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Defining biological subsets in systemic lupus erythematosus: progress toward personalized therapy

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Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous disease with respect to disease severity, response to treatment, and organ damage. The pathogenesis of SLE includes immunological mechanisms which are driven by both genetic and environmental factors. There are clear differences in the pathogenesis of SLE between patients of different ancestral backgrounds, including differences in genetic risk factors, immunological parameters, and clinical manifestations. Patients with high vs. low levels of type I interferon (IFN) in circulation represents one major biological subset within SLE, and these two groups of patients are present in all ancestral backgrounds. Genetic factors, autoantibodies, and levels of other cytokines all differ between high and low IFN patients. This distinction has also been important in predicting response to treatment with anti-type I IFN therapies, providing a precedent in SLE for biological subsets predicting treatment response. This review will highlight some recent developments in defining biological subsets of SLE based on disease pathophysiology, and the idea that improved knowledge of disease heterogeneity will inform our efforts to personalize therapy in this disease.

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory, an immune-mediated disease with heterogeneous clinical manifestations, affecting 0.1 % of the general population [1]. SLE affects all world populations, but is more common in some populations. For instance, SLE is 3–4 times more common in non-European ancestry compared to European ancestry in the United States [1]. The reasons for this disparity remain unclear, but it seems likely that differences in molecular pathogenesis and disease biology contribute to this phenomenon [1].

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SLE is highly heterogeneous clinically. A broad array of disease manifestations are observed, ranging from rash and arthritis to severe organ- and life-threatening disease [2]. This heterogeneity in SLE is particularly challenging in clinical practice, as we do not currently have good predictors of disease course, and we do not know which patients will develop specific disease features [3]. This is likely because we do not have a complete understanding of the pathogenesis of SLE in humans. A number of immunological mechanisms have been implicated, including dysregulation of the innate immune system, diminished clearance of apoptotic cells, and loss of self-tolerance by the adaptive immune system. These changes in the immune system result from an interaction of genetic, environmental, and hormonal risk factors [4].

While our knowledge about human SLE pathogenesis is incomplete, recent studies have documented many differences in the molecular features of SLE that distinguish important patient subgroups [5]. The genetic risk factors that predispose to SLE differ between world populations, and there are many differences in the molecular immune system between patients. In this review, we highlight some recent developments in defining biological subsets of SLE based on disease pathophysiology, and speculate how this knowledge may be useful for the development of effective targeted therapies for specific SLE phenotypes.

2. Clinical differences related to ancestral background

SLE has been described in each of the 6 populated continents; Europe, North America, South America, Africa, Asia, and Australia [6]. It is less commonly reported in Africa, but common in African descendants around the world [3]. Incidence and prevalence rates in African or Asian ancestry are approximately 2 to 3 times higher than in European ancestry populations [7–13]. The disease is also more common among Aboriginal than non-Aboriginal Australians [14, 15], and in First Nations or Native American groups in Canada and the United States [16, 17]. Differences in the prevalence of clinical manifestations of SLE have been noted for many years. For example, AA SLE patients have more nephritis as compared to EA patients [18–21]. SLE patients of AA descent experience increased morbidity and mortality compared to EA, in large part related to the increased frequency and severity of nephritis [22]. Table 1 lists differences in the prevalence of specific clinical manifestations according to ancestral background in SLE.

3. Immunological differences related to ancestral background

Given the differences in clinical disease outlined above, it is not surprising that immunological differences exist between SLE patients of different ancestral backgrounds. One such difference is in the prevalence of anti-Smith (anti-Sm) and anti-ribonucleoprotein binding protein (anti-RNP) autoantibodies in AA vs. EA SLE patients. Both of these autoantibodies are approximately 5-fold more common in AA than in EA SLE patients [23]. Interferon alpha (IFN- α) is a primary pathogenic factor in human SLE [24]. High levels of type I IFN can be observed in 40–50% of SLE patients [25], and this finding is relatively stable over time [26], suggesting that there is a high IFN group of patients within SLE. Supporting a causal role in disease, recombinant IFN- α therapy has resulted in de novo SLE [27, 28], which typically resolves when the IFN therapy is discontinued [29].

Elevated type I IFN is another immunological feature of SLE that differs between populations [25], and European ancestry SLE patients had lower serum type I IFN levels as compared to non-European ancestry patients. This finding was independent of other clinical variables in the study that involved over 1000 SLE patients of EA, AA or Hispanic-American ancestry [25]. A follow-up study used genetic markers to quantitatively designate ancestry. This study showed African ancestry was most strongly associated with the production of anti-RNP autoantibodies, and the presence of anti-RNP was associated with increased peripheral type I IFN in these patients [30]. When IFN-induced gene expression patterns are studied in blood cells from SLE patients of different ancestral backgrounds, increased type I IFN-induced gene expression was dependent upon anti-RNA-binding protein autoantibodies (anti-Ro, anti-La, anti-Sm, or anti-RNP) in AA SLE patients [31]. In EA SLE patients, increased IFN-induced gene expression was observed in subjects with and without anti-RNA-binding protein autoantibodies, suggesting that the regulation of IFN-induced gene expression in SLE patients differs between ancestral backgrounds [31]. Diversity in the IFN signature by ancestral background also extends to various cell types in peripheral blood. In a study of gene expression in CD4 T-cells, CD8 T-cells, monocytes, and B cells in AA and EA SLE patients and controls, different IFN-induced genes were expressed in the various cell types. Thus, while each cell type demonstrated an IFN signature, the particular transcripts making up that signature differed to a large degree between cell types [32]. Also, interestingly there was a greater degree of correlation in the strength of the IFN signature across cell types in AA patients as compared to EA patients, again suggesting differences in IFN pathway regulation between ancestral backgrounds [32].

