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SYSTEMIC LUPUS ERYTHEMATOSUS: GENETIC COMPONENTS

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ABSTRACT

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disorder characterized by the pro-duction of autoantibodies targeting nuclear components, leading to immune complex formation and tissue damage. The clinical manifestations of SLE are highly diverse, complicating disease classification and diagnosis. Genetic studies, including genome-wide association studies (GWAS), have identified numerous genetic risk factors—totalling over 183 loci—associated with SLE susceptibility and its various clinical forms. Epidemiological data indicate a familial aggregation of SLE, with heritability estimates ranging from 44% to 66%, and a notable prevalence of other autoimmune disorders within SLE-affected families. Monogenic forms of SLE, often presenting in childhood, highlight specific genetic defects, particularly within the complement pathway, whereas polygenic SLE typically arises from the interplay between multiple genetic variants and environmental factors. The role of the major histocompatibility complex (MHC) region, particularly HLA-DRB1, is significant across diverse populations, although ethnic-specific variations exist. Non-HLA loci also contribute substantially to SLE risk, with common variants exerting modest effects. Current research endeavors aim to elucidate the functional implications of these genetic variants and to integrate polygenic risk scores (PRS) into clinical practice for better diagnosis, prognosis, and understanding of SLE pathogenesis. Despite advancements, challenges remain in fully characterizing the genetic architecture of SLE and its implications for therapeutic development.

Keywords: *SLE; rheumatic disease; autoimmunity.*

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that is generally characterized by the production of antibodies against components of the nucleus. The auto-antibodies in SLE connects with related autoantigens, resulting the formation of immune complexes and tissue damage. There are a variety of clinical forms, so it is difficult to classify and define if the disease is a result of different diseases or a group of symptomatically connected diseases [59,60]. Moreover, classification includes the superposition of close states because almost 40 % of SLE patients have antiphospholipid antibodies or matching the symptoms of the immune response, such as mostly spread derivative syndrome of Sjogren with almost 25% of patients [1].

It seems that the genetic researches will be without results for SLE classification because of a vast variety of potential syndromic combinations. On the contrary, according to the first studies of genetic set of lupus families and later studies of genome-wide genetic association there are plural genetic risk factors for the development of SLE and specific disease forms [61]. In general, the list of genetic risk factors includes no less than 183 site location of genes [2]. The researches show that diseases that are similar to SLE develop from one gene mostly in childhood, diseases that are similar to SLE from many genes and because of environmental circumstances develop in later life [62]. They identify a few routes that differ from SLE patients in case of anti-nuclear autoimmunity involving creation and removing immune complexes with damaged remains of cells, inborn immune manners that limit immune reply to own nuclear components, and manners that manage the growth and activity of cells forming after diseases [3].

2. EPIDEMIOLOGY AND HERITABILITY OF SLE

According to new researches the rate of SLE is 0,3-31,5 cases per 100,000 individuals per year with the spread of the disease 517.5 cases per 100,000 individuals. SLE groups in families with the degree of danger (λS) measures SLE varying from 8 to 29. Besides, other disorders caused by antibodies and transitive genetic structures form the group of individuals with SLE [4]. The evaluation of genetic data distribution varies from 44 to 66 % for SLE with an assumed 26 % and 30%

genetic multiplicity with common and uncommon environmental circumstances, respectively. (44 + 26 + 30 = 100%). When the relapse of the disease concerns brothers or sisters (which means, lambda S: the rate of illness is higher among close relatives than among general group of respondents) SLE is like other connected with immune system inflammatory disorders, larger than rheumatoid arthritis (RA, lambda S = 8), almost like multiple sclerosis (λS = 20) and less than Celiac Disease and Primary Biliary Cirrhosis (CeD, PBC, λS = 60, 100 respectively) [5]. Obviously, because of variance in spread of illnesses in population brothers and sisters have the highest risk which is 2% (SLE), 8% (RA), 2% (MS), 3% (CeD) and 0.8% (PBC). Respectively, marks of heredity and λS are ~20% and 2.3 for myocardial infarction, 20–80% and 3 for type 2 diabetes, and 35% and 2.6 for gout [6].

