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Local Ancestry at the Major Histocompatibility Complex Region is Not a Major Contributor to Disease Heterogeneity in a Multiethnic Lupus Cohort

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Abstract

Objective.—Systemic lupus erythematosus (SLE) is an autoimmune disease resulting in debilitating clinical manifestations that vary in severity by race and ethnicity with a

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Barcellos had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. This research was supported in part by the Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health.

Study conception and design. Solomon, Lanata, Nititham, Taylor, Chung, Yazdany, Dall'Era, Pons-Estel, Tusié-Luna, Tsao, Morand, Alarcón-Riquelme, Barcellos, Criswell.

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Analysis and interpretation of data. Solomon, Lanata, Adams, Barcellos, Criswell.

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disproportionate burden in African American, Mestizo, and Asian populations compared with populations of European descent. Differences in global and local genetic ancestry may shed light on the underlying mechanisms contributing to these disparities, including increased prevalence of lupus nephritis, younger age of symptom onset, and presence of autoantibodies.

Methods.—A total of 1,139 European, African American, and Mestizos patients with SLE were genotyped using the Affymetrix LAT1 World array. Global ancestry proportions were estimated using ADMIXTURE, and local ancestry was estimated using RFMIXv2.0. We investigated associations between lupus nephritis, age at onset, and autoantibody status with both global and local ancestry proportions within the Major Histocompatibility Complex region.

Results.—Our results showed small effect sizes that did not meet the threshold for statistical significance for global or local ancestry proportions in either African American or Mestizo patients with SLE who presented with the clinical manifestations of interest compared with those who did not.

Conclusion.—These findings suggest that local genetic ancestry within the Major Histocompatibility Complex region is not a major contributor to these SLE manifestations among patients with SLE from admixed populations.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease resulting in debilitating clinical manifestations that vary in severity by race and ethnicity.¹ Disparities in presentation and prognosis of SLE place a disproportionate burden on African American, Mestizo (admixed individuals with Amerindian and European descent), and Asian populations. Differences in global ancestry, the percentage of the overall genome that comes from different ancestral populations for an individual, and local ancestry, the ancestral population from which a single nucleotide polymorphism (SNP) or other genetic variant originated, may contribute to these observed disparities.

Prior studies have established genetic ancestry related differences in risk of SLE; however, few have investigated the relationship between disease manifestations and global ancestry,^{2,3} and no studies, to date, have investigated the role of local ancestry in relation to specific disease manifestations. Prior studies have shown that increased global European ancestry is associated with a decreased risk of lupus nephritis⁴ and a prior study that investigated global genetic ancestry in multiple racial and ethnic groups observed distinct genes and pathways associated with development of lupus nephritis in each population.² Evidence for association between local ancestry and lupus nephritis has not been reported.

Additionally, previous genome-wide association studies in European patients have shown stronger associations of SLE risk loci in patients with anti-double-stranded DNA (dsDNA) autoantibodies.⁵ Further, ancestry has been associated with gene-expression related to autoantibodies, including anti-dsDNA.⁶ Because genetic profiles within the Major Histocompatibility Complex (MHC) have been linked to the production of autoantibodies, it is thought that racial and ethnic differences in autoantibody profiles are due to genetics.⁷

In the current study, we used genotype data for a large multiethnic SLE cohort to investigate both global and local ancestry associations in the MHC region with SLE manifestations. Human leukocyte antigen (HLA) alleles in the MHC are highly polymorphic and strongly associated with lupus pathogenesis,⁸ making this area of the genome a strong candidate for elucidating local ancestry differences, which may contribute to SLE manifestations. We estimated global and local ancestry proportions for all patients and assessed the relationship between ancestry and lupus nephritis, age at onset, and autoantibody profiles.

MATERIALS AND METHODS

Participants.

Written informed consent was obtained from all study participants, and the institutional review board at each collaborating center approved the study (University of California, San Francisco; Oklahoma Medical Research Foundation, Monash Health; and University of California, Los Angeles).

Participants were patients from established SLE cohorts and included individuals of European, African American, and Mestizo race and ethnicities. A total of 1,139 SLE cases were obtained from the United States, Australia, Spain, and Mexico. All participants fulfilled the American College of Rheumatology revised classification criteria for SLE.⁹ Participants were recruited from a variety of settings, including academic medical centers and community hospitals.

SLE manifestations.

