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Systemic lupus erythematosus as a genetic disease

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Abstract

Systemic lupus erythematosus is the prototypical systemic autoimmune disease, as it is characterized both by protean multi-organ system manifestations and by the uniform presence of pathogenic autoantibodies directed against components of the nucleus. Prior to the modern genetic era, the diverse clinical manifestations of SLE suggested to many that SLE patients were unlikely to share a common genetic risk basis. However, modern genetic studies have revealed that SLE usually arises when an environmental exposure occurs in an individual with a collection of genetic risk variants passing a liability threshold. Here, we summarize the current state of the field aimed at: (1) understanding the genetic architecture of this complex disease, (2) synthesizing how this genetic risk architecture impacts cellular and molecular disease pathophysiology, (3) providing illustrative examples that highlight the rich complexity of the pathobiology of this prototypical autoimmune disease and (4) communicating this complex etiopathogenesis to patients.

1. Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune syndrome that despite diverse manifestations is unified by the presence of humoral autoimmunity against

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Appendix A. Supplementary data

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components of the nucleus. The autoantibodies in SLE bind cognate autoantigens, leading to immune complex deposition and tissue damage. Because of the diverse clinical manifestations, optimal rules for SLE classification and the problem of whether SLE represents multiple diseases with a final common pathway leading to disease or an amalgamation of pathophysiologically linked diseases both remain areas of some controversy [1–8]. Further, overlap with other related conditions is often part of SLE classification, as many SLE patients (up to 40%) [9] also have antiphospholipid antibodies or have overlap autoimmune disease syndromes, most prevalently secondary Sjogren's syndrome (up to 25%) [10]. Given the diversity of possible syndromic combinations that could satisfy criteria for SLE classification, one might expect that genetic studies would be unrevealing. However, early studies of genetic linkage in multiplex lupus families and more recent studies of genome-wide genetic association have revealed numerous genetic risk factors for the development of SLE and specific disease manifestations. Together, this list of genetic risk factors for SLE now contains at least 183 loci (Supplemental Table 1). These studies reveal a spectrum of genetic factors that include monogenic routes to disease that are more common in childhood onset SLE and polygenic plus environmental routes that are more common with SLE onset later in life. They highlight several pathways that go awry in SLE patients on the path to anti-nuclear autoimmunity and disease, including: generation and clearance of immune complexes containing necrotic (or NETotic) cell debris, the innate immune pathways that restrain autoimmune responses against nuclear components, and the pathways that govern the development and maintenance of autoreactive lymphocytes (Supplemental Fig. 1, Supplemental Tables 1–3).

2. Epidemiology and heritability of SLE

Recent studies estimate SLE incidence of 0.3–31.5 cases per 100,000 individuals per year with prevalence estimates of 3.2–517.5 cases per 100,000 individuals [11–13]. SLE clusters in families with sibling risk ratio (λ_S) estimates in SLE ranging from 8 to 29 [14–17]. In addition, other autoimmune diseases [17,18] and intermediate phenotypes (i.e. clinical features, SLE-associated autoantibodies, type I interferon) also cluster in the families of individuals with SLE [19–22]. The explanation of phenotypic variance due to heritability has been estimated to range from 44 to 66% for SLE [17,23] with an estimated 26% and 30% of phenotypic variance due to shared and non-shared environmental factors, respectively [17]. (44 + 26 + 30 = 100%) With respect to the sibling recurrence risk ratio (that is, lambda S: the increased *relative risk* of disease that siblings of disease cases have over the general population), SLE is similar to other immune-mediated inflammatory diseases, higher than rheumatoid arthritis (RA, lambda S = 8), about the same as multiple sclerosis (λ_S = 20) and less than Celiac Disease and Primary Biliary Cirrhosis (CeD, PBC, λ_S = 60, 100 respectively) [24]. Of course, due to difference in underlying population disease prevalence, this corresponds to *absolute risk* to siblings of affected of 2% (SLE), 8% (RA), 2% (MS), 3% (CeD) and 0.8% (PBC) [24]. In comparison, respective estimates of the heritability and λ_S are ~20% and 2.3 for myocardial infarction [25], 20–80% and 3 for type 2 diabetes [26], and 35% and 2.6 for gout [27].

3. Environment, ancestry, race, ethnicity, sex, gender and SLE risk

It has been reported that SLE risk and clinical expression vary on the basis of race, geography and sex at birth, with the highest prevalence and greatest severity observed in females from several non-European derived populations [11–13,28–30]. For example, a recent cause of death analysis indicated that SLE is the 10th leading cause of death in females aged 15–24, whereas it is the 5th leading cause of death in females aged 15–24 in both African-American and Hispanic populations in the US [31]. It is tempting to speculate whether these differences could be due to genetic divergence [32] related to continental ancestry differences that characterize these populations [33]. It is important to note that population-level genetic differences arising from divergence is estimated to account for at most 16% of genetic variability in human populations [32] with the bulk of genetic variation arising from within population differences. The temptation to attribute population-level prevalence and severity differences to divergent genetic factors is due in part to examples of genetic variants with outsized impacts in other disease states (i.e. *APOL1* variants associated with risk for ESRD and protection from African sleeping sickness or *SLC16A11* and risk for type 2 diabetes in Mexican Americans) [34]. Disease risk alleles such as these that are only found in one continental ancestral population, presumably arise due to random chance and come about through historical founder or bottleneck effects. It is important to note, however, that based on twin studies, concordance rates of SLE for monozygotic twins are estimated to be approximately 25% [35–37]. While important population-level differences in SLE risk and severity have been described [38–40], these genetic risk factors need to be appropriately placed within the broader risk context in which they operate. That is, truly understanding the causes for observed population-level differences in prevalence and severity will require longitudinal studies comparing the relative contribution of systemic structural factors, environmental exposures, access to healthcare and population-level genetic differences to both SLE risk and the severity of disease expression, as has been outlined elsewhere [24,41]. It is neither fair to assume that population-level differences are due to underlying genetic differences nor that they are not. While either case could ultimately be proven true or true to a certain extent (that is, if population-level genetic differences are found to explain some of the increased risk of SLE), care must be taken to avoid perpetuating population-level health disparities by inaccurately attributing or inaccurately not attributing population-level differences to genetic causes [42–45]. We suspect that either error is likely to exacerbate health disparities.

In sum, despite evident clinical and suspected underlying molecular heterogeneity in terms of pathophysiology, SLE is a disease where genetic factors substantively impact risk. As there is a genetic contribution to SLE risk, a next question is – what is the genetic architecture [46] of SLE?

4. Monogenic SLE

SLE, like most polygenic traits, is suspected to most commonly arise from polygenic interactions with an environmental trigger. However, several monogenic routes to SLE or lupus-like disease have been described [47,48].

Recent studies systematically surveying all known lupus genes found mendelian genotypes in 7% of a large collection of childhood onset SLE cases with a predilection for innate immune defects [49]. As the sequenced gene panel constituted known causes of SLE and genes in GWAS intervals there may be either unknown genes that will be discovered or causal genes that are distal to the association interval and were therefore not included in the sequencing panel. Thus, the estimate of 7% likely represents a lower bound for the proportion of monogenic routes to childhood onset SLE.

As to which monogenic routes lead to SLE, it has long been known that genetic deficiency of the early components of the classical pathway of the complement cascade leads to SLE [50–54]. Indeed, genetic deficiency of C1q is likely the most penetrant genetic risk factor for SLE – more than 90% of individuals described in the literature with C1q deficiency have classical features of SLE [50,51], though notably, without the sex bias seen in adult-onset SLE. Whether the rest of the monogenic routes to SLE should be considered in the same nosology as classic SLE or whether they represent distinct entities remains somewhat controversial. Regardless, numerous other single gene routes lead to diseases with features of SLE and the wide-spread adoption of whole-exome sequencing in pediatric onset disease promises to more comprehensively define the monogenic contribution to SLE risk on a prospective basis [56–65]

While it is not crystal clear where some of these genes fit, they can for the most part be roughly grouped within the same general framework that has been applied to polygenic disease: generation and clearance of immune complexes containing necrotic (or NETotic) cell debris, the innate immune pathways that restrain autoimmune responses against nuclear components, and the pathways that govern the development and maintenance of autoreactive lymphocytes. It is worth noting, however that several genes that impact both monogenic and polygenic disease have roles in more than one of these pathways (Supplemental Fig. 2). We have summarized the monogenic disease pathways in Table 1. Further, the interested reader can find several high-quality reviews in the references [47,48].

5. Polygenic SLE

Our current understanding is that in the typical SLE patient, an accumulation of polygenic risk factors combine with an environmental trigger and this combination pushes that individual's liability beyond the threshold for disease development. If this is the typical scenario, which genes/genetic loci are responsible? We present a non-comprehensive list of bona fide SLE risk variants gleaned from the NHGRI/EBI GWAS catalog in Supplemental Table 1. It is non-comprehensive, as numerous examples of genes identified by candidate gene studies have been described that would qualify for association above the genome-wide significant level ($P < 5E\text{-}8 = 0.05$/estimated 1,000,000 independent genomic regions [106]) for this list if they had been identified in a GWAS scan [107–109]. Importantly and similar to other polygenic diseases, the vast majority of SLE cases included in these studies are of European ancestry with substantially smaller representation of Asian ancestry individuals [110]. To date only two studies of SLE as the primary trait in Amerindian/Hispanic/Latin American ancestry individuals have been reported, one GWAS [111] and one Immunochip based study [38]. Only one Immunochip based study [38] and no GWAS has been reported

in African Ancestry individuals with SLE. Genetic causes ultimately may not explain the increased prevalence and severity of SLE in African-American and Hispanic individuals in the US. However, without the knowledge of the genetic factors at play in these populations, the relative contribution of systemic structural factors, environmental exposures, access to healthcare and population-level genetic differences to SLE risk and the severity of disease expression cannot be determined.