3. MONOGENIC SLE

It is assumed that based on many of genes SLE more often appears as a result of the in-fluence of the environment. Nevertheless, some monogenic ways to SLE or lupus-like ill-nesses have been found [7].

Later investigations regularly exploring famous lupus genes revealed mendelian genotypes in 7% of a huge collection SLE instances beginning from childhood with a tendency for inborn immune defects [63]. If genes are not in the interval of panel reading proteins, then they could be unexplored genes or causative which are too far from panel to be read. Consequently, the low limit for the part of monogenic ways in childhood is 7% [8].

If there are not enough genetic components of the classical pathway of the complement cascade then monogenic routes to SLE take place. Actually, the lack of C1q is the most important feature for SLE - according to the literature 90% of adult respondents with the lack of C1q have distinctive signs of SLE, however without consideration of gender [64]. It is still unclear if remaining monogenic ways to SLE match this theory or they form separate units [9,10]. Despite the fact that large amount of single gene ways has symptoms of SLE popular research of decoding gene order could help to define the degree of threat of the disease in future [11].

Although there is no definition where the genes are situated, they can unite in the same manner as in a polygenic disease: creation and removing immune complexes with damaged remains of cells, the inborn immune manners that limit immune reply to own nuclear com-ponents, and manners that manage the growth and activity of cells forming after diseases [65,66]. Interesting enough, there are a few genes that take part either in monogenic or polygenic disease not only in one way [12].

4 POLYGENIC SLE

According to the current situation in a statistical SLE patient there is a combination of polygenic risk factors and an environmental trigger that tends to avoid the development of disease [67,68]. In this case it is interesting to find out what kind of genes influence on the development of the disease. There is an incomplete enumeration of real SLE risk options from the NHGRI/EBI GWAS catalog [13]. It is not full because a lot of cases of genes had the significance of genome level higher than the one that would qualify for association ($P < 5E\text{-}8 = 0.05$/estimated 1,000,000 independent genomic regions) if they had been defined in a GWAS scan [69]. It is worth mentioning that like other polygenic diseases, the most of SLE cases switched in these researches are of European origin with significantly smaller part of Asian origin examples [14,15]. Nowadays there are two researches of SLE as the basic feature in Amerindian/Hispanic/Latin American origin individuals have been announced. The first one is GWAS and the second one is an Immunochip based study. In African Origin examples with SLE only the Immunochip based study has been announced [70,71]. Eventually, genetic reasons could not comment on the dominance and heaviness of SLE in African-American and Hispanic persons [72]. Nevertheless, knowing the genetic factors in the populations, the relative contribution of systemic structural factors, environmental influence, access to healthcare and population-level genetic differences to SLE could help to value the risk and the heaviness of illness development [16].

Regarding pointed connections with SLE, a lot of studies have been done to assess the disease risk and connection biological function(s) with the disease risk. There is a partial overview of the index variations in 183 regions linked to SLE at a statistically significant level throughout the entire genome ($p < 5$ e-8) from the EBI/NHGRI GWAS catalog [73,74]. The transition from a peak of genetic association found in genome-wide scans to the under-standing of biological function represents a key challenge in the broader realm of intricate human genetics [17]. Nonetheless, comprehending the biological risk mechanisms of these variations is crucial for identifying potential new therapeutic strategies for SLE and other autoimmune diseases [75,76]. Multiple instances underscore the intricacy involved in grasping how these genetic variations connected to diseases mediate SLE risk and the challenges faced by researchers [18,19].