Four clinical manifestations, including anti-dsDNA autoantibody status, anti-Smith autoantibody status, lupus nephritis, and age of SLE onset, were studied. Lupus nephritis was defined as fulfilling the American College of Rheumatology renal classification criterion (>0.5 grams of proteinuria per day or 3+ protein on urine dipstick analysis) or having evidence of lupus nephritis on kidney biopsy.

Sample collections and genotyping.

DNA was collected from blood or saliva (Oragene DNA sample collection kits, DNAGenotek) from all study participants. Samples were genotyped using the Affymetrix LAT1 World array at the University of California, San Francisco, Institute of Human Genetics Genomics Core Facility. The Affymetrix LAT1 World array covers 817,810 SNP markers across the genome and was designed to include coverage for multiple diverse ethnic populations. Quality control procedures have been previously described.² Briefly, samples were filtered for a genotyping call rate less than 95%, discrepancies between reported and genetically assessed sex, and evidence of relatedness (one of each first-degree relative pairs removed, defined by identity by descent π -hat >0.25). Departure from Hardy-Weinberg equilibrium was assessed using European and Asian patients without lupus nephritis or anti-dsDNA autoantibodies. SNPs were removed from analysis if evidence of departure from Hardy-Weinberg equilibrium was present ($P < 5 \times 10^{-8}$ in self-identified European patients and $P < 1 \times 10^{-5}$ in self-identified Asian patients) or if genotyping call rates were below 95%. Standard Affymetrix Axiom metrics were also applied (Dish QC = 0.82 and default cluster

metrics of SNPlisher). After applying these quality control assessments, 1,139 participants and 722,240 SNPs were available for analysis.

Reference datasets.

We used 1000 Genomes (1000G)¹⁰ reference panel for individuals of European, African American, and Mestizo ancestry. To improve our reference on Indigenous American ancestry, we used an external dataset consisting of 43 individuals with more than 95% Indigenous American ancestry to identify the subset of 1000G with more than 95% Indigenous American ancestry.¹¹ ADMIXTURE¹² was run unsupervised including all Amerindian 1000G patients combined with the 43 nonadmixed patients, assuming 2 subpopulations ($K = 2$, Indigenous American and other). Nonadmixed 1000G Indigenous American patients were used for downstream ancestry inference.

Global ancestry estimation.

We used ADMIXTURE to determine the percentage of the overall genome belonging to each ancestral population. We first combined our sample data with 1000G genotype data and pruned SNPs for linkage disequilibrium, removing each SNP with an R^2 value greater than 0.1 in a 50 SNP sliding window advanced by 10 SNPs each time, as recommended.¹² This left 162,159 SNPs for global ancestry estimation. We then ran ADMIXTURE unsupervised assuming 5 subpopulations ($K = 5$, European, African, East Asian, South Asian, and Indigenous American). We used known labels from 1000G to determine the ancestry of the estimated proportions for each patient with SLE and placed them into European, African American, and Mestizo subgroups.

Phasing and HLA imputation.

To ensure a high density within the MHC region of the genome for local ancestry estimation, HIBAG¹³ was used to impute classical HLA alleles (HLA- A, B, C, DRB1, DQB1, DQA1, DQB1, and DPB1). HIBAG includes pretrained models for African American and Mestizo populations and is well suited for HLA allele imputation in the admixed SLE samples. Imputed alleles with more than 0.5 posterior probability were retained for downstream analysis, as recommended. Genotype data were phased with all populations together using BEAGLEv5.1,¹⁴ 1000G as a reference panel, and GRCh37 genetic map positions in centimorgans.

Local ancestry inference.

Genome-wide local ancestry inference was estimated separately in African American and Mestizo patients using a machine learning algorithm, RFMixv2.0.¹⁵ For each population, RFMixv2.0 requires four inputs: (1) phased haplotypes admixed patients, (2) phased reference haplotypes, (3) a file with labels for the reference populations, and (4) genetic map positions. For African American samples, the reference population consists of all nonadmixed African and European 1000G patients. For Mestizo samples, the reference population consists of the 24 nonadmixed Indigenous American 1000G patients, as well as 24 randomly sampled African and European 1000G patients. RFMix was run using recommended input parameters of five minimum number of reference haplotypes per

tree node and three expectation maximization iterations. The number of generations since admixture occurred that were used as input parameters were 6 and 11 for African American and Mestizo patients, respectively, according to previous estimates for populations in the United States.¹⁶

Statistical analysis.

Global ancestry.—To test for association between global ancestry proportions and SLE manifestations, we used two-sample bootstrapping to compare the mean ancestry between patients with SLE manifestations (with lupus nephritis, younger than median age at onset, presence of anti-dsDNA autoantibodies, and presence of anti-Smith autoantibodies) with patients with SLE without these manifestations.