Studies have compared the circulating level of B-cell activating factor (BAFF, or BLYS) in SLE patients between ancestral backgrounds as well [33]. BAFF levels were shown to be higher in AA SLE patients as compared to EA SLE patients. These data could identify patient subgroups that may respond to BAFF inhibitors, such as belimumab. Interestingly, BAFF is induced by type I IFN, and is thus considered an IFN-induced gene [34]. While in vitro data may not always predict correlations between cytokine levels in circulation in humans in vivo, in this case a strong correlation was observed between circulating BAFF levels and type I IFN levels in both ancestral backgrounds [33]. This finding could suggest that blocking type I IFN could also block BAFF in the same patients, if the type I IFN is a major factor inducing BAFF in SLE. Tumor necrosis factor alpha (TNF- α) is another cytokine that has been studied in a large multi-ancestral group of SLE patients [35]. TNF- α levels are not significantly different between SLE patients of different ancestral backgrounds, and the levels of TNF- α were not correlated with type I IFN in the patients [35].

4. Genetic predisposition and contribution to diversity

Familial aggregation studies in lupus support the idea that SLE has a genetic basis, and that for most SLE cases inheritance is complex [36]. The concordance rate of lupus in monozygotic twins (24–58%) is higher than dizygotic twins (2–5%), supporting the idea that genetics plays a large role in the predisposition to SLE [5]. Some monogenic causes of SLE have been reported [37, 38], but these are rare cases and it seems that for most patients the disease is caused by multiple risk factors acting in concert.

Genome-wide association studies (GWAS) have greatly increased our knowledge of the genetic basis of SLE in recent years, and these studies also support the idea of multi-factorial inheritance. To date, GWAS are based on European and Asian populations, thus the findings of these studies are likely to be most relevant for these ancestral backgrounds [39, 40]. When alleles discovered in European ancestry were tested for association in AA SLE patients, there were some alleles which overlapped, and some which did not [41]. A GWAS in AA SLE patients is currently underway, and it is likely that this will identify some novel alleles that have not been observed in other ancestral backgrounds.

Studies have supported the idea that different SLE-risk genes are related to different disease manifestations in SLE. For example, polymorphisms in integrin subunit alpha M (ITGAM), signal transducer and activator of transcription 4 (STAT4), apolipoprotein L1 (APOL1), platelet-derived growth factor receptor, alpha (PDGFRA), and hyaluronan synthase 2 (HAS2) have been associated with greater risk of nephritis in SLE patients [42–47]. While some of these polymorphisms such as ITGAM and STAT4 are also general SLE risk factors, APOL1, PDGFRA, and HAS2 are genes that seem to be specifically associated with risk of nephritis in SLE and are not general SLE-risk genes [48].

Autoantibodies also demonstrate familial aggregation in SLE families, in both SLE-affected and unaffected family members, suggesting a genetic basis for autoantibody formation [23]. Polymorphisms in interferon regulatory factor (IRF) 5, IRF7, STAT4, and other known SLE-risk loci have been associated with the production of particular autoantibodies [44, 49–52], further supporting the case that autoantibody formation in SLE has a genetic component, and that subsets of patients defined by autoantibodies are genetically different. In previous work, we have shown that many first-degree relatives of SLE patients had significantly higher serum IFN- α levels compared to healthy unrelated individuals [53, 54]. These data suggest that IFN- α is a heritable risk factor in SLE, and thus genetic factors which lead to high IFN- α may be concentrated in lupus families [53]. These studies suggest that the differences in IFN- α level between patients of different ancestral backgrounds could relate to genetic differences between populations. Familial studies have also demonstrated similar results for TNF- α as well as IL-10 [55, 56], further supporting the idea that genetic thresholds for cytokine production and signaling contribute to the risk of SLE.