To illustrate, considering the example of NCF1.Arg90His, it might be assumed that pinpointing a genetic variant altering the amino acid sequence as the most strongly correlated with the disease would simplify efforts towards functional characterization, as compared to defining the role of a regulatory variant [77,78]. Conversely, the case of ptpn22.arg620trp presents a different scenario. Being one of the initial autoimmune risk alleles identified and linked to several autoimmune diseases, this variant has undergone extensive research [79,80]. Recent reviews have identified six potential independent mechanisms through which this variant altering the amino acid sequence could pose a risk for autoimmune diseases [20,21].

Furthermore, apart from the complexity arising from plausible mechanisms influenced by changes in the amino acid sequence, not every alteration in DNA impacting the amino acid sequence necessarily changes the amino acid sequence itself [81]. For instance, a coding change in ITGAM, ITGAM. arg77His, poses a risk for SLE in various populations. However, subsequent studies revealed that the risk variant of the single nucleotide polymorphism altering the amino acid sequence in ITGAM also modifies the function of a transcriptional enhancer regulating ITGAM mRNA levels [22].

It is crucial to highlight that in the context of intricate human genetics, it is widely believed that most causal variants identified through genome-wide association studies result in functional effects related to gene expression regulation. There are instances of common genetic disease-associated variants altering the long-range regulation of genes located hundreds of kilobases away [82,83]. With these considerations in mind, if a disease-associated variant is observed to impact the expression of a potential gene in the region, it could potentially be deemed the causal variant [23,24]. This was the initial assumption in the genetic association studies of SLE with IRF5, a gene within the canonical type I interferon pathway. Numerous proposed causal variants linked to IRF5 displayed functional biological effects. Nonetheless, upon conducting detailed mapping of these putative causal variants with adequately powered sample sizes and dense genotyping, this locus did not withstand statistical scrutiny [84]. A similar scenario is observed with the association involving STAT4. Despite early studies identifying variations within STAT 4 associated with rheumatoid arthritis and SLE, a subsequent study revealed that rs11889341, a variant consistently linked with SLE across various ancestries, does not regulate STAT4 expression but affects the expression of a neighboring gene, STAT1 [25,26].

Not all SLE associations are as straightforward as STAT4 and IRF5, as recent research has identified a novel enhancer increasing SLE risk over 15 kb upstream of the promoter for MIR3142HG, a long non-coding RNA gene processing micro-RNA-146A (mir-146a) [85,86]. The protective allele of this enhancer loops to physically interact with the mir-146a promoter, boosting the expression of this gene, which subsequently limits type I interferon production in peripheral blood mononuclear cells [87]. Conversely, the risk allele leads to changes in NF-kb and BHLHE40 binding, inhibiting epigenetic modifications and chromatin structure, thereby reducing the expression of this immune-regulatory non-coding RNA [27,28].

Lastly, adding to the complexity of identifying functional SLE risk variants is BLK, a kinase highly expressed in B-cells downstream of the B-cell receptor. Previous studies have identified polymorphisms proximal to the promoter affecting expression throughout B-cell development [88,89]. However, BLK is located on a large polymorphic inversion on chromosome 8, varying across global populations and has been shown to modulate SLE risk in-dependently of the two promoter polymorphisms particularly in European ancestry populations [90,91]. This modulation presumably occurs through long-range interactions between the promoter and enhancer, affecting changes in the three-dimensional chromatin structure [29,30].

Considering the typical polygenic genetic architecture of SLE, multiple factors contribute to the complexity of identifying functional variants linked to the disease [92,93].

Given the typical polygenic genetic makeup of systemic lupus erythematosus, a number of inquiries emerge: can the collective polygenic risk alleles be of use in diagnosing or predicting SLE? How much does the total burden of polygenic risk alleles contribute to SLE in a standard scenario [94,95]? What size of a group of SLE patients and control individuals will be needed to identify all of the polygenic risk loci associated with SLE? How many distinct polygenic risk loci will be uncovered in SLE [31]?

