytokine necessary for plasmacytoid dendritic cell production of type I IFN in response to TLR9 stimulation. Tartrate-resistant acid phosphatase (TRAP), which is encoded by the ACP5 gene, regulates OPN levels. TRAP colocalizes and interacts with OPN mostly in osteoclasts, macrophages and dendritic cells[68]. Decreased TRAP expression causes increased phosphorylation of OPN and increased expression of IFN-stimulated genes following TLR9 stimulation[68,69]. Homozygous mutations in ACP5 causes Spondyloenchondrodysplasia (SPENCD), a rare immuno-osseous disorder with overlapping features of lupus[68–70].

The ISG15 is a ubiquitin-like protein that stabilizes the levels of intracellular ubiquitin-specific peptidase 18 (USP18). USP18 exerts a negative regulatory effect on type I interferon signaling by competing with JAK1 for IFNAR2 (interferon α/β receptor 2) binding[71]. In absence of ISG15, USP18 is degraded via a proteasome, allowing JAK1 to bind IFNAR2 and increasing antiviral activity[16,71]. Consequently, mutations in either USP18 or ISG15 result in aberrant type I interferon induction. Significantly higher levels of ISG15 were observed in SLE patients compared to healthy controls, besides correlating with lymphocytopenia in active SLE patients before treatment [72].

In addition to ISG15, USP18 and ACP5, the role of OTU Deubiquitinase 1 (OTUD1) is worth mentioning as mutations of genes involved in the IFN signal regulation. OTUD1 gene encodes for a widely expressed deubiquitinase that removes the poly-ubiquitin chains on IRF3 to suppress interferon activity[15,16]. Loss-of-function missense mutations in OTUD1 had been associated with many different autoimmune diseases, including early onset-SLE[73].

IV. B cell and T cell self-tolerance pathway

The immune homoeostasis refers to the immune system's precise balance between immunological response to pathogen infection and immune

tolerance to self-antigens. As a consequence of the random nature of B cell receptor (BCR) evolution, some BCRs detect self-antigens. To prevent autoimmunity, these autoreactive B cells are eliminated through multiple steps in B cell development. However, self-tolerance and autoimmunity may manifest if one of these mechanisms fails[29].

An example of defects in B-cell development causing monogenic SLE is protein kinase C-δ (PKC-δ) deficiency. PKC-δ, encoded in the PRKCD gene, is a pro-apoptotic signaling kinase essential in B cell survival and apoptosis[74]. Homozygous missense mutation in PRKCD in three siblings with childhood-onset SLE was responsible for reduced PKC-δ expression[75]. The absence of PKC-δ led to chronic B cell receptor signaling, decreased apoptosis, accumulation of immature transitional B cells and increased response to stimulation[14]. Moreover, PKC-δ is a negative regulator in T cell proliferation so the deficiency of PKC-δ also led to increased T cell activation contributing to T cell autoimmunity[74].

A mutation in the RAG2 gene found in a lupus patient is another example of B cell tolerance disruption[76]. Recombination-activating 1 and 2 genes (RAG1/2) are critical enzymes involved in the V(D)J recombination of the BCR[77]. Homozygous loss-of-function mutations of RAG1 and RAG2 have been associated with severe combined immunodeficiencies, whereas heterozygous mutations have been linked to autoimmunity. RAG1/2 are required not only for V(D)J recombination but also for BCR editing, suggesting that the break in central B cell tolerance is secondary to defective receptor editing[76].

Polygenic Systemic Lupus Erythematosus

The strength of the contribution of generic risk variants varies among autoimmune diseases. From monogenic diseases, where a single genetic variant causes a pathogenesis with a minimal environmental influence, to polygenic diseases where multiple variants of modest effect combine with environmental influences to cause autoimmunity[11].

Prior to the GWAS era, the analyses were limited to the genetic variants surrounding candidate genes chosen based on prior biological understanding (candidate gene method). Although the candidate gene approach identified multiple associations, they were difficult to replicate[78]. Consequently, since the development of GWAS in 2005[79], the focus of complex diseases research has shifted to common variants with small effect sizes. GWAS is a hypothesis-free method for identifying genomic variants that are statistically associated with the risk of a disease or a specific trait. This strategy led to an exponential growth in the number of genetic variants associated with complex traits and diseases, such as autoimmune disorders.

According to the GWAS catalog, almost 6,800 genetic variants have been associated with autoimmune disorders (EFO_0005140) based on 576 studies; 1,285 of these variants have been associated with SLE in 66 studies (as of June 2023; all associations in the catalog included).