5. Interferon regulatory factors as an example of genetics driving diversity in human SLE

IRF5 is a transcription factor that can induce type I IFN-related and other inflammatory gene expression downstream of Toll-like receptor engagement [57], and variants in the IRF5 gene have been associated with risk of SLE [38–42]. SLE patients carrying the IRF5 risk haplotype have higher serum IFN- α , and also are more likely to have either anti-double stranded DNA (anti-dsDNA) or anti-RNP antibodies [49, 58]. Interestingly, the impact of IRF5 genotype upon type I IFN levels was dependent upon having these autoantibodies, and thus the associations between genotype and immune system phenotypes suggested a pathogenic model [49]. In this model, the immune complexes made by the autoantibodies serve as an endogenous trigger for type I IFN production, and chronic stimulation of the

pathway by immune complexes in combination with the SLE-risk IRF5 isoform results in over-production of IFN and risk of SLE [59]. Genetic association data would support this model, as the risk of SLE related to IRF5 is largely confined within this group of anti-Ro and/or anti-dsDNA autoantibody positive, high IFN patients [49].

While IRF5 haplotypes are similar across ancestral backgrounds, the SLE-risk haplotype was not found in African populations, and was found in AA populations at a rate that would be expected due to admixture [49]. These data could suggest that the SLE-risk haplotype was of European origin, or possibly that this haplotype had gone to extinction in Africa. Recent studies of ancient Neanderthal DNA have supported a third idea – that the SLE-risk haplotype of IRF5 is actually of Neanderthal origin [60]. This surprising result explains the geographic restriction of the haplotype, as it occurs in populations that overlapped with the Neanderthal range. It also provides a fascinating example of pre-Homo sapiens evolution affecting the risk of autoimmune disease in modern human populations. Some modern human genetic variations in Toll-like receptors have also recently been shown to originate from Neanderthals and another early hominid population, the Denisovans [61, 62], suggesting that the diversity in our immune system genes extends far beyond the recent evolution of Homo sapiens.

IRF7 is a transcription factor that is related to IRF5, functioning to induce type I IFN and inflammatory gene expression downstream of Toll-like receptors. Genetic variations in IRF7 have also been associated with SLE [63]. A similar model is observed in which the IRF7 gene variant is associated with autoantibody formation as well as higher type I IFN levels in circulation, and the effect of IRF5 and IRF7 genotypes together was additive [51]. Interestingly, the particular genetic polymorphism and autoantibody differed between ancestral backgrounds, again suggesting human diversity within a shared mechanism of disease, parallel to that observed with IRF5.

6. Type I IFN as a method to discover novel genes in SLE

The above studies outline functional work determining the impact of known susceptibility loci upon IFN levels and other immune phenotypes in SLE. Given that type I IFN is a pathogenic factor in SLE, another approach is to screen for genes related to high IFN in SLE patients. In this approach, studies have used a case-case design, comparing patients with high IFN to those with low IFN, which should identify genes related to high IFN in SLE while excluding those genes that are not related to IFN. This study design reduces the complexity and heterogeneity between the comparator groups, resulting in greater statistical power for discovery. Using this approach, studies have identified a number of novel loci related to IFN in SLE patients, including Protein Kinase, CGMP-Dependent, Type I (*PRKG1*), Purine Nucleoside Phosphorylase (*PNP*), and others [64–66]. *PRKG1* codes for the soluble isoforms of the cyclic GMP-dependent protein kinase (I α and I β). Co-expression analyses in public datasets support the importance of this gene in immune cell types such as dendritic cells and NK cells [64], and coding change mutation in this gene has been linked to cutaneous T cell lymphoma [67]. *PNP* is involved in nucleotide salvage and homeostasis, and human deficiency of the *PNP* gene results in a disorder characterized by defective T- and B-cell immunity and autoimmune features such as immune-mediated thrombocytopenia and

others [68]. The polymorphism identified does not cause complete deficiency, but given the above the gene is of high interest in SLE pathogenesis.

The associations between PRKG1 and PNP and type I IFN in SLE were limited to patients of European ancestry. In other backgrounds, different genes have been linked to the high IFN phenotype, such as *LRRC20*, *ANKS1A*, and *EPHA5* [65, 66]. Thus, these data again emphasize that while high IFN is observed in SLE patients of various ancestral backgrounds, it is likely that different factors result in a high IFN phenotype in the different ancestral backgrounds. These differences are likely to be important as we begin to target the type I IFN pathway therapeutically in SLE.

7. Treatment considerations

A number of therapies targeting various aspects of the immune response are currently in development for SLE [69]. Ideally, these would improve upon the current standard of non-specific immunosuppression and correct some of the specific abnormalities of the immune system in SLE patients [69]. Some case series and open-label studies have reported successful treatment of lupus nephritis with rituximab. Reduction of disease activity and proteinuria was observed in patients with lupus nephritis receiving rituximab along with other immunosuppressants such as azathioprine, mycophenolate mofetil (MMF), cyclophosphamide and corticosteroids [70–72]. Clinical improvements have also been reported when using rituximab in membranous lupus nephritis [73]. Despite these encouraging early results, rituximab did not meet endpoints in controlled trials but study design issues also may have played a role, as the placebo group was on numerous background immunosuppressive medications including a fraction on medium to high dose glucocorticoids [74]. It is possible that rituximab has no effect in SLE, and that the early smaller and less-well controlled studies were misleading. Many clinicians are still using rituximab in SLE however, and another possibility is that the medication works better in some subsets of patients that were present in the smaller studies in greater proportion than the larger controlled trials. This issue illustrates a major difficulty in applying personalized approaches to trials – conventional trial design is not optimized to identify important subset effects which could enable more personalized therapies [69].