To deal with some of these questions, the common approach has been utilizing a weighted average of the risk allele genotype for a subset of independent variations with proof of genetic link as an effect size (odds ratio or beta). This is then applied to compute a "polygenic risk score" (PRS) [32,33]. It is worth mentioning that the discussion of the present condition of polygenic risk scores possibly applies mainly to European and East Asian ancestral groups, as many of the genome-wide association studies (GWAS) have been carried out in these populations, and the application of polygenic risk scores across various populations might not be effective and could potentially worsen existing health discrepancies [34,35].

Regarding the usefulness of PRS in differentiating between SLE cases and controls, it is not surprising that due to the issue of missing heritability and a maximum monozygotic twin concordance rate of about 40%, the average difference in PRS means is only around 10%, with the area under the receiver operator characteristic curve at most approximately 0.71 [96]. While implementing PRS in SLE could assist in better understanding the genetic contribution specific to ancestral populations in population-level dissimilarities seen in SLE severity and prevalence, they are not particularly helpful for classification when applied to broad populations comprising a mix of SLE cases and control subjects [97,98]. Nonetheless, despite the limitation that PRS does not have sufficient power to distinguish between SLE cases and controls, they could still prove beneficial in certain situations [36]. Langefeld et al. documented that in individuals with the highest genetic load among European ancestry SLE patients, there was a nonlinear increase in disease risk [37]. It implies that once a specific genetic liability threshold is reached, developing the disease becomes more probable in individuals with a higher genetic risk. Individuals with the highest genetic load have an absolute risk ranging from 2% to 10% (odds ratio of 25-125 times the prevalence of 84.7 per 100,000) [38]. In a separate study, Knevel and colleagues used PRS scores in a retrospective manner to assist in differentiating patients with unspecified inflammatory arthritis [39]. They calculated a probability for each of the five common types of inflammatory arthritis (rheumatoid arthritis, gout, SLE, spondyloarthritis, and psoriatic arthritis) based on the PRS for each disease. By employing this method, they achieved an area under the receiver operator curve exceeding 0.8 in independent patient groups who were subsequently diagnosed by a rheumatologist with one of these forms of inflammatory arthritis [99,100]. These studies indicate that while current polygenic risk models may not be able to effectively differentiate between SLE cases and controls, evaluating the polygenic risk contribution to SLE could still have a role in prognosis, diagnosis, or differential diagnosis of SLE in the future [40]. At present, PRS likely underestimates the overall genetic contribution to SLE in an individual for several reasons. Firstly, while risk loci or intervals have been identified, the causal variant is often unknown [101]. Second, rare variants in disease genes seem to partly contribute to this, although the extent remains unclear. Third, it is probable that not all risk variants for SLE have been identified yet. Integration of genome-wide genetic data into polygenic risk scores in other phenotypes has resulted in scores that are comparable to monogenic mutation risk in aggregate [41]. Additionally, environmental risk factors for SLE have been recognized, but the impact of the exposome and the interactions between the epigenome and genetic risk factors are not fully understood. The integration of genetic data from family members significantly reduces the sample sizes needed for accurate phenotype prediction using PRS. As the factors that currently limit the accuracy of PRS models are addressed in SLE, PRS may prove to be clinically useful for this disease [42].

How many risk variants contribute to the risk of SLE and how large of a GWAS sample size is needed to identify them? The largest GWAS study conducted so far included 208,370 individuals of East Asian descent (13,377 SLE cases and 194,993 controls), although a substantial number of controls were enrolled through population-wide biobanking initiatives [43]. This study discovered 113 genetic risk regions for SLE in individuals of East Asian descent, some of which have multiple independent effects. In our analysis, we found 183 loci listed in the GWAS catalog. This list is incomplete as additional risk intervals have been uncovered in fine mapping or follow-up studies that are strongly linked to SLE at the genome-wide level but were not included in the GWAS catalog. Examples of this include associations with IRF3 and GPR173, which were linked to SLE at the genome-wide level but not included in the catalog. It has been recognized for some time that for common complex dis-eases, the size of the GWAS sample directly correlates with the number of identified loci [44]. Additionally, numerous independent haplotypes are needed to maximize the accuracy of differentiating cases of common polygenic inflammatory diseases from controls. It has been estimated that for most common polygenic traits, hundreds to thousands of risk loci explain 50% of the risk, necessitating a sample size of approximately 1,000,000 to generate polygenic risk scores that explain 90% of the risk. These risk variants of small effect size span the entire genome and are associated with the disease. If this model holds true in SLE, similar to other polygenic traits like height, a core set of risk alleles modifying core disease genes/pathways are likely responsible for the majority of genetic risk, with approximately 1,000,000 independent haplotypes each contributing a small amount [45].