As for the reported genetic associations with SLE, numerous studies have been carried out to begin to understand which genetic variations most likely explain disease risk (fine mapping studies) and which biological function(s) of these genetic variations mediate disease risk (functional studies). We present a non-comprehensive summary of the index variants in 183 regions associated with SLE at the genome-wide significant level ($P < 5$ E-8) from the EBI/NHGRI GWAS catalog [110] in Supplementary Table 1. Indeed, moving from an genome-wide genetic association scan peak to biological function is a central challenge for the broader field of complex human genetics [112]. Despite this challenge, understanding the biological risk mechanisms of these variants will perforce nominate novel therapeutic approaches for SLE and other autoimmune diseases. Several examples serve to highlight the complexity of understanding how these disease-associated genetic variations mediate SLE risk and the challenge for the field.

First, turning to the example of the NCF1.Arg90His, it would seem that identifying a non-synonymous (that is amino acid sequence altering) genetic variant as the most strongly associated with disease would make functional characterization a straightforward endeavor when compared to defining the function of a regulatory variant. The case of PTPN22.Arg620Trp serves as a counter-example. As one of the first described autoimmune risk alleles and as a risk allele for multiple autoimmune diseases, it has been studied extensively. Recent reviews have identified six independent potential mechanisms through which this non-synonymous variant could confer risk for autoimmune disease [113,114].

Second, if multiple plausible candidate mechanisms arising from amino acid sequence change were not complicated enough, not all changes in DNA that affect amino acid sequence merely affect amino acid sequence. A non-synonymous coding change in *ITGAM*, ITGAM. Arg77His, confers risk for SLE in multiple populations [115,116]. However, follow-up studies also identified the risk variant of the single nucleotide polymorphism that alters ITGAM amino acid sequence also alters the function of a transcriptional enhancer that regulates *ITGAM* mRNA levels [117].

Third, it is important to note that the broader field of complex human genetics widely believes that most GWAS identified causal variants will result in gene expression regulatory functional effects [112,118,119]. Indeed, there are examples of common complex genetic disease associated variants that alter long-range regulation of genes hundreds of kilobases away [120,121]. With this in mind, it would seem that if a particular disease associated variant was shown to impact expression of a candidate gene in the region, then it should probably be the causal variant. This was the supposition of early studies of the genetic association of SLE with IRF5, a canonical type I interferon pathway gene. Indeed, it has had numerous proposed causal variants, all with functional biological effects [122–

130]. However, the fine mapping of these putative causal variants did not stand up to statistical scrutiny once this locus was examined with sufficiently powered sample sizes and genotyping of sufficient density [131]. The association with *STAT4* provides a related example. Since early studies identified variations within *STAT4* with rheumatoid arthritis and SLE [132], the biological effects of this association have been attributed to STAT4 activity [133]. However, a follow-up study demonstrated that, rs11889341, the variant with consistent association with SLE across multiple ancestries does not regulate expression of *STAT4*, but does regulate expression of a nearby gene, *STAT1* [134].

Fourth, even though the biological effects of most polygenic variants are mediated through gene regulation, not all SLE associations are as straightforward as *STAT4* and *IRF5*. Indeed, recent work has defined a novel SLE risk enhancer more than 15 kb upstream of the promoter for *MIR3142HG*, a long non-coding RNA gene from which micro-RNA-146A (mir-146A) is processed [135]. The protective allele of this immune cell specific enhancer loops to physically associate with the mir-146A promoter and drive expression of this gene, which subsequently inhibits type I interferon production in PBMCs. The risk allele leads to altered NF-kB and BHLHE40 binding and this alteration inhibits the epigenetic modifications and chromatin conformation, such that expression of this immune-regulatory non-coding RNA is decreased.

Finally, if the possibilities for functional SLE risk variants were not complicated enough, one last consideration is *BLK*. BLK is a B-cell expressed kinase downstream of the B-cell receptor. Prior work identified promoter proximal polymorphisms affecting expression throughout B-cell development [136,137]. However, *BLK* is present on a large polymorphic inversion on chromosome 8 that varies across global populations and in European ancestry populations has been shown to modulate SLE risk independently of the two promoter polymorphisms [138,139]. It presumably does so through long-range promoter/enhancer interactions and changes in 3-D chromatin structure.

In light of the typical polygenic genetic structure of SLE, several questions arise: are aggregate polygenic risk alleles useful in diagnosis or prediction of SLE? How much risk does the aggregate polygenic risk allele burden contribute to SLE in the typical scenario? How large a cohort of SLE patients and control individuals will be necessary to define all of the polygenic risk loci for SLE? How many independent polygenic risk loci will be found in SLE?

The typical approach to address several of these questions has been to use an effect size (odds ratio or beta) weighted average of the risk allele genotype for a subset of independent variants with evidence of genetic association and use this to calculate a so-called polygenic risk score (PRS). As an important aside, our discussion of the current state of polygenic risk scores likely only applies to European and East Asian ancestry populations, as most of the GWAS scans performed have been in these ancestral population groups and the application of polygenic risk scores across populations may [39,140] or may not prove useful, potentially exacerbating existing health disparities [45].

As for the utility of PRS in distinguishing SLE cases from controls, not surprisingly, given the problem of missing heritability and the monozygotic twin concordance rate of ~40% at most, the typical difference in mean PRS of only ~10% with areas under the receiver operator characteristic curve of at most ~0.71 [39]. While application of PRS to SLE may help us better understand the ancestral population genetic contribution to population-level differences that are observed in SLE severity and prevalence [140], they are (in their present state) unlikely to be particularly useful for classification when applied to broad populations that include a mixture of both SLE cases and controls. Despite this drawback, that PRS is not well powered to distinguish SLE cases from controls, they may yet prove useful in select circumstances. Langefeld, et al. reported that in individuals in the highest quartile of genetic load in European ancestry SLE patients, increased risk exhibited nonlinear increases in disease risk [38]. This analysis indicates that after a certain genetic liability threshold is met, disease development much more likely than in individuals with lower genetic risk. Indeed, those with the highest genetic load have absolute risk from 2 to 10% absolute risk (odds ratio of 25–125 X prevalence of 84.7 per 100000 [13]). Separately, Knevel, et al. retrospectively applied PRS scores to aid in the differential diagnosis of patients presenting with undifferentiated inflammatory arthritis [141]. In that report, a probability was derived for each of five common forms of inflammatory arthritis (rheumatoid arthritis, gout, SLE, spondyloarthritis and psoriatic arthritis) weighted based on PRS calculated for each disease. Using this approach, they achieved an area under the receiver operator curve >0.8 in independent cohorts of patients who had subsequently been diagnosed by a rheumatologist with one of these forms of inflammatory arthritis. These studies suggest that while our current polygenic risk models cannot yet (and may not ever, given the monozygotic twin concordance rate of ~40%) be able to distinguish SLE cases from controls [39,61,142,143], evaluation of the polygenic risk contribution to SLE may still play a role in prognosis [142,143], diagnosis or differential diagnosis of SLE in the future. In their current state, polygenic risk scores likely underestimate the overall genetic contribution to SLE in any given individual for at least five reasons. First, while risk loci or risk intervals have been identified, in many cases the causal variant is not yet known. It is not uncommon for the causal variant to carry a different relative risk than the first GWAS-identified markers. This is a function of differences in local linkage disequilibrium and minor allele frequencies between associated markers and the causal variant which may not have been well-genotyped or well-imputed. Second, the contribution of rare variants in disease genes appears to contribute in part [144–148], but the extent of this contribution remains incompletely defined at present. Third, it seems likely that we have not yet defined all of the risk variants that contribute to SLE. In other disease phenotypes, integration of genome-wide genetic information into polygenic risk scores leads to scores that in aggregate have been reported to be comparable to monogenic mutation risk [149,150]. Fourth, while several environmental risk factors for SLE have been identified, the impact of exposome and subsequent interactions between the epigenome and genetic risk factors likewise remain incompletely defined. Similarly, in other phenotypes, integration of exposome- and genome-wide information into polygenic risk scoring leads to improvement in test characteristics to those more closely approximating clinical tests [151]. Fifth, integration of genetic information of family members drastically reduces the sample sizes required for a given phenotype prediction accuracy with PRS [152]. As these factors contributing to decreased

accuracy of current PRS models are addressed in SLE, PRS may yet be proven to have clinical utility for this disease.