Ancestry is one important source of diversity in response to therapy. For example, response to mycophenylate mofetil varies by ancestral background, with a large study showing that AA and Hispanic-American SLE patients were more likely to respond [75]. Another study has suggested that Asian SLE patients might respond to lower doses of mycophenylate mofetil than European ancestry subjects [76]. While early belimumab studies suggested better responses in European ancestry [77], in follow up studies, no difference was observed between EA, AA, and other ancestral backgrounds from the United States in terms of response at 0–6 months [78]. In this study, and at 18–24 months the response rate remained similar between EA and AA patients [78].

Less is currently known about how biological phenotype impacts response to treatment in SLE, and this represents a critical frontier that would likely be more promising than stratifying patients by ancestral background [69]. In the two phase II trials of anti-IFN- α

drugs in SLE, both trials were characterized by subset effects, in which the baseline level of type I IFN was an important predictor of response to therapy [79]. This type of pre-treatment pathway assessment holds great promise for rationally directing therapies, and hopefully this represents the future of SLE treatment.

8. Conclusions

In conclusion, clinical practice and molecular studies strongly support the idea that SLE patients represent different pathogenic subsets, from genetics to immune phenotype to the clinical manifestation of disease. These are impacted somewhat by ancestral background, which likely represents differential recent human evolution in the immune system, and there is also evidence of early hominid genetic contribution to the immune pathways implicated in SLE. Most of these common inherited immune system polymorphisms likely evolved and were maintained in the genome to assist in defending us from pathogens, but can also predispose to autoimmunity in certain situations and combinations. This fascinating degree of human diversity of the immune system cannot be ignored, and it seems likely that we will have to include the concept of biological subsets in clinical trial design if we are to be successful in many of the heterogeneous autoimmune diseases such as SLE. It is not easy to generalize at exactly which stage of trial to incorporate subsets, and to what degree. Likely these decisions would have to be based upon the pre-clinical animal and pre-clinical human in-vitro data as well as knowledge of the human biological diversity such as is reviewed above. It is critical for us to understand and define the biological heterogeneity in SLE if we are to implement personalized therapies, and there is a good deal of exciting work in this area that will facilitate these efforts and hopefully improve treatment of patients with this difficult disease.

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References

1. Borchers AT, Naguwa SM, Shoenfeld Y, Gershwin ME. The geoepidemiology of systemic lupus erythematosus. *Autoimmun Rev.* 2010; 9:A277–87. [PubMed: 20036343]
2. Jimenez S, Cervera R, Font J, Ingelmo M. The epidemiology of systemic lupus erythematosus. *Clin Rev Allergy Immunol.* 2003; 25:3–12. [PubMed: 12794256]
3. Gonzalez LA, Toloza SM, Alarcon GS. Impact of race and ethnicity in the course and outcome of systemic lupus erythematosus. *Rheum Dis Clin North Am.* 2014; 40:433–54. vii–viii. [PubMed: 25034155]
4. Ghodke-Puranik Y, Niewold TB. Immunogenetics of systemic lupus erythematosus: A comprehensive review. *J Autoimmun.* 2015; 64:125–36. [PubMed: 26324017]