Local ancestry.—To test for the association between local ancestry and SLE manifestations, we performed the nonparametric test statistic proposed by Montana and Prichard¹⁷ for admixture mapping. The equation for the test statistic is included below.

$$T(I, k) = \frac{(\bar{z}_{i,d}(k) - \bar{z}_{i,c}(k)) - (\bar{q}_d(k) - \bar{q}_c(k))}{SD(\bar{z}_{i,d}(k) - \bar{z}_{i,c}(k))}$$

The variables are defined as follows: $\bar{z}_{i,d}(k)$ is the average local ancestry of those with the SLE manifestation (lupus nephritis, younger age at onset, presence of anti-dsDNA and anti-Smith autoantibodies) at locus I for ancestry k and $\bar{z}_{i,c}(k)$ is the average local ancestry for SLE without the manifestations. The term $\bar{q}_d(k)$ is the genome-wide average of ancestry k among cases and $\bar{q}_c(k)$ is defined similarly for controls. The variance $Var(\bar{z}_{i,d}(k) - \bar{z}_{i,c}(k))$ of the test statistic at a given locus was empirically estimated as the sum of variance of average ancestry among patients with SLE manifestations and without. The SD follows as the square root of the variance. These terms were estimated using RFMix.

Tests were conducted within the MHC region (chr6:28477797–33448354), extended to candidate SNPs previously known to be associated with either SLE or lupus nephritis risk (Total N = 191), and finally extended genome wide. A list of candidate SNPs can be found in the Supplementary Materials. Multiple hypothesis testing was addressed using the false discovery rate. For genome-wide analyses, tests were corrected for the total number of windows output by RFMix; for candidate SNP analyses, for the total number of windows spanning the preselected SNPs; and finally, for HLA-specific analyses, for the total number of windows estimated within the MHC region. Complete details of how RFMix defines windows for local ancestry inference are described in this article.¹⁵

RESULTS

Participants and global ancestry estimation.

Global ancestry estimation identified a total of 236 African American, 306 Mestizo, and 597 European patients with SLE. Admixed patients (African American and Mestizo patients) were included in downstream analyses. On average, African American patients were 80.7%

African and 19.3% European, and Mestizo patients were 48.9% Indigenous American, 6.1% African, and 45.0% European (Table 1).

Global ancestry associations.

Within each racial and ethnic group, we tested for association between global ancestry proportions and SLE manifestations. There were no significant associations between global ancestry and SLE manifestations in African American or Mestizo patients.

Local ancestry associations.

We investigated the association between local ancestry and SLE manifestations. We investigated whether local ancestry spanning chromosome 6:28477797–33448345, which included HLA class I, II, and III regions, was associated with lupus nephritis, age at onset, anti-dsDNA autoantibody status, and anti-Smith autoantibody status, separately for each admixed population. In African American and Mestizo patients, RFMix estimated 50 and 85 windows of local ancestry, respectively.

Local ancestry differences between patients with SLE with and without the manifestations of interest were small throughout all the windows in the MHC region. On average, the difference in European ancestry in African American patients was 3.62% for lupus nephritis, 0.58% for age at onset, 0.20% for anti-Smith autoantibodies, and 0.01% for anti-dsDNA autoantibodies. In Mestizo patients, the average difference in European ancestry between patients with and without SLE manifestations was 3.30% for lupus nephritis, 0.14% for age at onset, 8.1% for anti-Smith autoantibodies, and 6.3% for anti-dsDNA autoantibodies. After correction for multiple hypothesis testing, no significant differences were observed in local ancestry between patients with SLE with and without the manifestations of interest in African American or Mestizo populations.

Results for anti-dsDNA autoantibodies showed the smallest nominal *P* values. Although no results reached statistical significance in our analysis, we report the top 10 results for differences in local ancestry with anti-dsDNA autoantibodies in both African American patients and Mestizo patients in Table 2. Figures 1A and 1B show the small differences in local ancestry observed in African American and Mestizo patients with SLE with and without anti-dsDNA autoantibodies.