How many risk variants contribute to SLE risk and how large a GWAS samples size will be required to define them all? The largest GWAS study to date employed a total sample size of 208,370 individuals of East Asian Ancestry (13,377 SLE cases and 194,993 control individuals), though a large portion of the controls were recruited as part of population-wide biobanking efforts [153]. This GWAS identified 113 genetic risk regions for SLE in East Asian ancestry individuals, several of which include multiple independent effects [110,153] In our analysis, there are 183 loci reported in the GWAS catalog. (See Supplementary Table 1). This is an incomplete list, as several other risk intervals have been identified in fine mapping or follow-up studies that are significantly associated with SLE at the genome wide level ($P < 5E-8$) but were identified as part of fine mapping or GWAS follow-up studies and therefore are not included in the GWAS catalog. The associations with *IRF3* and *GPR173* are both examples that have been reported to be associated with SLE at the genome-wide level, but are not part of the GWAS catalog [108,109] It has long been known that for common complex disease, GWAS sample size (on a logarithmic scale) directly correlates with the number of loci identified [154,155]. Further, the number of independent haplotypes that maximize the area under the receiver operating characteristic curve in terms of differentiating cases of common polygenic inflammatory disease from control individuals is in the thousands [156] and similar findings of hundreds of GWAS markers maximizing the AUC were recently also reported for SLE [39]. Taken together with analyses estimating that for most common polygenic traits GWAS hundreds to thousands of risk loci explain the first 50% of risk, typical sample of ~1,000,000 will be required to generate polygenic risk scores that explain 90% of risk and at this level, thousands of risk variants of very small effect size spanning the entire genome are associated with disease [157]. Indeed, these estimates are in essence very similar to the omnigenic model of complex polygenic traits. In this model, the most strongly associated variants impact genes operating in core disease pathways/cell- or tissue-types, but the whole of the genome is associated at an extremely low level [158]. If this model holds true in SLE as it appears to have in other polygenic phenotypes, such as height [159], then a core set of risk alleles that modify the action of core disease genes/pathways are likely to explain the bulk of genetic risk, but ultimately each of the estimated ~1,000,000 independent haplotypes present in the genome [106] will contribute some nearly infinitesimal amount.

6. Overlap of Monogenic SLE with Polygenic SLE

One argument for lumping monogenic SLE together with polygenic SLE, is the observation that several of the genes that lead to monogenic SLE either lie within risk loci or have been established as the putative biological risk effectors in large polygenic SLE cohorts (Supplemental Fig. 3). This overlapping list includes: complement component *C4* [160], *TREX1* [161], *IFIH1* [162], *IKZF1* [163], *DNASE1L3* [164], *RELA* [94] and *RNASEH2C* [38,67,153]. The overlap also includes two genes that cause chronic granulomatous disease [165] and where loss of function variants increase risk for SLE: *NCF1* & *NCF2* [166,167]. For several of these genes, *TREX1*, *IFIH1*, *NCF1*, *NCF2* and *DNASE1L3*, there is correspondence in terms of mutations present in monogenic SLE

cases and observation of non-synonymous risk variants in large SLE cohorts. This is not yet clearly the case for *RNASEH2C* and *RELA*, an exception that serves to highlight one of the challenges of assigning causality to biological risk effectors in polygenic disease. Mutations in both *RNASEH2C* and *RELA* have been reported as monogenic routes to SLE or lupus like disease [67,94]. However, both lie within an SLE genetic association interval on chromosome 11 that has been associated with SLE in cohorts derived from multiple continental ancestral groups across the globe [38,110,111,140,153,168]. Whether the biological risk effector for this genetic association relates to the function of *RNASEH2C*, *RELA*, both or neither (in one study [38], the most strongly associated variant lies within the canonical promoter of another gene, *OVOL1*, loss of which has recently been reported to lead to inflammatory skin disease in mice [169]) has not yet been established. Thus, it seems that each enumerable combination of biological risk effectors could plausibly explain the genetic association at the locus that spans *RELA-RNASEH2C-OVOL1*.

The example of *DNASE1L3*, which encodes a secreted deoxyribonuclease, further lends support to the idea that multiple biological mechanisms could be responsible for any given GWAS association signal despite the presence of monogenic risk genes within the association interval. Initial GWAS studies revealed association with PXK [115], a phox-homology kinase that plays a role in B-cell receptor internalization [170]. Subsequently, genetic association in this region was reported for autoimmune diseases related to SLE, systemic sclerosis [171,172], rheumatoid arthritis and type 1 diabetes [173]. However, these non-SLE autoimmune disease associations were due to non-synonymous variation in a nearby gene, *DNASE1L3*, one of the routes to monogenic lupus. Further, neutralizing autoantibodies directed against DNASE1L3 have been observed in >50% of sporadic SLE cases with lupus nephritis and correlate with disease activity measures [174]. A recent follow-up genetic association study reported two independent association signals for SLE in this region, one signal that parsimoniously converges on the non-synonymous variant in *DNASE1L3* that confers risk for multiple autoimmune diseases and another that localizes to the region containing *PXK*, over 200,000 bp away [164].

Related to the overlap between monogenic and polygenic routes to SLE are several questions that are still in the early stages of investigation, but promise to further illuminate the genetic structure of SLE.

Are private mutations segregating with proband status a common finding in multiplex families with SLE?

Do sporadic cases of childhood onset SLE commonly arise from *de novo* gene mutations?

How commonly does *de novo* mutation in monogenic SLE genes explain discordance for disease in monozygotic twin pairs, where one of the twins is a proband?

Do some sporadic cases of SLE represent a mixture of polygenic and monogenic risk architecture?

Do rare, functional variants that are not well captured by current GWAS methodologies also contribute to risk at polygenic SLE risk loci?

Do somatic mutations contribute risk in the approximately 7–15% of SLE patients who present with disease onset later in life (age > 50–65 years)?

Several groups have started to address these questions. As to the question of private mutations, Delgado-Vega, et al. recently reported the results of an investigation in two large multi-case Icelandic familiies [65]. Whole exome sequencing was performed on the most distantly related individuals with SLE in each pedigree and targeted genotyping was performed to allow for analysis of co-segregation with proband status. Filtering novel variants that were potentially pathogenic yielded a list of nineteen novel candidates for SLE. Those that co-segregated with disease were independently analyzed in a population-based cohort to see if there was an increased burden of mutation or aggregation of rare variants within–/near- genes in SLE patients greater than would be expected by chance. This analysis identified *FAM71E1* as a novel candidate for SLE risk. Curiously, the mutation they reported in *FAM71E1*, while rare, does not appear to be private. Indeed, the global population frequency reported by dbSNP is 0.7% in a survey of 28,538 individuals [175]. Subsequent work delineated a role for this gene as a regulator of type I interferon production in response to cytosolic DNA through its interactions with RAB2B, cGAS and STING [176,177]. Since other regulators of the cytosolic DNA sensing pathway that include cGAS and STING impact monogenic SLE, these findings agree with and extend our understanding of rare variation in SLE. Larger multiplex family studies looking for private mutations promise to further extend our understanding of the genetic architecture of SLE.

As to the questions surrounding the role of de novo variation in SLE, several groups have searched for *de novo* mutations. The design of these studies exploits the observation that every human being who is born is a mutant, since the de novo germline mutation rate is ~38 mutations per child and 1.2% of these mutations are in exons [178]. These studies typically employ whole-exome sequencing (see [179] for a review) of individuals with SLE attempting to enrich for *de novo* mutations by, for example, looking only at individuals without a family history of SLE (or another autoimmune disease) who have onset of disease during childhood, assuming that the presence of SLE in these individuals who lack risk from family history is more likely to arise from mutations occurring in the germline of the individual with disease.

Several groups have investigated whether *de novo* mutations explain SLE risk by sequencing affected child-unaffected parent trios. Altogether, 101 such trios have been sequenced [180,181] One study identified potentially contributory *de novo* mutations in/affecting *MAZ*, *LTB4R2*, *ISX*, *RBM10*, *SMARCA2*, *PPARA* [180]. The other study found several candidate *de novo* mutations and was able to identify an excess of rare variation in *DNMT3A* and *PRKCD* in an independent population-level cohort and *C1QTNF4*, which was bioinformatically determined to be intolerant to missense variation (ExAC gene-level constraints Z = 3.17) and the *de novo* mutation was shown to impact NF-kB signaling [181]. In a related study, the presence of disease explanatory *de novo* mutation was assessed in a monozygotic twin pair that was discordant for SLE [182]. While divergent missense *de novo* mutations were not able to be validated, the twins did diverge for a copy number variation in a histone gene cluster that has been correlated with disease activity in a large cohort of

pediatric lupus patients [183]. Future application of this kind of study design promises to add to and refine the list of monogenic causes of SLE.

As to whether sporadic cases are more likely to arise from polygenic versus monogenic contribution to risk, simulation studies indicate that under the assumption of polygenic genetic architecture, sporadic cases are expected to be relatively common [148]. For SLE, under the assumption of 0.3% disease prevalence, λ_S of 30 and heritability of 65%, both theoretical and simulated results predict >95% of cases would be sporadic. Despite these expectations, many rare variant or monogenic associations have been reported in SLE. Therefore, it may be that some proportion of the cases that are observed arise from a contribution both rare or monogenic contributions along with polygenic contributions. Almlöf, et al. sought to address this in a survey in 71 SLE patients [61]. They calculated scores for polygenic SLE risk using ImmunoChip data for patients and their parents and resequenced the patients. Strikingly, they found that one out of seven SLE patients inherited a heterozygous rare missense variant in genes described to cause monogenic SLE and that this was more likely to be inherited from the parent with the lower SLE risk in terms of polygenic risk score.