5. Sanchez E, Nadig A, Richardson BC, Freedman BI, Kaufman KM, Kelly JA, et al. Phenotypic associations of genetic susceptibility loci in systemic lupus erythematosus. *Annals of the rheumatic diseases*. 2011; 70:1752–7. [PubMed: 21719445]
6. Pons-Estel GJ, Catoggio LJ, Cardiel MH, Bonfa E, Caeiro F, Sato E, et al. Lupus in Latin-American patients: lessons from the GLADEL cohort. *Lupus*. 2015; 24:536–45. [PubMed: 25697768]
7. McCarty DJ, Manzi S, Medsger TA Jr, Ramsey-Goldman R, LaPorte RE, Kwok CK. Incidence of systemic lupus erythematosus. Race and gender differences *Arthritis Rheum*. 1995; 38:1260–70. [PubMed: 7575721]
8. Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth *Arthritis Rheum*. 1995; 38:551–8. [PubMed: 7718010]
9. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis Rheum*. 2007; 56:2092–4. [PubMed: 17530651]
10. Samanta A, Feehally J, Roy S, Nichol FE, Sheldon PJ, Walls J. High prevalence of systemic disease and mortality in Asian subjects with systemic lupus erythematosus. *Ann Rheum Dis*. 1991; 50:490–2. [PubMed: 1877855]
11. Hochberg MC. The incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970–1977. *Arthritis Rheum*. 1985; 28:80–6. [PubMed: 3966940]
12. Cooper GS, Parks CG, Treadwell EL, St Clair EW, Gilkeson GS, Cohen PL, et al. Differences by race, sex and age in the clinical and immunologic features of recently diagnosed systemic lupus erythematosus patients in the southeastern United States. *Lupus*. 2002; 11:161–7. [PubMed: 11999880]
13. Molina JF, Molina J, Garcia C, Gharavi AE, Wilson WA, Espinoza LR. Ethnic differences in the clinical expression of systemic lupus erythematosus: a comparative study between African-Americans and Latin Americans. *Lupus*. 1997; 6:63–7. [PubMed: 9116721]
14. Bossingham D. Systemic lupus erythematosus in the far north of Queensland. *Lupus*. 2003; 12:327–31. [PubMed: 12729060]
15. Segasothy M, Phillips PA. Systemic lupus erythematosus in Aborigines and Caucasians in central Australia: a comparative study. *Lupus*. 2001; 10:439–44. [PubMed: 11434580]
16. Boyer GS, Templin DW, Lanier AP. Rheumatic diseases in Alaskan Indians of the southeast coast: high prevalence of rheumatoid arthritis and systemic lupus erythematosus. *J Rheumatol*. 1991; 18:1477–84. [PubMed: 1765971]
17. Peschken CA, Esdaile JM. Systemic lupus erythematosus in North American Indians: a population based study. *J Rheumatol*. 2000; 27:1884–91. [PubMed: 10955328]
18. Hopkinson ND, Doherty M, Powell RJ. Clinical features and race-specific incidence/prevalence rates of systemic lupus erythematosus in a geographically complete cohort of patients. *Ann Rheum Dis*. 1994; 53:675–80. [PubMed: 7979581]
19. Ward MM, Studenski S. Clinical manifestations of systemic lupus erythematosus. Identification of racial and socioeconomic influences. *Arch Intern Med*. 1990; 150:849–53. [PubMed: 2327845]
20. Hochberg MC, Boyd RE, Ahearn JM, Arnett FC, Bias WB, Provost TT, et al. Systemic lupus erythematosus: a review of clinico-laboratory features and immunogenetic markers in 150 patients with emphasis on demographic subsets. *Medicine (Baltimore)*. 1985; 64:285–95. [PubMed: 2412088]
21. Johnson SR, Urowitz MB, Ibanez D, Gladman DD. Ethnic variation in disease patterns and health outcomes in systemic lupus erythematosus. *J Rheumatol*. 2006; 33:1990–5. [PubMed: 16924690]
22. Danila MI, Pons-Estel GJ, Zhang J, Vila LM, Reveille JD, Alarcon GS. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. *Rheumatology*. 2009; 48:542–5. [PubMed: 19233884]
23. Ramos PS, Kelly JA, Gray-McGuire C, Bruner GR, Leiran AN, Meyer CM, et al. Familial aggregation and linkage analysis of autoantibody traits in pedigrees multiplex for systemic lupus erythematosus. *Genes Immun*. 2006; 7:417–32. [PubMed: 16775618]