5. GENETICS IN SLE

A Brief Background

The hereditary component in the development of systemic lupus erythematosus (SLE) is significantly substantial, accounting for approximately 66% of the heritability based on studies involving twins. In recent years, research utilizing genome-wide association studies (GWAS) has enhanced our knowledge regarding the genetic factors influencing SLE. GWAS, an unbiased method, employs arrays of single nucleotide polymorphisms (SNPs) spanning the entire genome to genotype 500,000 to 5,000,000 SNPs in both SLE patients and healthy individuals. By identifying and focusing on regions associated with the disease, high-density SNP analysis has revealed differences in allele frequencies between patients and

healthy controls, suggesting potential disease-causing variants or their proxies. Up to now, approximately 100 genetic loci linked to SLE susceptibility have been pinpointed, primarily in European and Asian populations, elucidating around 30% of the heritability of SLE [46].

Classical And Non-Classical Human Leukocyte Antigen (HLA) Locus In SLE

Among the genetic loci studied, the major histocompatibility complex (MHC) region on chromosome band 6p21 is recognized as the most diverse in the human genome, encompassing MHC class I (HLA-A, -B, -C, -E, -F, and -G), class II (HLA-DP, -DM, -DO, -DQ, and -DR), and class III genes (complement system and inflammatory genes) [102]. Due to the considerable challenges posed by the high genetic variability and linkage disequilibrium within and around HLA genes, typing classical HLA alleles and identifying causal genes and variants in large populations has been difficult and expensive using traditional genotyping methods [47]. However, HLA imputation offers a solution by accurately predicting individual-level classical HLA alleles at a two-field resolution based on neighboring SNPs and ethnicity-matched reference data. This approach has been successfully applied in large-scale genetic studies of autoimmune diseases like systemic lupus erythematosus (SLE) [48,49].

In the MHC region, the main genetic signal associated with SLE has been pinpointed to HLA-DRB1 in the class II regions or the HLA-DRB1-associated long-range haplotypes in various ancestral groups. However, the identification of specific genetic variants driving SLE development has been challenging due to the complex ethnically specific linkage patterns and allelic heterogeneity, leading to inconsistent associations across populations [103]. For in-stance, different alleles of HLA-DRB1 were found to be more prevalent in SLE patients of Asian or European descent [104]. Recent research has revealed specific SLE risk haplotypes in MHC class II alleles shared among different ancestries, highlighting the importance of understanding ethnic differences in the genetic associations of the disease [50,51].

In addition to classical alleles, the analysis of HLA amino acid residues has provided insights into the ethnic-specific associations with SLE. By examining specific amino acid positions in HLA-DRB1, researchers have identified critical residues linked to SLE susceptibility across different populations [105,106]. Furthermore, studies have shown that certain amino acid changes in major HLA genes are associated with primary SLE signals, particularly at key positions like 11 and 13 in HLA-DRB1. These findings underscore the importance of amino acid-level analysis in unraveling the complex genetic basis of SLE [52,53].