Similarly, Belot, et al. recently sequenced a panel of 147 genes containing all known and probable SLE causing genes in a collection of 117 childhood onset SLE probands [49]. In addition to providing a lower bound for childhood onset SLE cases arising from monogenic routes, their study provides additional data to estimate the relative contribution of individuals with both polygenic and monogenic risk. In addition to the ~7% of childhood onset SLE patients in their cohort who had mendelian genotypes, they found that 27% of SLE probands and 4.6% of controls had at least one rare, predicted damaging mutation in their panel of known and probable SLE causing genes. Allelic forms of genes that confer SLE resistance may be present in the controls. Thus, these data provide a similar lower bound estimate that 15–20% cases of childhood onset SLE arise from a combination of heterozygosity for a rare or monogenic variant and polygenic/environmental risk factors. We suspect that the relative proportion of both monogenic and mixed monogenic/polygenic/environmental risk models decreases with age at diagnosis, though to our knowledge, these studies have not yet been completed. In addition to cohort and population-based surveys of monogenic and polygenic disease risk interaction, family-based studies promise to reveal whether interaction between monogenic and polygenic risk alleles is the norm. Initial studies suggest that if not typical, these kinds of interactions are likely to be common [70].

Taken together with examples of rare highly penetrant genetic variants, these findings help estimate the relative monogenic and polygenic contribution to disease risk. It is worth noting, that more robust estimates would be expected in terms of both monogenic and polygenic disease once the full list of causal polygenic and monogenic SLE risk alleles is defined. For polygenic SLE disease risk alleles, this list is still being refined – not all putative causal variants have been identified at SLE risk loci (Supplementary Table 2). For monogenic disease, it is safe to assume that our current monogenic SLE risk gene lists (Table 1) are likewise incomplete, as several recent reviews of monogenic SLE have seen an ever-lengthening list of monogenic SLE genes as next-generation sequencing is applied to ever larger cohorts of childhood-onset SLE patients.

In sum, the current understanding of the field is that most cases of adult-onset SLE arise from polygenic risk factors interacting with an environmental trigger (Fig. 1). This is supported by the prediction that even in diseases with a polygenic genetic architecture, sporadic cases are still expected to predominate [184]. Nonetheless, as discussed above, there is considerable overlap between polygenic and monogenic SLE risk genes and the actual genetic architecture of individual SLE patients is just beginning to be revealed to in many cases constitute a mixture of polygenic and monogenic risk. As SLE cohort sizes increase, more population-level genetic studies are able to be carried out due to the decreased cost of sequencing and efforts organized around population-level and EMR-based genetic studies, our understanding of the true genetic architecture of SLE will continue to be refined. We have summarized key variables influencing individual risk and severity of SLE in Table 2. (Table 2)

7. Role of somatic mutations in SLE

One might ask whether somatic mutation contributes risk in patients with SLE onset later in life. In an analogous manner to inheriting a rare monogenic SLE risk variant in the context of higher polygenic risk score from one parent, we might expect that individuals who develop SLE later in life, but have intermediate to low polygenic risk scores would either require a strong environmental influence or might have a late-onset genetic lesion that amplifies their underlying disease risk. The recent description of the VEXAS (vacuoles, E1 Enzyme, X-linked, autoinflammatory, somatic) syndrome provides an example of what might be occurring in SLE. This syndrome of adult-onset myeloid driven auto-inflammation leads to various inflammatory and hematologic complications and is characterized by somatic mutations in *UBA1* [185]. Indeed, many patients meet classification/diagnostic criteria for Relapsing Polychondritis and a sequencing study of a Relapsing polychondritis cohort has revealed that ~7% of RP patients carried a somatic mutation in *UBA1* [186]. That somatic mutations in a single gene could cause an adult-onset inflammatory disease is a striking finding. Are similar mechanisms in part contributing to the phenotype of late-onset SLE? Late-onset SLE tends to present with more mild disease manifestations and disease course, but with an increase in mortality and damage that has been attributed to accumulation of comorbidities that correlate with aging [187–190]. There are several possible explanations for the observed mild SLE manifestations – it may be that late-onset SLE patients merely bear less genetic liability than their younger-age at onset counterparts, or it may be that somatic mutations only affect a subset of cells within late-onset SLE patients, thereby limiting the severity of their disease manifestations. In autoimmune diseases like SLE, there are at least two potential mechanisms through which somatic mutations could precipitate disease: either through increased genetic risk (i.e. somatic mutations in polygenic or monogenic SLE risk genes) or mutations in the autoantigens themselves that lead to neoepitope formation. The latter situation has been described at least once – Bachmann, et al. previously described somatic mutation within the sequence that encodes the La autoantigen in a patient with both SLE and Sjögren's syndrome. This mutation led to expression of an alternatively spliced isoform of La protein and the development of autoantibodies against this mutant La was noted in SLE and Sjögren's patients in a larger cohort. Importantly, expression of this mutant form of La

in otherwise healthy mice led to the development of a lupus-like autoimmune disease [191]. As similar short tandem repeats as the one that gave rise to the mutant La protein are present in several autoantigen systems in a variety of autoimmune diseases, it has been proposed that this kind of neoepitope formation due to somatic mutation may represent a more general mechanism of auto-antigenicity in several autoimmune diseases [192]. As for the latter case – increased accumulation of somatic variations in late-onset SLE cases, comprehensive surveys of somatic mutation in SLE cohorts have not yet been carried out. However, with modern surveys of healthy tissue, there is increasing realization that many somatic mutations previously considered driver mutations in cancer are tolerated at a higher level than previously thought [193–197]. Application of similar next-generation sequencing somatic mutation survey techniques to SLE promises to increase our understanding and reveal the complexity of the genetic architecture of SLE. To date few groups have looked at somatic mutation in terms of genetic risk at all. However, a study of childhood-onset SLE with lymphoproliferation revealed putative causal somatic mutations in *NRAS*, *TNFAIP3* and *PI3KCD* in a cohort of seven patients with SLE and lymphoproliferation [62]. In contradistinction to innate immune pathway disruption in childhood onset SLE, we expect that mutations that confer survival advantage or apoptosis resistance (such as *PRKCD*) in an autoreactive lymphocyte would result in somatic, adult- or elder-onset SLE in a similar manner to somatic mutations in *FAS* leading to autoimmune lymphoproliferative syndrome (ALPS) [198–200].

8. Missing heritability in SLE

There is divergence between the observed heritability of SLE and that explained by common genetic variants identified by GWAS studies. This divergence, termed the “missing heritability” problem of GWAS has been observed in many complex diseases with polygenic inheritance patterns. Some of the divergence could be explained by differences in heritability estimate methods and results across time and populations. For example, a recent study using the entire population of Taiwan yielded an estimate of SLE heritability of 44%, substantially lower than prior estimates of ~66%, though differences in methodology and population-level differences could also potentially explain the difference in heritability estimates. Another potential source of this missing heritability is rare or *de novo* variation in SLE risk genes, as discussed above. That is, if rare or de novo variation substantially contributes liability for SLE, this might explain part of the gap. While initial population-level studies of other autoimmune diseases [144,145] have not supported a broader role for rare functional variants in contributing to this missing heritability, it remains possible that rare variants or *de novo* variants could substantively contribute in a subset of SLE patients. Indeed, resequencing studies of GWAS-identified SLE risk genes have identified an excess burden of rare functional variants in *ITGAM*, *BLK*, *BANK1* and in the regulatory region of several other GWAS identified SLE risk genes [146–148].

Another potential source where missing heritability could be hiding is within the GWAS signal itself. That is, association signals identified by GWAS commonly represent a set of variants that are in high linkage disequilibrium (that is inherited in a correlated manner) with one or more causal variants. Rarely, the index marker from a GWAS study does, in fact, turn out to be the causal variant [116,135]. More commonly, however, the causal

variant is not genotyped in any given study and resequencing, imputation or follow-up fine mapping studies are required to localize the putative causal variant(s) and develop arguments supporting functional links between these variants, causal gene function and intermediate cellular phenotypes that recapitulate what is seen in diseased individuals. (reviewed in [112]) If the causal variant(s) has/have not been identified then the risk estimates, made based on markers in LD with the causal variant, may be inaccurate. One example is the association of SLE with the Human Leukocyte Antigen locus on chromosome 6. This region has been associated with many other autoimmune diseases and in those diseases, it appears that specific mutations that alter the presentation of self-peptides by antigen presenting cells by class II major histocompatibility complex molecules are the major factors impacting disease risk at this locus. In SLE on the other hand initial GWAS and follow-up studies estimated the relative risk contributed by HLA in the 1.5–3-fold increased risk range for most variants with substantial allele frequency [38,115]. However, recent elegant work has shown that variation in copy number of *C4A* and *C4B* [160], the genes encoding complement component C4 drive the bulk of the increased liability at this locus. Whereas, the index variants identified by GWAS studies in SLE would have estimated the contribution of this locus to SLE relative risk at ~2, once the causal variants were identified, this risk estimate increased to ~7-fold change in relative risk dependent on C4 copy number and sex

9. Large risk effects in SLE are not quite oligogenic

A comprehensive survey of the relative monogenic and polygenic contributions to SLE risk has not been carried out. The resequencing studies by Almlöf, et al. [61] and Belot, et al. [49] represent important first steps towards defining whether and how polygenic and monogenic risk factors combine to drive risk in a particular individual with SLE. Applying similar approaches to larger population-based cohorts and family-based disease registries promises to further inform our understanding of what typically drives risk in SLE. Keeping in mind that even in polygenic diseases, sporadic cases are still expected to predominate [184], is there any evidence for oligogenic (that is a small number of disease genes that disproportionately contribute to disease risk [201]) inheritance in SLE? Indeed, there are several common genetic variations that increase the relative risk for SLE considerably more (> 2× relative risk) than is common amongst GWAS identified polygenic risk factors (Table 3). Notable amongst these risk factors are three examples that challenge prior dogmas or point to apparent paradoxes regarding SLE risk and underlying pathophysiology. Future studies aiming to define whether human SLE can arise from an oligogenic combination of moderately penetrant risk alleles as is the case in murine genetic models of SLE are, of course, warranted.