24. Niewold TB. Interferon alpha as a primary pathogenic factor in human lupus. *Journal of interferon & cytokine research: the official journal of the International Society for Interferon and Cytokine Research*. 2011; 31:887–92.
25. Weckerle CE, Franek BS, Kelly JA, Kumabe M, Mikolaitis RA, Green SL, et al. Network analysis of associations between serum interferon-alpha activity, autoantibodies, and clinical features in systemic lupus erythematosus. *Arthritis Rheum*. 2011; 63:1044–53. [PubMed: 21162028]
26. Petri M, Singh S, Tesfayone H, Dedrick R, Fry K, Lal P, et al. Longitudinal expression of type I interferon responsive genes in systemic lupus erythematosus. *Lupus*. 2009; 18:980–9. [PubMed: 19762399]
27. Ronnblom LE, Alm GV, Oberg KE. Possible induction of systemic lupus erythematosus by interferon-alpha treatment in a patient with a malignant carcinoid tumour. *J Intern Med*. 1990; 227:207–10. [PubMed: 1690258]
28. Niewold TB. Interferon alpha-induced lupus: proof of principle. *J Clin Rheumatol*. 2008; 14:131–2. [PubMed: 18525429]
29. Niewold TB, Swedler WI. Systemic lupus erythematosus arising during interferon-alpha therapy for cryoglobulinemic vasculitis associated with hepatitis C. *Clin Rheumatol*. 2005; 24:178–81. [PubMed: 15565395]
30. Ko K, Franek BS, Marion M, Kaufman KM, Langefeld CD, Harley JB, et al. Genetic ancestry, serum interferon-alpha activity, and autoantibodies in systemic lupus erythematosus. *The Journal of rheumatology*. 2012; 39:1238–40. [PubMed: 22505704]
31. Ko K, Koldobskaya Y, Rosenzweig E, Niewold TB. Activation of the Interferon Pathway is Dependent Upon Autoantibodies in African-American SLE Patients, but Not in European-American SLE Patients. *Frontiers in immunology*. 2013; 4:309. [PubMed: 24101921]
32. Sharma S, Jin Z, Rosenzweig E, Rao S, Ko K, Niewold TB. Widely divergent transcriptional patterns between SLE patients of different ancestral backgrounds in sorted immune cell populations. *J Autoimmun*. 2015; 60:51–8. [PubMed: 25921064]
33. Ritterhouse LL, Crowe SR, Niewold TB, Merrill JT, Roberts VC, Dedek AB, et al. B lymphocyte stimulator levels in systemic lupus erythematosus: higher circulating levels in African American patients and increased production after influenza vaccination in patients with low baseline levels. *Arthritis Rheum*. 2011; 63:3931–41. [PubMed: 22127709]
34. Sjostrand M, Johansson A, Aqrawi L, Olsson T, Wahren-Herlenius M, Espinosa A. The Expression of BAFF Is Controlled by IRF Transcription Factors. *Journal of immunology*. 2016; 196:91–6.
35. Weckerle CE, Mangale D, Franek BS, Kelly JA, Kumabe M, James JA, et al. Large-scale analysis of tumor necrosis factor alpha levels in systemic lupus erythematosus. *Arthritis and rheumatism*. 2012; 64:2947–52. [PubMed: 22488302]
36. Niewold TB. Advances in lupus genetics. *Current opinion in rheumatology*. 2015; 27:440–7. [PubMed: 26218512]
37. Al-Mayouf SM, Sunker A, Abdwani R, Abrawi SA, Almurshedi F, Alhashmi N, et al. Loss-of-function variant in DNASE1L3 causes a familial form of systemic lupus erythematosus. *Nature genetics*. 2011; 43:1186–8. [PubMed: 22019780]
38. Namjou B, Kothari PH, Kelly JA, Glenn SB, Ojwang JO, Adler A, et al. Evaluation of the TREX1 gene in a large multi-ancestral lupus cohort. *Genes and immunity*. 2011; 12:270–9. [PubMed: 21270825]
39. Harley JB, Alarcon-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXXK, KIAA1542 and other loci. *Nat Genet*. 2008; 40:204–10. [PubMed: 18204446]
40. Han JW, Zheng HF, Cui Y, Sun LD, Ye DQ, Hu Z, et al. Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. *Nat Genet*. 2009; 41:1234–7. [PubMed: 19838193]
41. Sanchez E, Comeau ME, Freedman BI, Kelly JA, Kaufman KM, Langefeld CD, et al. Identification of novel genetic susceptibility loci in African American lupus patients in a candidate gene association study. *Arthritis and rheumatism*. 2011; 63:3493–501. [PubMed: 21792837]