DISCUSSION

Although SLE manifestations vary greatly by race and ethnicity, studies in multiethnic populations are lacking and reasons for the striking differences in clinical manifestations are poorly understood. Studies have previously identified differential genetic risk factors for different race and ethnicities; however, few studies have investigated genetic differences contributing to clinical manifestations, which have been observed to differ by race and ethnicity. In this study, we used two measures of genetic ancestry, global and local ancestry, to identify associations with clinical manifestations of SLE in two admixed populations, including African American and Mestizo patients. It is important to note that global ancestry associations with SLE outcomes might not be due to genetics alone. Global ancestry estimations can be a proxy for other race and ethnicity related characteristics, such as skin

color, physical appearance, and exposures such as structural racism.¹⁸ It is therefore difficult to disentangle the association of SLE disease manifestations from global genetic ancestry versus factors, which may be due to social determinants of health. In contrast, local ancestry measures are independently assorted throughout the genome, and therefore are a better measure to capture associations between genetic ancestry and SLE disease manifestations.

We did not observe any significant differences in local ancestry across the MHC region in African American or Mestizo patients with SLE with lupus nephritis status, age at onset, anti-dsDNA, or anti-Smith autoantibody status. The absence of differences in local ancestry according to the presence versus absence of more severe disease manifestations suggests that local ancestry is not a large contributor to the observed differences in SLE manifestation severity in African American and Mestizo patients in this study. Although some studies have suggested that genetics may be responsible for the observed differences, recent studies suggest that social determinants of health are a large contributor to these differences.¹⁹

A major strength of our study was the use of a clinically well-characterized multiethnic patient with SLE cohort allowing for analyses to extend beyond populations of European descent. Although SLE is more prevalent and severe in African American and Mestizo populations, multiethnic studies are lacking. Additionally, all patients were genotyped on the same Affymetrix LAT1 WorldArray platform, which has increased coverage for admixed populations.

Although the total sample size ($n = 1,139$) was large, we had limited power for genome-wide analyses within each admixed subpopulation. The small sample size of each admixed population may be one reason for negative findings. Power for local ancestry analyses is dependent on multiple factors: the magnitude of the association between the SNP and the outcome of interest, the proportion of admixture, and the minor allele frequency difference between the ancestral populations. With a small sample size and a lack of previous genome-wide association studies to identify SNPs associated with the specific manifestations of interest, we are only powered to identify windows that have a large minor allele frequency difference between the ancestral populations. Additionally, local ancestry is highly dependent on the choice of reference panels and assumes that the populations included in reference panels are the same populations that gave rise to admixture in the study participants. Care was taken to select appropriate reference populations, such as excluding patients from the African Ancestry in Southwest US and African Caribbean in Barbados from African reference panels as well as selecting Indigenous American reference samples in 1000G using an external reference, but our reference population for local ancestry estimation in Mestizo patients was small ($n = 24$) and still contained a small (<5%) amount of admixture. Our results may be biased by our reference panels and can be improved as better references are developed.

To our knowledge, this is the first study to investigate local ancestry associations with specific manifestations of SLE. Within the MHC region, we did not observe large differences in local ancestry in either African American or Mestizo patients. Future studies with larger numbers of admixed individuals as well as more appropriate, larger reference datasets may lead to improved local ancestry estimates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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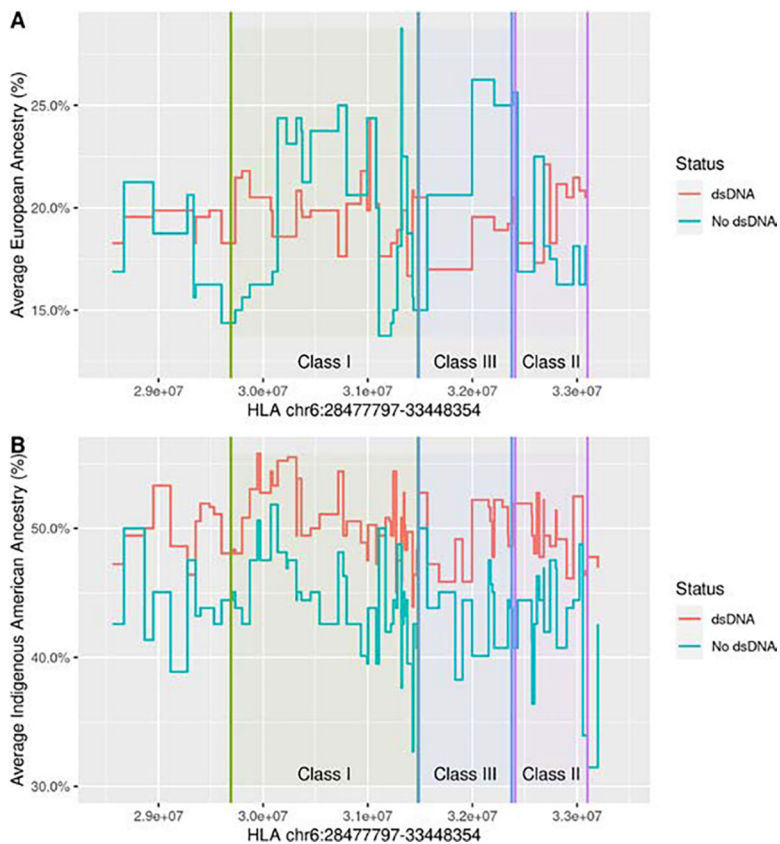


Figure 1.