The first example is that of X-chromosome copy number. Based on studies demonstrating disease modulatory effects of sex hormones in murine lupus models, prior dogma held that the sex difference in SLE risk was due to sex hormones. This dogma persisted for so long that there are several trials documenting inefficacy of testosterone treatment for SLE [202,203]. Further, careful examination demonstrated that combined oral contraceptives were non-inferior to placebo looking at SLE flare as an outcome [204]. More recent studies have demonstrated that X-chromosome copy number confers increased risk for SLE, in contradistinction to the idea that hormonal differences predominately explain the difference

in SLE risk. This has been shown in several studies and large SLE cohorts have been noted to have increased rates of both Klinefelter Syndrome (47, XXY) and Trisomy X (47, XXX) relative to what would be expected based on their prevalence in the general population [168,205–207]. These findings agree with animal studies indicating that sex chromosome complement confers risk for lupus-like and multiple sclerosis-like disease in mice [208]. These data suggest the presence of a gene-dose effect in SLE and add a counterexample that challenges prior dogma that the sexual dimorphism observed in autoimmune diseases is due to hormonal effects [209]. Note that these data challenge and do not overturn the idea that sex hormones impact SLE risk. Indeed, sex hormones clearly impact immune responses that are important for the development of SLE (reviewed in [210,211]) and the paired observations that menopause is a risk factor for incident SLE [212] and while the risk for SLE begins around menarche, rates of incident SLE begin to trail off after menopause [213] suggest that female sex hormone changes likely contribute to SLE disease development. Curiously, while aneuploidy for 47, XXX is increased in SLE and Sjogren's Syndrome, this is not observed in other female predominant autoimmune diseases, rheumatoid arthritis and primary biliary cholangtis [207]. Suffice it to say, the increased female predominance of SLE is likely complex and not explained only simply by X chromosome copy number or by hormonal effects, but by a complex interplay of both. GWAS and candidate gene studies have identified variants in genes at several loci on the X chromosome that are robustly associated with SLE and might explain the putative X-chromosome gene dose effect. These include *TLR7*, Xq28 (*IRAK1*/*MECP2*) and *CXorf21*/*TASL* [168,214,215]. Curiously, these associations potentially implicate type I interferon production downstream of TLR7 signaling, a pathway that has long been known to be sexually dimorphic [213,216] and contains several other SLE risk genes (Fig. 2).

While incompletely understood, the role of type I interferon signaling in SLE pathogenesis is well-established, with recent FDA approval of type I interferon targeted therapies [217,218]. Even more curiously, type I interferon production downstream of TLR7 signaling is modulated both by sex chromosome complement and by the influence of sex hormones [219–221]. In the effort to deconvolute these effects, a recent study looked at this pathway in males, females and transgender individuals receiving cross-sex hormone therapy. That study found increased type I interferon production in response to a TLR7 ligand, R848, whereas testosterone levels positively correlated with type I interferon responses in the presence of one X chromosome and negatively correlated with type I interferon responses in the presence of two X chromosomes [222]. Future studies in large cohorts of transgender individuals receiving (or not receiving) cross-sex hormone therapy that seek to define whether and how this complex interaction between sex chromosome complement and sex hormone levels might also contribute to SLE risk promise to further our understanding of this strong genetic effect.

In an effort to understand the gene dose effect that has been proposed to explain sex chromosome aneuploidy association with SLE, one question that arises is, how might genes on the X chromosome exert biological effects? Typically, one of X chromosome is silenced or lyonized, so that gene expression is suppressed via epigenetic processes [223]. Indeed, a recent cohort study examining X-chromosome inactivation in the sizeable GTEx cohort across multiple tissue types revealed that X-inactivation escape is variable and incomplete

inactivation affects at least 23% of X-chromosome genes [224]. The prevailing hypotheses advanced for how these genes might confer risk despite lyonization is that they are either members of the small subset of genes that consistently escape X-inactivation [224], or they escape X-chromosome inactivation in certain disease relevant cellular contexts, such as lymphocyte activation[223,226,227]. Recent and future efforts to map genes that escape X-inactivation in lupus patients [225–229] and better understand the impact of sex hormones on SLE risk promise to improve our understanding of these substantial risk factor for disease development.

The second dogma challenging example is that of the association with HLA. While association of HLA has long been established for SLE and other autoimmune diseases, the complex linkage disequilibrium structure of this portion of the genome [230] has proven challenging to deconvolute. It was long suspected that in SLE, HLA risk alleles specifically altered antigen processing and presentation on MHC class II molecules [133] in a manner similar to that described in other autoimmune diseases, such as rheumatoid arthritis, where the specific MHC class II variants that confer disease risk exhibit altered binding and subsequent presentation of disease relevant self-antigens [231]. However, it was recently observed that genes for complement component C4 (*C4A* & *C4B*), which are located in the Human Leukocyte Antigen locus (HLA) on chromosome 6, appear to be the predominant contributors to SLE and Sjogren's syndrome risk at this locus [160]. At this locus, which has been associated with nearly every single immune-mediated disease that is known, C4 copy numbers explain most of the risk of SLE and Sjogren's Syndrome. Importantly, there also appears to be an additional, independent, contribution that is likely related to HLA class II expression levels from a locus in the XL9 region. Importantly, this variation in complement C4 copy number corresponds to 7-fold variation in disease risk and curiously, the partitioning of risk is sexually dimorphic with increased risk for SLE in males and protection from another sexually dimorphic complement-related condition, schizophrenia.

The third example is that of a non-synonymous coding sequence variant in NCF1, one of the genes for that when mutated leads to chronic granulomatous disease. This non-synonymous variant, NCF1.Arg90His, leads to reduced reactive oxygen species production and confers 2–3.5-fold increased risk of SLE as well as increased risk for Sjogren's syndrome and rheumatoid arthritis [166]. This apparent paradox – that variants that partially phenocopy mutations in this gene that lead to immunodeficiency also confer risk for autoimmune disease – highlights the link between primary immunodeficiencies and autoimmune disease [232,233]. Indeed, autoimmune diseases are observed to have higher prevalence in individuals with primary immunodeficiency (~25%) than the general population (~3%) [232–234]. Connecting back to monogenic paths to SLE, genetic deficiency of the early components of the classical pathway of the complement cascade leads to SLE. A distinction should be drawn between the role of complement and antigenic material clearance during the initiation of SLE and in the presence of established disease. Indeed, the presence of complement proteins is likely disease exacerbating once SLE has been established – they serve to fan the flames of immune complex driven inflammation as evidenced by the successful application of complement inhibitor therapy in refractory lupus nephritis and thrombotic microangiopathy associated with SLE [235,236]. Whether there is a broader role for complement pathway inhibition in SLE remains to be determined. The idea that

inappropriate clearance of dead cellular debris provides a source of immunogenic material to drive immunopathologic responses in SLE is not new [237], but is an area of recent interest as the innate immune pathways that regulate this response become better defined [238]. Initial studies of mice with the NCF1.His90 risk variant indicate defects in macrophage efferocytosis and polarization of T follicular helper (T_{fh}) cells towards the class-switch promoting Tfh2 subset [239]. The observation that a coding change in NCF1 confers substantial SLE risk reinforces the importance of clearance of dead cell debris in SLE.

Based on our current understanding, the evidence does not support SLE as a classic oligogenic disease. SLE typically arises from either monogenic mutation leading to childhood onset disease development or more commonly the cumulative contribution of multiple polygenic risk factors beyond a liability threshold or occasionally a mixture of these two scenarios. That said, several risk factors of relatively large effect size have been described in population-level SLE cohorts that have helped illuminate the etiology and pathogenesis of SLE.