The human major histocompatibility complex (MHC) region harboring the human leukocyte antigen (HLA) was the first locus identified to be associated with SLE and still represents the strongest susceptibility factor[9,80]. The high degree of genetic diversity between populations and linkage disequilibrium in the HLA region has made genotyping and identification of causal variants challenging[78,81]. HLA-DRB1, in the MHC class II region, has long been identified as the main SLE association signal throughout the entire MHC region[81]. Nevertheless, it has been difficult to identify which genetic variants drive the development of SLE since ethnicity-specific linkage disequilibrium and allelic heterogeneity lead to highly inconsistent allelic associations among populations[81]. Studies in Asian SLE patients, revealed an increased risk of SLE conferred by HLA-DRB1*09:01 and HLA-DRB1*15:01 (and its correlated HLA-DQB1*06:02) while European studies showed an increased risk conferred by HLA-B*08:01, HLA-B*18:01, HLA-DQB1*02:01, HLA-DRB3*02:00 and HLA-DQA*01:02 and the class III SNP rs74290525[82]. Also, a recent trans-ancestral study demonstrated that HLA DRB1*03:01 - DQA1*05:01 - DQB1*02:01 and DRB1*15:01/03 - DQA1*01:02 - DQB1*06:01 were SLE-risk haplotypes in MHC class II alleles which are shared across ancestries including European, African and Hispanic Amerindian ancestries. Interestingly, a local analysis on Amerindian-European mixed-ancestries samples showed that the HLA risk alleles had a European origin, while protective alleles or haplotypes were Native American[83].

While HLA is the major signal in GWAS studies in Asian, European and African populations, in Hispanic Amerindian populations the IRF5-TNPO3 surpasses the HLA signal in significance. IRF5 remains one of the best non-HLA loci associated with SLE along with other interferon regulators such as IRF7 and IRF8[84]. Interferon regulatory factor 5 (IRF5) is involved in a variety of inflammatory signaling pathways and mediates interferon

activation and apoptosis through complex transcriptional regulation[85]. Recently, rs4728142 variant was identified as a functionally causal variant of SLE, by integrating genetic studies, epigenomic analysis and CRISPR editing[86]. Expression QTL studies suggest an association between rs4728142 alleles and IRF5 expression involving SLE pathogenesis[85].

Nonetheless, the largest drawbacks of GWAS studies are that multiple regions of the genome remain unexplored as well as the SNVs associated may just be markers in linkage disequilibrium with others and not the causal mutations[87]. More crucially, the influence of rare variants is often overlooked. GWAS studies were designed primarily to capture common variation (Minor Allele Frequency [MAF] > 5%) and therefore have limited ability to detect low-frequency variants (0.5% < MAF < 5%) and rare variants (1%<MAF). Thus, it is not surprising that most variants currently associated with lupus are common variants (Figure 1).

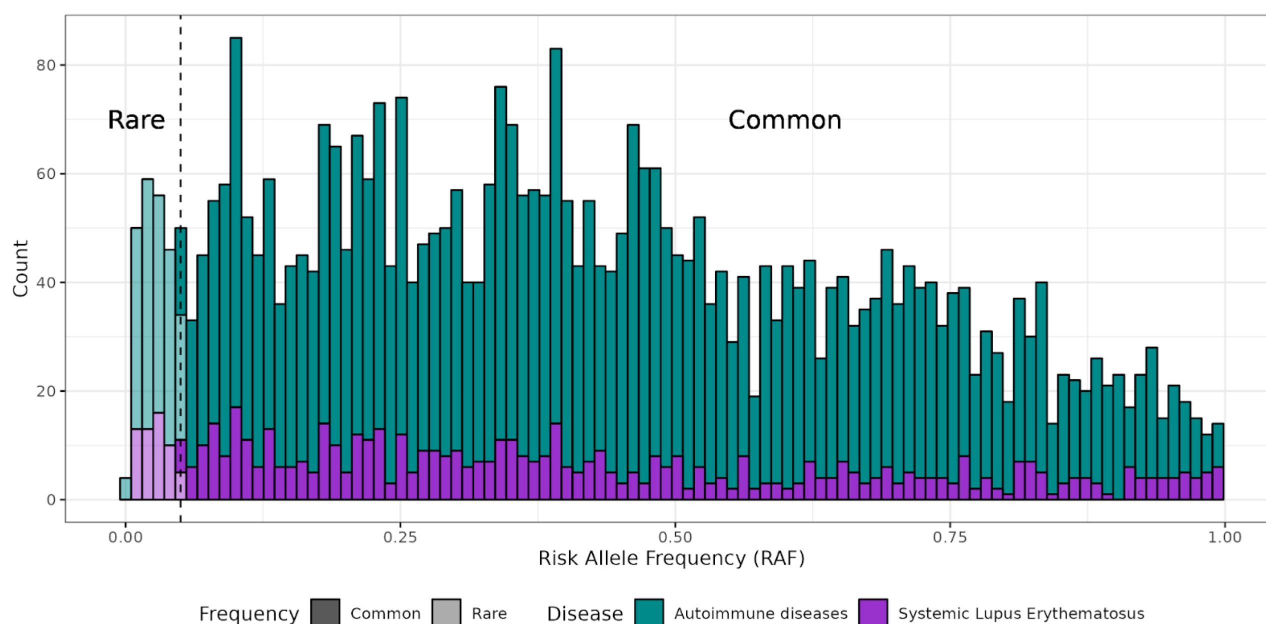

Figure 1. Distribution of Risk Allele Frequency of GWAS Catalog variants associated with autoimmune disorders (EFO_0005140; green) and associated with SLE (EFO_0002690; purple).