(A) Difference in European ancestry in African American patients with and without anti-dsDNA autoantibodies in the MHC region and (B) difference in Indigenous American ancestry in Mestizo patients with and without anti-dsDNA autoantibodies in the MHC. Anti-dsDNA, anti-double-stranded DNA; HLA, human leukocyte antigen; MHC, Major Histocompatibility Complex.

Table 1.Patient characteristics by global ancestry group^{*}

	African American (n = 236)	Mestizo (n = 306)
Female, n (%)	224 (94.9)	282 (92.2)
Age at onset, mean (SD)	33 (13)	30 (11)
Lupus nephritis, n (%)	127 (54.0)	164 (53.6)
Anti-dsDNA, n (%)	156 (66.1)	181 (69.1)
Anti-Smith, N (%)	61 (26.0)	58 (26.5)

^{*}Anti-dsDNA, anti-double-stranded DNA.

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Table 2.

Top 10 MHC region local ancestry associations with anti-dsDNA in African American and Mestizo patients*

Population	Chr	Start	End	N SNPs	Test statistic	P value	Bonf.	Genes
African American	6	32740856	32804570	180	-2.639	0.008	1	<i>HLA-DOB, TAP2</i>
	6	32900072	32965062	115	-2.606	0.009	1	<i>HLA-DMB, HLA-DMA, BRD2</i>
	6	32804570	32900072	220	-2.559	0.010	1	<i>TAP2, PSMB8, LOC100507463, TAPI, PSMB9, LOC100294145</i>
	6	29871484	30072511	615	-2.545	0.011	1	<i>HLA-J, AK097625, HCG4B, BC035647, HLA-A, AK309533, HCG9, ZNRDI-AS1, UNQ6501, ZNRDI, PPP1R1I, RNF39, TRIM31</i>
	6	33022970	33081403	320	-2.541	0.011	1	<i>HLA-DPA1, HLA-DPB1, HLA-DPB2</i>
	6	33098524	33198592	105	-2.541	0.011	1	<i>COL11A2, RXRB, JA611279, SLC39A7, HSD17B8, MIR219-1, RING1</i>
	6	29354621	29486613	275	-2.528	0.011	1	<i>OR12D2, OR11A1, 6MI-18, OR10C1, OR2H1, MAS1L</i>
	6	29486613	29601560	200	-2.528	0.011	1	<i>LOC100507362, DQ573101, UBD, GABBR1, SNORD32B, OR2H2</i>
	6	30072511	30088156	40	-2.528	0.011	1	<i>TRIM31</i>
	6	29733179	29798642	185	-2.490	0.013	1	<i>HCG4, LOC554223, HLA-G, HLA-H</i>
Mestizo	6	29711747	29733179	30	-3.5042	0.0005	0.07	<i>HLA-F-AS1, IFITM4P</i>
	6	29601560	29711747	235	-3.4001	0.0007	0.09	<i>MOG, ZFP57, HLA-F, HLA-F-AS1</i>
	6	29733179	29798642	185	-3.3546	0.0008	1	<i>HCG4, LOC554223, HLA-G, HLA-H</i>
	6	29354621	29400280	125	-3.3063	0.0009	1	<i>OR12D2, OR11A1, 6MI-18</i>
	6	29530628	29601560	125	-3.2287	0.0012	1	<i>GABBR1, SNORD32B, OR2H2</i>
	6	29798642	29871484	180	-3.1844	0.0015	1	<i>HLA-H, HLA-J, AK097625</i>
	6	29486613	29530628	75	-3.1194	0.0018	1	<i>LOC100507362, DQ573101, UBD, GABBR1</i>
	6	29400280	29486613	150	-3.0572	0.0022	1	<i>6MI-18, OR10C1, OR2H1, MAS1L</i>

* Bonf., Bonferroni; Chr, Chromosome; anti-dsDNA, anti-double-stranded DNA; MHC, Major Histocompatibility Complex.