10. Gene-environment interactions in SLE

As we noted, while monogenic routes to SLE have been described, the more typical route to SLE is that of polygenic risk contribution past a liability threshold combined with an environmental trigger. Advances in both capturing environmental exposures (the exposome) and characterizing their proximate impacts on gene expression (the epigenome) promise to advance our understanding of the impact of environmental triggers on SLE expression and help in working backwards, so to speak, from genetic risk variants to epigenetic changes to environmental triggers. However, each level of separation from direct interaction with the genome introduces an additional order of magnitude in terms of possible combinatorial interactions. Genetic epistasis has long been postulated in complex polygenic disease phenotypes, but has not been demonstrated. It appears that most genetic effects for complex traits best fit an additive model [240–242]. Whether this is due to statistical power requirements that are an order of magnitude higher than those for single variant effects or whether our current statistical and biological models are insufficient to account for epistasis remains and area of active investigation in human genetics [243,244]. Further, as discussed above, current GWAS sample sizes are underpowered to detect all single variant associations at a threshold that passes adjustment for multiple testing. Thus, it stands to reason that more environmental triggers that rely in part on gene X environment interactions that are mediated through distal effects (signal transduction pathways, etc.) would likely require similar sample sizes to demonstrate. In diseases with relatively lower prevalence (relative to e.g. type 2 diabetes or coronary artery disease), the number of affected individuals required to detect such effects may well exceed the affected population of entire continents [157].

Several candidate environmental triggers have been investigated, including ultraviolet light exposure, smoking, silica exposure, exogenous hormone exposure, pollutant/chemical exposures, microbiome composition and prior infection [245–247]. Of these, prior Epstein-Barr virus (EBV) infection is particularly noteworthy, as there is evidence implicating EBV in both the maturation of the autoantibody response in SLE patients in a way that suggests molecular mimicry [248] and evidence that the EBV transcription factor, EBNA-2

specifically interacts with genetic risk variants not just for SLE, but a variety of related disorders of immune dysregulation [249]. While studies to date have implicated prior EBV infection, the truest test of this hypothesis, just as with any hypothesized environmental trigger, would entail randomized placebo-controlled interventions to prevent or reverse the exposure and thereby prevent disease development [250]. In the case of EBV, this would likely take the form of a vaccine. To date, efforts to develop a vaccine that protects against EBV have been unsuccessful [251,252], likely due to its particular biology as a virus that is shed in saliva, has been successful in establishing life-long latent infection in 95% of the adult worldwide population and has exploited several host factors to avoid immune detection [253]. Nonetheless, continued efforts to develop EBV vaccines [251,254] and recent advances in vaccine development arising from the COVID-19 pandemic [254,255] hold promise to nominate novel approaches to EBV vaccination that will hopefully be positioned to formally test this hypothesis. Indeed, application of mRNA vaccine technology may well find application as a tolerance-inducing therapy for several autoimmune disease states [256].

Nevertheless, if EBV is a causal trigger for SLE development through genetic variant specific EBNA-2 interactions, this would set SLE apart from other complex diseases that arise from gene X environment interaction. In this case, the environmental risk factor (EBNA-2) would directly interact with the variations in the DNA that confer genetic risk. As a consequence, the complexity of possible interactions would be reduced by many orders of magnitude. Understanding gene X environment influences would thereby be a more tractable problem.

If EBV is truly an environmental trigger for SLE, we suspect that in the coming decades SLE will not just be the prototypical systemic autoimmune disease, but also the prototypical disease to study gene X environment disease and will be used to apply and develop methods to understand gene X environment interaction. The insights gained and approaches developed from studying this unique disease would find broad application to other diseases.

While a necessary step to truly understand the genetics of SLE, we suspect that deep understanding of gene X environment interactions in SLE will be fraught, due to the relatively low prevalence of disease, underlying clinical and molecular heterogeneity, and the overwhelming complexity that higher order gene X environment interactions represent.

11. Clinical considerations and communicating genetic risk in SLE

As physicians and scientists considering the overwhelming complexity of the thousands of putative SLE genetic risk alleles, their interaction with as yet incompletely defined environmental triggers and the stochastic nature of immune responses, communicating an accurate picture of the risk landscape of SLE to patients poses an even bigger challenge. Indeed, patients' perception of risk is influenced by many factors, including cognitive ability (numerical literacy & complexity), emotional traits (optimism vs. pessimism), comfort with uncertainty, a priori beliefs, the experience of their family and community, and their perception of the consequences. Please refer to the review by Lautenbach, et al. [257] for an excellent overview of some challenges related to communicating the risk of complex genetic

disease to patients. Certainly, it appears that in the coming decades genetic information will be routinely available in clinical care. Perhaps, some combination of polygenic risk scores, genome sequencing for rare variants, exposome and biomarker data will allow us to better predict who will get SLE and how best to treat it.

12. Summary, challenges & opportunities

There are several important aspects of SLE as a genetic disease that we did not cover in depth and will present challenges to the field of lupus genetics in the coming years.

Two notable aspects relate to nosology and the lumper/splitter issue. In the same way that it remains incompletely clear whether monogenic SLE syndromes should be considered bona fide SLE or whether they should be thought of as distinct entities, it may be that statistical power to detect and characterize genetic effects will improve if subphenotypes are considered. Early efforts to define the genetics of intermediate SLE phenotypes (i.e. renal disease, cardiac disease in neonatal lupus, serum type I interferon, etc. [258–263]) hold promise to improve our understanding of the heterogeneity of SLE manifestations at the molecular level. That is, in many ways it may be more useful to think of SLE as a collection of endophenotypes that share the final common pathway of anti-nucleic acid anti-nucleoprotein autoimmunity. Even so, some clinical phenotypes of SLE, such as lupus nephritis, may themselves be sufficiently heterogeneous in their pathobiological mechanisms as to preclude genetic classification until improved classification schemes are developed [7]. In the case of lupus nephritis, thrombotic, inflammatory and renal filtration defects are the predominant pathobiologic mechanisms in a given individual and it stands to reason that the genetic mechanisms that facilitate expression of this trait likely differ based on the underlying pathobiology.

Conversely, a shared genetic basis across autoimmune diseases has long been suspected based on the observation that some families contain multiple individuals who are each affected by unique autoimmune diseases and the observation that the presence of one autoimmune disease in a given individual is a risk factor for the development of other autoimmune diseases in that individual. Thus, it may be more useful to think of autoimmune diseases like SLE as endophenotypes of autoimmunity. Efforts seeking to re-classify autoimmune diseases conventionally thought of as distinct entities have demonstrated some evidence of shared molecularly defined pathobiologic mechanisms (endophenotypes or pathotypes) that span disease states[264,265].

In terms of understanding the polygenic contribution to disease risk, moving GWAS hits to the kind of understanding of mechanism that would allow novel therapy development is a non-trivial problem [112]. This is true even in apparently straightforward cases, such as with PTPN22, where an amino acid sequence change leads to disease risk [113,114]. Thus, understanding how hundreds to thousands of common genetic variants of small effect size (relative risk <2) combine to perturb immune pathways leading to autoimmunity and disease development in SLE is the next great challenge in terms of translating advances in the field of lupus genetics into interventions that improve care for SLE patients. Even so, the observation that GWAS scans identified components of the type I interferon [38] and

BAFF signaling pathways [266], which are targeted by recent FDA-approved drugs for SLE, anifrolumab and belimumab respectively, means that rising to the challenge of tackling this complexity promises to nominate novel candidate therapeutic approaches to SLE.

While the complexity of polygenic SLE presents a huge challenge, the simplicity of monogenic SLE may present a huge opportunity. While understanding monogenic SLE, may not seem broadly applicable, each of the monogenic routes to SLE or SLE-like disease likely represent core disease risk nodes or pathways that may be amenable to therapeutic intervention. The story of PCSK9 inhibitor development for prevention and treatment of atherosclerotic cardiovascular disease (ASCVD) highlights the opportunity. The identification of rare gain-of-function variants in familial hypercholesterolemia and loss-of-function variants in individuals with extremely low cholesterol levels spurred the development of inhibitors of this pathway [267]. The time from identification of this pathway to effective medical therapies that could, in principle, be used in the entire population of individual with or at risk for ASCVD was less than fifteen years. In the same way, all of the monogenic routes to SLE represent novel candidates for therapeutic manipulation to prevent or treat all forms of SLE. This is because the polygenic and monogenic SLE risk genes comprise a shared molecular network (Supplemental Fig. 3).

In summary, SLE is a disease phenotype wherein genetic variation contributes to disease risk. While monogenic routes to SLE have been described, the more typical route to SLE is that of polygenic risk contribution past a liability threshold combined with an environmental trigger. Genomic studies have illuminated key disease pathways of defects in self-antigen clearance, innate immune pathways that respond to auto-antigen associated damage, and autoreactive lymphocyte development and maintenance (Supplemental Fig.s 1 and 2). Future studies promise to refine our understanding of the pathways involved in disease development and expression as well as illuminate the heterogeneity of disease, the relationship to other autoimmune diseases and the impact of genetic variation on disease prevalence and severity. The extent to which genome-wide genetic information will impact prevention, diagnosis, prognosis and therapy likewise remains to be seen. It is worth noting, however that the two pathways that novel therapies approved for SLE in the past 50 years target (BAFF pathway and the type I interferon pathway) are both represented amongst SLE GWAS hits. Thus, further bridging the gap between genetic variation and biological mechanism promises to uncover additional much needed approaches to prevent disease and therapy (glucocorticoid) associated damage.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box

Example language to explain genetic risk of SLE to patients

Note, we present this in a didactic/lecture fashion, but an interactive format, where the patient's current understanding is assessed and this language is tailored to their understanding and concerns we expect would lead to a more fruitful discussion.