42. Chung SA, Brown EE, Williams AH, Ramos PS, Berthier CC, Bhangale T, et al. Lupus nephritis susceptibility loci in women with systemic lupus erythematosus. *Journal of the American Society of Nephrology: JASN*. 2014; 25:2859–70. [PubMed: 24925725]
43. Freedman BI, Langefeld CD, Andringa KK, Croker JA, Williams AH, Garner NE, et al. End-stage renal disease in African Americans with lupus nephritis is associated with APOL1. *Arthritis & rheumatology* (Hoboken, NJ). 2014; 66:390–6.
44. Taylor KE, Remmers EF, Lee AT, Ortmann WA, Plenge RM, Tian C, et al. Specificity of the STAT4 genetic association for severe disease manifestations of systemic lupus erythematosus. *PLoS Genet*. 2008; 4:e1000084. [PubMed: 18516230]
45. Sigurdsson S, Nordmark G, Garnier S, Grundberg E, Kwan T, Nilsson O, et al. A risk haplotype of STAT4 for systemic lupus erythematosus is over-expressed, correlates with anti-dsDNA and shows additive effects with two risk alleles of IRF5. *Hum Mol Genet*. 2008; 17:2868–76. [PubMed: 18579578]
46. Sanchez E, Nadig A, Richardson BC, Freedman BI, Kaufman KM, Kelly JA, et al. Phenotypic associations of genetic susceptibility loci in systemic lupus erythematosus. *Annals of the rheumatic diseases*. 2011; 70:1752–7. [PubMed: 21719445]
47. Lin CP, Adrianto I, Lessard CJ, Kelly JA, Kaufman KM, Guthridge JM, et al. Role of MYH9 and APOL1 in African and non-African populations with lupus nephritis. *Genes and immunity*. 2012; 13:232–8. [PubMed: 22189356]
48. Iwamoto T, Niewold TB. Genetics of human lupus nephritis. *Clinical immunology*. 2016
49. Niewold TB, Kelly JA, Kariuki SN, Franek BS, Kumar AA, Kaufman KM, et al. IRF5 haplotypes demonstrate diverse serological associations which predict serum interferon alpha activity and explain the majority of the genetic association with systemic lupus erythematosus. *Annals of the rheumatic diseases*. 2012; 71:463–8. [PubMed: 22088620]
50. Kariuki SN, Kirou KA, MacDermott EJ, Barillas-Arias L, Crow MK, Niewold TB. Cutting edge: Autoimmune disease risk variant of STAT4 confers increased sensitivity to IFN-alpha in lupus patients in vivo. *J Immunol*. 2009; 182:34–8. [PubMed: 19109131]
51. Salloum R, Franek BS, Kariuki SN, Rhee L, Mikolaitis RA, Jolly M, et al. Genetic variation at the IRF7/PHRF1 locus is associated with autoantibody profile and serum interferon-alpha activity in lupus patients. *Arthritis Rheum*. 2010; 62:553–61. [PubMed: 20112359]
52. Cherian TS, Kariuki SN, Franek BS, Buyon JP, Clancy RM, Niewold TB. Brief Report: IRF5 systemic lupus erythematosus risk haplotype is associated with asymptomatic serologic autoimmunity and progression to clinical autoimmunity in mothers of children with neonatal lupus. *Arthritis and rheumatism*. 2012; 64:3383–7. [PubMed: 22674082]
53. Niewold TB, Hua J, Lehman TJ, Harley JB, Crow MK. High serum IFN-alpha activity is a heritable risk factor for systemic lupus erythematosus. *Genes Immun*. 2007; 8:492–502. [PubMed: 17581626]
54. Postal M, Sinicato NA, Pelicari KO, Marini R, Lavras Costallat LT, Appenzeller S. Clinical and serological manifestations associated with interferon-alpha levels in childhood-onset systemic lupus erythematosus. *Clinics (Sao Paulo)*. 2012; 67:157–62. [PubMed: 22358241]
55. Mangale D, Kariuki SN, Chrabot BS, Kumabe M, Kelly JA, Harley JB, et al. Familial aggregation of high tumor necrosis factor alpha levels in systemic lupus erythematosus. *Clin Dev Immunol*. 2013; 2013:267430. [PubMed: 24187561]
56. Grondal G, Kristjansdottir H, Gunnlaugsdottir B, Arnason A, Lundberg I, Klareskog L, et al. Increased number of interleukin-10-producing cells in systemic lupus erythematosus patients and their first-degree relatives and spouses in Icelandic multicase families. *Arthritis Rheum*. 1999; 42:1649–54. [PubMed: 10446864]
57. Cham CM, Ko K, Niewold TB. Interferon regulatory factor 5 in the pathogenesis of systemic lupus erythematosus. *Clin Dev Immunol*. 2012; 2012:780436. [PubMed: 23251221]
58. Niewold TB, Kelly JA, Flesch MH, Espinoza LR, Harley JB, Crow MK. Association of the IRF5 risk haplotype with high serum interferon-alpha activity in systemic lupus erythematosus patients. *Arthritis Rheum*. 2008; 58:2481–7. [PubMed: 18668568]
59. Salloum R, Niewold TB. Interferon regulatory factors in human lupus pathogenesis. *Transl Res*. 2011; 157:326–31. [PubMed: 21575916]