The individual effects of common variation on susceptibility are modest, with odds ratios between 1.01 and 2.5 at most[84]. Therefore, common variants associated with SLE only explain around 30% and 24% of total phenotypic variance in European and East Asian populations, respectively[88–90]. Several hypotheses have been proposed to aid in the discovery of this "missing heritability", such as increasing sample sizes of GWAS or studying rare and structural variants that were not captured by SNP-chips used in GWAS[91]. The interest in exploring the impact of rare variants in autoimmunity has grown exponentially as their discovery may close the gap between highly penetrant variants causing monogenic disease and the prevalent but low-pathogenic GWAS alleles [11]. Several different strategies are being used to discover new rare variants associated with the disease, as there is yet no standardized method.

Next-generation sequencing (NGS) technologies, such as whole-genome sequencing (WGS) and whole-exome sequencing (WES), have allowed for the discovery of rare SNPs with a MAF<0.005 in both coding and noncoding regions of the human genome[11]. However, measuring and statistically analyzing rare variation is still challenging.

In order to investigate the relevance of rare variation in SLE, Delgado-Vega et al (2018) analyzed WES data from five patients from two large well-studied Icelandic SLE multi-case families using clinical and linkage data[92]. By sequencing the most distantly related individuals in each family and then performing a genotyped-based follow-up of the variants identified in other affected family members, they investigated whether rare, likely pathogenic variants, were co-segregating with the disease through several generations. They identified multiple rare and likely pathogenic variants in 19 genes cosegregating with disease through several generations. Remarkably, they discovered clusters of rare variants segregating with the disease in each family instead of single alleles.

Jones et al (2019) used hierarchical screening approach for identifying putative regulatory elements within close proximity to SLE SNPs, screening those regions for potentially causative rare variants by high resolution melt analysis and functional validation. Using this strategy in 15 SLE associated loci in 143 SLE patients, they identified 7 new variants including 5 SNPs and 2 insertions. The identified novel variants were located in genes IRF5, ETS1, ITGAM1 and TNIP1; four of the five SNPs identified in this study were within predicted transcription factor binding sites [87].

Martínez-Bueno and Alarcón-Riquelme (2019) integrated a genome-wide-based imputation method with a very strict case-control burden test and a sequence kernel association (SKAT) test to look for associations between protein coding genes in European populations [12]. A set of 98 genes were identified in the study as promising candidates for association with SLE through rare variation, with effects on a variety of functions in various organs and tissues. Among the best-hits simultaneously associated in both the burden and SKAT tests, they found some genes previously associated with the disease through common variation such as TMEM55B, SPATA8, PRDM1 and HLA-DRB1.

The most recent advances in the identification of rare variants causing early onset lupus, revealed a gain-of-function mutation in TLR7 in a 7-years-old Spanish girl[39]. TLR7 is essential for antiviral immunity induction, but TLR7 expression dose is also a crucial pathogenic component in SLE. TLR7 has been observed to escape X-inactivation increasing the risk of women to develop lupus[93]; similarly, the CXorf21 locus also escapes X-inactivation and seems to be closely linked with TLR7 and SLE[94]. The most remarkable aspect of the TLR7^{Y264H} mutation finding is that it also caused the disease in animal models since the amino acid sequence containing the mutation is highly conserved across species.

Conclusions

In the last few decades, the development of new technology and worldwide collaboration efforts have allowed advancement from exploratory candidate genes to large-scale genome-wide scans evaluating millions of SNPs in thousands of individuals from various populations. Currently, genetic research is focused on identifying causative variants, their methods of action and the role of rare variation. While the main challenge is still the clinical validation of the functional impact and pathogenicity of variants identified in massive cohort studies, all of this research is providing priceless insight into the architecture of not just systemic lupus erythematosus but also autoimmunity. Multi-omic studies comprising information on gene expression, epigenetics, gene-gene interactions and the study of rare and novel variants as well as copy number variation will provide a basis for further advancement in the area such as advances in early diagnosis and classification or the development of much-needed therapies.

Conflicts Of Interest

The authors have no conflicts of interest to declare.

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