Patient with lupus: I have heard that lupus is a genetic disease. Does this mean that I will pass it on to my children?

Physician: Since I can't predict the future, I can't say for sure if your children will get lupus. I can say that it is unlikely. You are correct. Genes play a role in whether a person gets lupus. There are four facts that I want to share with you about genes in lupus to help you understand how likely it is for you to pass lupus on to your children. I also have some simple steps your relatives can take to make their risk even lower.

First, there are hundreds or maybe thousands of genes that each only slightly change the risk for lupus. It is kind of like a weird lottery ticket. The more winning lottery numbers you pick the bigger the payout. In lupus, the more lupus risk genes you have the more likely you are to get lupus.

Second, lots of patients that I see ask whether they will pass on the lupus gene to their kids. There is no single lupus gene. Rarely, we do see families where a single lupus gene travels through the family. In those families, most people with that gene get lupus. However, lupus patients in these families usually get severe lupus as children.

Third, in populations with high risk of lupus, we see lupus in at most one in 300 people [13]. This is about one quarter of 1%. Having a parent, sibling or child with lupus increases this risk about twenty times, which sounds like a lot [14,17,24]. But, since lupus is so rare, the overall chance of lupus for one of your children is still very low. In high risk populations, having a parent, sibling or child with lupus still only changes the risk from one in 300 to 1 in 20. This means that at most the risk of lupus in a child is 5%. Remember, 5% is a worst-case scenario, most studies find that the overall risk of lupus in children who have a parent with lupus is much lower, closer to 2 in 100 or 2% [17].

Fourth, even if someone gets one of these single lupus genes or get lots of lupus risk genes from their parents, this does not guarantee lupus. When we look at people who have lupus and also have an identical twin – they share all of the same genes – the twin gets lupus only about 30–40% of the time. We know that there are things in the environment that trigger lupus. Lots of research is being done to figure out precisely what that the triggers are.

Finally, if you are worried, there are steps your relatives can take to lower the risk of lupus. These include, not smoking, using sun protection and maintaining a healthy lifestyle.

Check out the lupus initiative – it has lots of great videos about these recommendations:

https://thelupusinitiative.org/

Another thing to consider. We are still trying to understand how the immune response goes wrong in lupus patients leading to immune attack on their own bodies. You and your relatives may be able to help by signing up for research studies or registries. The results may not benefit you, but may help us develop better treatments for future generations of lupus patients.

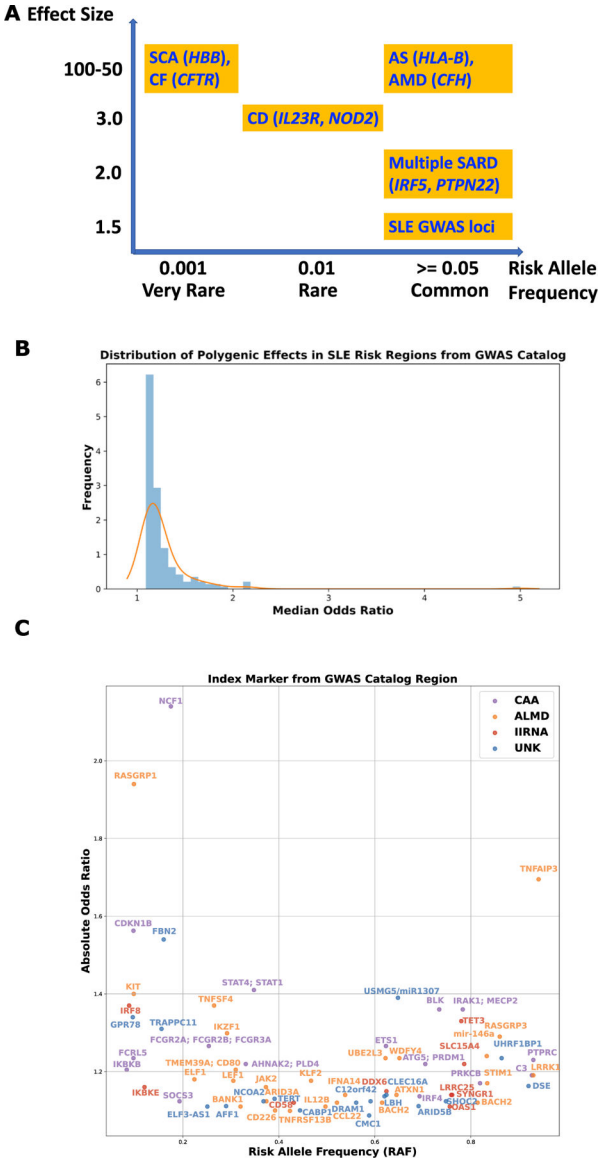

Fig. 1.

Most polygenic effects are common variants of small effect size A) Well-known examples of genetic disease causal variants demonstrating relationship between effect size and minor allele frequency. SCA: Sickle Cell Anemia, *HBB*: hemoglobin beta subunit; CF: Cystic Fibrosis, *CFTR*: CF transmembrane conductance regulator; AS: Ankylosing Spondylitis, *HLA-B*: major histocompatibility complex, class I, B; AMD: Age-Related Macular Degeneration, *CFH*: complement factor H; CD: Crohn's disease, *IL23R*: interleukin 23 receptor, *NOD2*: nucleotide binding oligomerization domain containing 2; SARD: Systemic Autoimmune/Rheumatic Disease, *IRF5*: interferon regulatory factor 5, *PTPN22*: protein tyrosine phosphatase non-receptor type 22. SLE GWAS Hits: Most significantly associated marker in a region B) The vast majority of loci listed in the GWAS catalog (Supplemental Table 1) exhibit small effect size (Odds Ratio < 2) C) Inverse relationship between minor allele frequency and effect size – risk alleles with balanced frequency in the population from

Pathway identified genes in GWAS catalog have smaller effects near risk allele frequency of 0.5. ALMD: Autoreactive lymphocyte maintenance and development; CAA: Clearance of autoantigens; IIRNA: Innate immune response to nucleic acid/nucleoprotein complexes; UNK: Unknown relationship to existing SLE pathways.

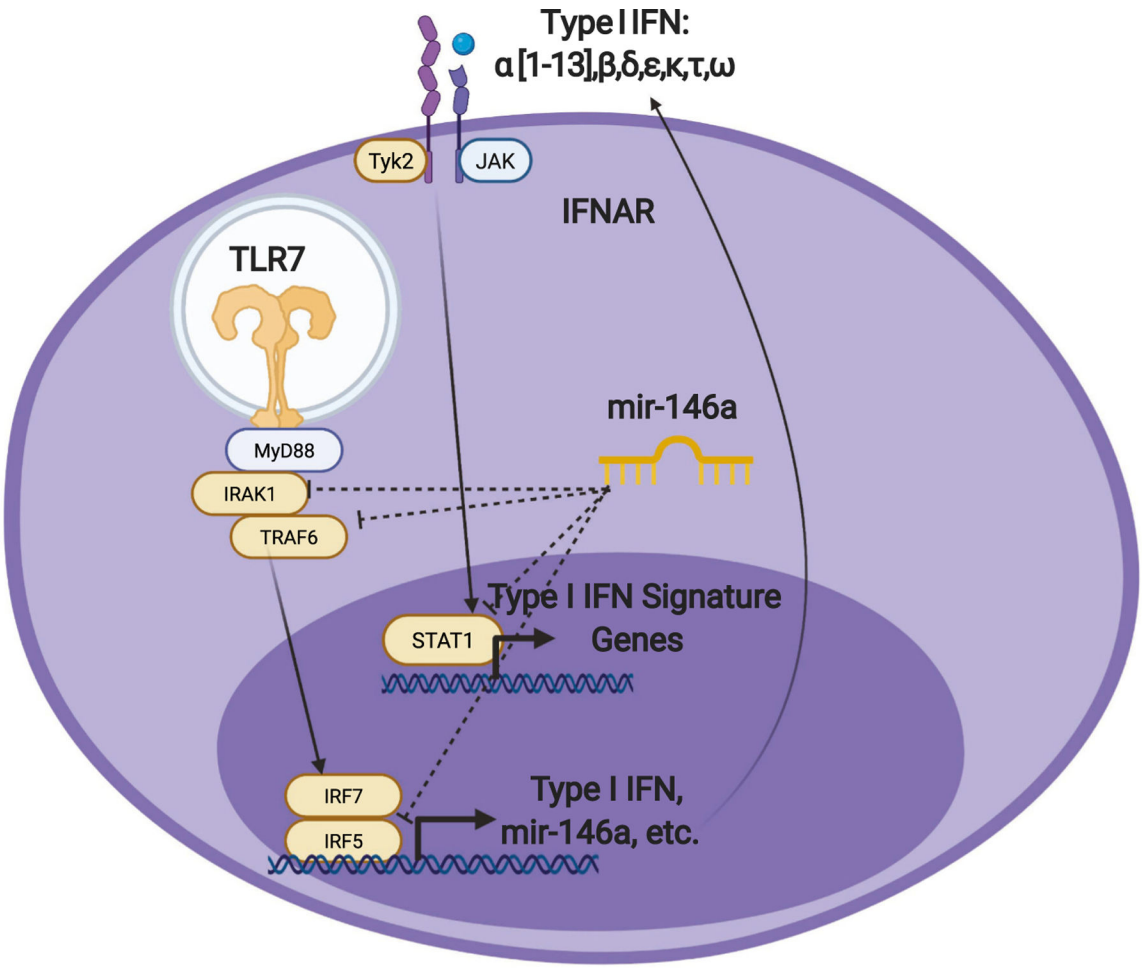

Fig. 2.