Given the vital role of HLA molecules in autoantibody production, investigations into the impact of SLE-associated HLA variants on autoantibody generation and lupus-related tissue damage are ongoing. Notably, specific amino acid positions in HLA molecules have been linked not only to SLE susceptibility but also to autoantibody production, particularly in driving lupus nephritis [107]. Studies have also revealed associations between certain amino acid residues in the peptide-binding groove of HLA class I and II molecules and a higher risk of SLE, as well as autoantibody production in different populations. These findings shed light on the mechanisms underlying SLE development and the potential role of specific HLA variants in autoimmune responses [54].

Non-HLA Loci In SLE

The complex genetic basis of systemic lupus erythematosus (SLE) is supported by numerous disease-associated genetic regions with small effects that meet the significance threshold for SLE association. The contribution of HLA and non-HLA variants to phenotypic variation in SLE has been estimated at 2.6% and ~28%, respectively [108]. With increasing sample sizes in genetic studies, detecting small-effect variants associated with SLE has be-come more powerful, leading to the identification of additional risk loci [109]. Ancestral analysis using SNP arrays specific to different ethnicities has facilitated the discovery of new SLE loci and improved the localization of causal variants using robust statistical and bioinformatics approaches [55].

As of the time of writing, approximately a hundred non-HLA loci have been linked to susceptibility to SLE. Most of these signals are due to common variants with modest effects that also impact the risk of other inflammatory conditions. For example, a high-effect variant in the NCF1 gene has been identified in ethnically diverse populations, affecting the production of reactive oxygen species in patients with SLE and other autoimmune disorders [110,111]. Reduced copy number of NCF1 has also been associated with increased SLE susceptibility. While some large-effect common variants in NCF1 remain undetected due to insufficient coverage in existing SNP arrays [56].

International collaborative efforts in SLE genetics involving diverse ancestral populations have not only identified reliable SLE loci explaining part of the heritability of SLE, but also highlighted variability in SLE variants across different

ancestries [112]. Cross-ethnicity meta-analyses between Chinese and European populations have shown substantial similarities in the genetic basis of SLE, with consistent association signals and effect estimates across reported risk loci. Population-specific differences in SLE susceptibility can be attributed to variations in allele frequencies [57].

Evaluating individual genetic susceptibility to SLE can be done by calculating a Weighted Genetic Risk Score (WGRS), based on the number of risk alleles at different loci in an individual weighted by their respective odds ratios [113]. Studies have shown that populations with high frequencies of SLE risk alleles tend to have a higher prevalence of SLE. Furthermore, a higher WGRS for SLE is associated with early onset and more severe manifestations of the disease, indicating a stronger genetic predisposition to SLE and a less favorable prognosis [58].

4. CONCLUSION

The exploration of genetic components in systemic lupus erythematosus (SLE) has significantly advanced our understanding of this complex autoimmune disorder. Through genome-wide association studies (GWAS) and other genetic analyses, over 183 loci have been linked to SLE susceptibility, underscoring the polygenic nature of the disease. These studies highlight the crucial role of both monogenic and polygenic factors, with monogenic forms often presenting early in life due to specific genetic defects, particularly in the complement pathway, and polygenic forms emerging from a combination of multiple genetic variants and environmental influences.

The major histocompatibility complex (MHC) region, especially HLA-DRB1, remains a critical focus due to its significant association with SLE across various ethnic groups, despite the observed ethnic-specific variations. Non-HLA loci also play a substantial role in the genetic predisposition to SLE, with many common variants contributing modestly but cumulatively to disease risk.

While advancements in genetic research have provided valuable insights into the eti-ology and pathogenesis of SLE, challenges persist in translating these findings into clinical practice. The development and application of polygenic risk scores (PRS) hold promise for improving diagnosis, prognosis, and personalized treatment strategies, though their current utility is limited by the complexity of the genetic architecture and the need for more extensive, diverse population studies.

Future research efforts must focus on further elucidating the functional mechanisms of identified genetic variants, understanding gene-environment interactions, and addressing disparities in genetic studies across different populations. These endeavors are essential for advancing therapeutic development and achieving more effective management of SLE, ultimately improving patient outcomes.

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