60. Sankararaman S, Mallick S, Dannemann M, Prufer K, Kelso J, Paabo S, et al. The genomic landscape of Neanderthal ancestry in present-day humans. *Nature*. 2014; 507:354–7. [PubMed: 24476815]
61. Dannemann M, Andres AM, Kelso J. Introgression of Neandertal- and Denisovan-like Haplotypes Contributes to Adaptive Variation in Human Toll-like Receptors. *Am J Hum Genet*. 2016; 98:22–33. [PubMed: 26748514]
62. Deschamps M, Laval G, Fagny M, Itan Y, Abel L, Casanova JL, et al. Genomic Signatures of Selective Pressures and Introgression from Archaic Hominins at Human Innate Immunity Genes. *Am J Hum Genet*. 2016; 98:5–21. [PubMed: 26748513]
63. Fu Q, Zhao J, Qian X, Wong JL, Kaufman KM, Yu CY, et al. Association of a functional IRF7 variant with systemic lupus erythematosus. *Arthritis Rheum*. 2011; 63:749–54. [PubMed: 21360504]
64. Kariuki SN, Ghodke-Puranik Y, Dorschner JM, Chrabot BS, Kelly JA, Tsao BP, et al. Genetic analysis of the pathogenic molecular sub-phenotype interferon-alpha identifies multiple novel loci involved in systemic lupus erythematosus. *Genes and immunity*. 2015; 16:15–23. [PubMed: 25338677]
65. Kariuki SN, Franek BS, Kumar AA, Arrington J, Mikolaitis RA, Utset TO, et al. Trait-stratified genome-wide association study identifies novel and diverse genetic associations with serologic and cytokine phenotypes in systemic lupus erythematosus. *Arthritis Res Ther*. 2010; 12:R151. [PubMed: 20659327]
66. Koldobskaya Y, Ko K, Kumar AA, Agik S, Arrington J, Kariuki SN, et al. Gene-expression-guided selection of candidate loci and molecular phenotype analyses enhance genetic discovery in systemic lupus erythematosus. *Clin Dev Immunol*. 2012; 2012:682018. [PubMed: 22988468]
67. da Silva Almeida AC, Abate F, Khiabani H, Martinez-Escala E, Guitart J, Tensen CP, et al. The mutational landscape of cutaneous T cell lymphoma and Sezary syndrome. *Nature genetics*. 2015; 47:1465–70. [PubMed: 26551667]
68. Sasaki Y, Iseki M, Yamaguchi S, Kurosawa Y, Yamamoto T, Moriwaki Y, et al. Direct evidence of autosomal recessive inheritance of Arg24 to termination codon in purine nucleoside phosphorylase gene in a family with a severe combined immunodeficiency patient. *Hum Genet*. 1998; 103:81–5. [PubMed: 9737781]
69. Postal M, Sinicato NA, Appenzeller S, Niewold TB. Drugs in early clinical development for Systemic Lupus Erythematosus. *Expert Opin Investig Drugs*. 2016; 25:573–83.
70. Vigna-Perez M, Hernandez-Castro B, Paredes-Saharopulos O, Portales-Perez D, Baranda L, Abud-Mendoza C, et al. Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. *Arthritis Res Ther*. 2006; 8:R83. [PubMed: 16677395]
71. Diaz-Lagares C, Croca S, Sangle S, Vital EM, Catapano F, Martinez-Berriotxo A, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. *Autoimmun Rev*. 2012; 11:357–64. [PubMed: 22032879]
72. Pepper R, Griffith M, Kirwan C, Levy J, Taube D, Pusey C, et al. Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids. *Nephrol Dial Transplant*. 2009; 24:3717–23. [PubMed: 19617257]
73. Jonsdottir T, Sundelin B, Welin Henriksson E, van Vollenhoven RF, Gunnarsson I. Rituximab-treated membranous lupus nephritis: clinical outcome and effects on electron dense deposits. *Ann Rheum Dis*. 2011; 70:1172–3. [PubMed: 21367763]
74. Ramos-Casals M, Diaz-Lagares C, Khamashta MA. Rituximab and lupus: good in real life, bad in controlled trials. Comment on the article by Lu et al. *Arthritis Rheum*. 2009; 61:1281–2. [PubMed: 19714598]
75. Isenberg D, Appel GB, Contreras G, Dooley MA, Ginzler EM, Jayne D, et al. Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. *Rheumatology (Oxford)*. 2010; 49:128–40. [PubMed: 19933596]
76. Weng MY, Weng CT, Liu MF. The efficacy of low-dose mycophenolate mofetil for treatment of lupus nephritis in Taiwanese patients with systemic lupus erythematosus. *Clin Rheumatol*. 2010; 29:771–5. [PubMed: 20195879]

77. Mitka M. Treatment for lupus, first in 50 years, offers modest benefits, hope to patients. JAMA. 2011; 305:1754–5. [PubMed: 21540415]
78. Collins CE, Dall’Era M, Kan H, Macahilig C, Molta C, Koscielny V, et al. Response to belimumab among patients with systemic lupus erythematosus in clinical practice settings: 24-month results from the OBSERVE study in the USA. Lupus Sci Med. 2016; 3:e000118. [PubMed: 26835146]
79. Niewold TB. Connective tissue diseases: Targeting type I interferon in systemic lupus erythematosus. Nat Rev Rheumatol. 2016; 12:377–8. [PubMed: 27225301]
80. Richman IB, Taylor KE, Chung SA, Trupin L, Petri M, Yelin E, et al. European genetic ancestry is associated with a decreased risk of lupus nephritis. Arthritis and rheumatism. 2012; 64:3374–82. [PubMed: 23023776]
81. Golder V, Connelly K, Staples M, Morand E, Hoi A. Association of Asian ethnicity with disease activity in SLE: an observational study from the Monash Lupus Clinic. Lupus. 2013; 22:1425–30. [PubMed: 23942610]
82. Peschken CA, Katz SJ, Silverman E, Pope JE, Fortin PR, Pineau C, et al. The 1000 Canadian faces of lupus: determinants of disease outcome in a large multiethnic cohort. J Rheumatol. 2009; 36:1200–8. [PubMed: 19369456]

Key points

- Major biological subsets exist with the diagnosis of SLE, such as the distinction between high and low circulating type I interferon
- SLE manifests differently in various ancestral backgrounds, both clinically and molecularly
- Knowledge of the pathogenic factors that are most relevant to a given individual will be critical in designing more successful clinical trials and personalizing therapy for SLE.

Table 1

SLE manifestations with increased prevalence in specific ancestral backgrounds.

Ancestral background	Manifestations with increased prevalence	References
African-American	Discoid rash Nephritis Proteinuria	[19–21]
Amerindian *	Renal disease	[3, 80]
Asian	Renal disease	[81]
European-American	Photosensitivity Malar rash	[82]

* Indicating subjects with ancestry from Native American populations