Sexually dimorphic TLR7 signaling pathway contains numerous polygenic SLE risk genes. [Created with BioRender.com].

Table 1

Genetic loci associated with monogenic lupus or lupus-like disease.

Gene(s)	Gene Name	Locus	Protein	Inheritance	Pathway	Phenotype	Reference
ACP5	Acid phosphatase 5,tartrate resistant	19p13.2	TRAP	AR	Nucleic acid sensing and degradation Type I IFN	SPENCD, SLE	[66]
ADAR1	Adenosine deaminase, RNA specific	1q21.3	Adenosine deaminase, RNA specific	AR/AD	Type I IFN	AGS, SLE	[67,68]
C1QA	Complement C1q A chain	1p36.12	C1q	AR	Complement	Complement deficiencies, SLE	[69]
C1QB	Complement C1q B chain	1p36.12	C1q	AR	Complement	Complement deficiencies, SLE	[69]
C1QC	Complement C1q C chain	1p36.12	C1q	AR	Complement	Complement deficiencies, SLE	[69]
C1R	Complement component C1r	12p13.31	C1r	AR	Complement	Complement deficiencies, SLE	[70]
C1S	Complement C1s	12p13.31	C1s	AR	Complement	Complement deficiencies, SLE	[71]
C2	Complement C2	6p21.33	C2	AR	Complement	Complement deficiencies, SLE	[72]
C4A/C4B	Complement C4A	6p21.33	C4	AR	Complement	Complement deficiencies, SLE	[73]
C8A/C8B/C8G	Complement C8	1p32.2, 9q34.3	C8	AR	Complement	Complement deficiencies, SLE	[74,75]
CYBB	Cytochrome b-245 beta chain	Xp21.1-p11.4	NADPH oxidase 2	X-linked	Phagocytosis, ROS generation	Chronic granulomatous disease	[76]
DNASE1	Deoxyribonuclease 1	16p13.3	DNASE1	AD	Nucleic acid sensing and degradation	SLE	[77]
DNASE1L3	Deoxyribonuclease 1 like 3	3p14.3	DNASE1L3	AR	Nucleic acid sensing and degradation	SLE	[78]
FAS	Fas cell surface death receptor	10q23.31	FAS	AD	Apoptosis	ALPS	[79]
FASLG	Fas ligand	1q24.3	FASL	AD	Apoptosis	ALPS	[80]
IFIH1	Interferon induced with helicase C domain 1	2q24.2	MDA-5	AD	Type I IFN	AGS, SLE	[67,81]
IKZF1	IKAROS family zinc finger 1	7p12.2	Ikaros	AD	B cell development and tolerance	SLE, immunodeficiency	[82,83]
ISG15	ISG15 ubiquitin-like modifier	1p36.33	ISG15	AR	Type I IFN	AGS	[84]
KRAS	KRAS proto-oncogene, GTPase	12p12.1	KRAS	AD	RAS-MAPK signaling	Noonan syndrome	[85,86]

Gene(s)	Gene Name	Locus	Protein	Inheritance	Pathway	Phenotype	Reference
MAN2B1	Mannosidase alpha, class 2B member 1	19p13.13	Lysosomal Alpha-mannosidase	AR	Metabolism of carbohydrates	Alpha-mannosidosis	[87]
P2RY8	P2Y receptor family member 8	Xp22.33 Yp11.2	P2RY8	AD	Germinal Center B cell migration	SLE, APS	[88]
PTEN	Phosphatase and tensin homolog	10q23.31	PTEN	AD	PI3K signaling	SLE, PTEN hamartoma syndrome, Cowden Syndrome	[60]
PEPD	Peptidase D	19q13.11	Prolidase	AR	Aminopeptidase activity	Prolidase deficiency	[89]
PRKCD	Protein kinase C delta	3p21.1	PRKCD	AR	Self-tolerance	SLE	[90]
PSMA3	Proteasome subunit alpha 3	14q23.1	PSMA3	AD	Proteasome	CANDLE	[91]
PSMB4	Proteasome subunit beta 4	1q21.3	PSMB4	AD	Proteasome	CANDLE	[91]
PSMB8	Proteasome subunit beta 8	6p21.32	PSMB8	AD	Proteasome	CANDLE	[91]
PTPN11	Protein tyrosine phosphatase, non-receptor type 11	12q24.13	PTPN11	AD	RAS-MAPK signaling	Noonan syndrome	[86,92]
RAG2	Recombination activating gene 2	11p12	RAG2	AR/AD	Self-tolerance	SLE	[93]
RELA	RELA proto-oncogene, NF-kB subunit	11q13.1	RELA, NF-kb p65	AD	NF-kB, type I IFN	RELA haploinsufficiency, SLE	[94]
RNASEH2A	Ribonuclease H2 subunit A	19p13.13	RNASE H2 Complex	AR	Nucleic acid sensing and degradation	AGS	[67,95]
RNASEH2B	Ribonuclease H2 subunit B	13q14.3	RNASE H2 Complex	AR	Nucleic acid sensing and degradation	AGS	[67,95]
RNASEH2C	Ribonuclease H2 subunit C	11q13.1	RNASE H2 Complex	AR	Nucleic acid sensing and degradation	AGS	[67,95]
SAMHD1	SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1	20q11.23	SAMHD1	AR	Type I IFN	AGS, SLE, FCL	[67,96,97]
SAT1	spermidine/spermine N1-acetyltransferase 1	Xp22.11	SAT1	XLR	Polyamine metabolism, Type I IFN effector	SLE	[98]
SH0C2	SHOC2 leucine rich repeat scaffold protein	10q25.2	SHOC2	AD	RAS-MAPK signaling	Noonan syndrome	[86]
SLC7A7	Solute carrier family 7 member 7	14q11.2	SLC7A7	AR	Amino acid transporter	Lysinuric protein intolerance	[99]
S0CS1	Suppressor of Cytokine Signaling 1	16p13.13	SOCS1	AD	Cytokine Signaling	SOCS1 Haploinsufficiency	[100,101]
TNFRSF13B	Tumor necrosis factor receptor superfamily member 13B	17p11.2	TACI	AD	B cell survival and proliferation	Smith-Magenis-Sydrome, Haploisufficiency for TACI	[102]
TMEM173	transmembrane protein 173	5q31.2	STING	AD	type I interferon	SAVI	[103]
TNFAIP3	Tumor Necrosis Factor Alpha Induced Protein 3	6q23.3	A20	AD	NF-KB & Ubiquitination	HA20	[104]
TREX1	three prime repair exonuclease 1	3p21.31	TREX1	AD	Nucleic acid sensing and degradation	AGS, FCL	[105]

AGS, Aicardi-Goutieres Syndrome; AD, autosomal dominant; ALPS, autoimmune lymphoproliferative syndrome; AR, autosomal recessive; XLR, X-linked Recessive CANDLE, chronic atypical neutrophilic.

dermatosis with lipodystrophy and elevated temperature; FCL, familial chilblain lupus; HA20, haploinsufficiency of A20; SAVI, STING-associated vasculopathy with onset in infancy; SLE, systemic lupus erythematosus; SPENCD, Spondyloenchondrodysplasia.

Table 2

Key variables in genetic architecture & severity of SLE.

Variable		Genetic Architecture	Severity
Age	Adult-onset Childhood-onset Elder/late-onset	Polygenic Monogenic polygenic, possible somatic contribution not yet defined	less severe more severe less severe, but with more comorbidities, contributing to increased mortality
Sex at birth	Females	lower genetic load w/X-chromosome & hormones	less severe
	Males	higher genetic load & more severe disease due to lack of x-chromosome & hormones	more severe
Gender	Women Men	High quality studies of gender affirming therapy to disentangle relative contribution of hormones and sex chromosomes not yet reported *	unknown *
Inheritance pattern	sporadic	mix of de novo and multiple polygenic risk alleles	wide distribution
	multiplex	private or rare mutations mixed with multiple polygenic risk alleles.	more severe

* such studies promise to clarify our understanding of the impact of sex and gender on SLE risk

Table 3

Genetic contributions in polygenic SLE with considerably high relative risk for the disease compared to most GWAS identified susceptibility loci.

Genetic Factor	Risk	Pathway
X-chromosome copy #	9×	TLR7? CXorf21/TASL? Foxp3? IRAK1/MECP2?, etc.?
C4A/C4B copy number	7×*	clearance of cellular debris, immune complex formation
NCF1.Arg90His	2–3.5X**	Netosis? Efferocytosis? TLR signaling? Affinity maturation?
IRF5 putative regulatory variant	2×	Innate/Adaptive Immune TF - Interferon
TREX1 mutation	25×	cytosolic DNA sensor - Interferon

*Depending on sex.

**Depending on ancestral population.