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Impact of Genetic Ancestry and Sociodemographic Status on the Clinical Expression of Systemic Lupus Erythematosus in American Indian–European Populations

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Objective. **American Indian–Europeans, Asians, and African Americans have an excess morbidity from systemic lupus erythematosus (SLE) and a higher prevalence of lupus nephritis than do Caucasians. The aim of this study was to analyze the relationship between genetic ancestry and sociodemographic characteristics and clinical features in a large cohort of American Indian–European SLE patients.**

Methods. **A total of 2,116 SLE patients of American Indian–European origin and 4,001 SLE patients of**

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European descent for whom we had clinical data were included in the study. Genotyping of 253 continental ancestry-informative markers was performed on the Illumina platform. Structure and Admixture software were used to determine genetic ancestry proportions of each individual. Logistic regression was used to test the association between genetic ancestry and sociodemographic and clinical characteristics. Odds ratios (ORs) were calculated with 95% confidence intervals (95% CIs).

Results. **The average American Indian genetic ancestry of 2,116 SLE patients was 40.7%. American Indian genetic ancestry conferred increased risks of renal involvement ($P < 0.0001$, OR 3.50 [95% CI 2.63–4.63]) and early age at onset ($P < 0.0001$). American Indian ancestry protected against photosensitivity ($P < 0.0001$, OR 0.58 [95% CI 0.44–0.76]), oral ulcers ($P < 0.0001$, OR 0.55 [95% CI 0.42–0.72]), and serositis ($P < 0.0001$, OR 0.56 [95% CI 0.41–0.75]) after adjustment for age, sex, and age at onset. However, age and sex had stronger effects than genetic ancestry on malar rash, discoid rash, arthritis, and neurologic involvement.**

Conclusion. **In general, American Indian genetic ancestry correlates with lower sociodemographic status and increases the risk of developing renal involvement and SLE at an earlier age.**

Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organ systems and affecting women ~9 times more than men. The severity of SLE varies widely among different ethnic groups. In African American, Hispanic/Mestizo, and Asian population groups, there is an excess morbidity from disease-related damage as compared to individuals of European ancestry (Caucasians) (1–3). In particular, non-Europeans have been shown to have an earlier age at disease onset and a higher occurrence of lupus nephritis than their European counterparts (4–9). The underlying nature of these disparities has not been defined, and differences in socioeconomic status and genetic factors have been proposed (10,11).

The contemporary American Indian–European (also called Hispanic/Mestizo) populations are a recent admixture derived from the original American Indian inhabitants, European settlers (primarily from Spain), and, to some degree, West Africans brought to the Americas as a consequence of the slave trade. They live mainly in Mexico, Puerto Rico, Cuba, South or Central America, and the US. The contribution of each parental population and the degree of admixture vary across regions in the Americas depending upon the local pattern of interaction among the different ethnic groups (12,13). We have previously shown that an increased proportion of the American Indian genome correlates with the presence of an increased number of risk alleles (14). Also, the role of socioeconomic factors in increasing morbidity and mortality in SLE among American Indian–European individuals has been previously shown (7,10,15). All data to date derive from self-reported ethnicity, subject to cultural subjectivity of one's own or physician-assessed estimates of ancestry.

Ancestry-informative markers are commonly used to estimate the average ancestral proportions for major source populations in admixed groups and are useful to efficiently account for population stratification (admixture) in genetic epidemiology studies with unrelated individuals (16,17). The use of self-reported ethnicity in genetic and epidemiologic studies has been much discussed in the literature (18,19). Some investigators have asked whether accounting for self-reported ethni-

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city alone might be sufficient to control for the confounding effect in genetic and epidemiologic studies. Furthermore, the understanding of background ancestries is essential to identifying genome-wide associations in complex traits (20). Understanding how genetic, socioeconomic, and cultural factors each contribute to health outcomes in SLE is essential to determine the optimal medical and social management of these patients.

The aim of the current study was to estimate the ancestral proportions in the largest sample collected to date of SLE patients of American Indian–European origin from different countries in the Americas, and to determine the relationship between genetic ancestry, sociodemographic characteristics, and clinical features. We used a set of 253 highly informative ancestry-informative markers to determine American Indian, European, Asian, and African genetic contributions in the sample. In general, we found that American Indian genetic ancestry correlated with lower sociodemographic status. Clinically, American Indian genetic ancestry conferred an increased risk of renal involvement, which correlated with the self-reported or physician-assessed American Indian–European ethnicity. On the other hand, European genetic ancestry increased the risks of photosensitivity, oral ulcers, and serositis and, to a lesser degree, the risks of malar and discoid rash and arthritis, while American Indian genetic ancestry protected against these risks.

PATIENTS AND METHODS

Populations. Three groups of patients were included in the study. The first set was an American Indian–European population of patients with SLE who were recruited from 4 countries (Argentina, Mexico, Peru, and Chile) through a multicenter collaboration within Latin America (the Genoma de Lupus Eritematoso Sistemico Network [GENLES] consortium) and from the US at the Lupus Family Registry and Repository (LFRR) in Oklahoma and assembled at the Oklahoma Medical Research Foundation (OMRF). This combined population included 1,384 SLE patients (American Indian–European SLE set 1). The second set was an American Indian–European population that included 732 nonoverlapping SLE patients (American Indian–European SLE set 2) from Colombia and different states in the US (from the LFRR at OMRF, the University of California Los Angeles, the University of California San Francisco, the University of Southern California, and the PROFILE Study Group at the University of Alabama at Birmingham). Finally, an additional European population was included that consisted of 4,001 SLE patients who were recruited through a multicenter collaboration within the US and who were also assembled at the OMRF (European SLE set). Therefore, the study included a total of 2,116 SLE patients of American Indian–European origin and 4,001 European SLE patients. All patients fulfilled the American College of Rheumatology (ACR) criteria for the classification of SLE (21). All subjects provided informed consent for participation in this study. The study was approved by the various institutional review boards at each of the participating institutions.

Sociodemographic data. The following sociodemographic data were collected for the patients in American Indian–European SLE set 1: physician-assessed ancestry, sex, age at onset (defined as age at date of presentation of the first ACR criteria), formal education in years, medical coverage (which could be public, institutional partial or complete, private partial or complete, or none), and socioeconomic level as defined by the Graffar scale (low, medium, high, or poverty) (22). The socioeconomic status was determined by questionnaires including information on 6 categories: family monthly income, occupation of the head of the household, percentage of family income spent on food, type and characteristics of residence (owner occupied, rented, or shared with extended family), place of residence, and the presence of chronic illnesses in other family members. Points are given for each category, and the sum is used to assign participants to 1 of 6 socioeconomic status bands (lowest to highest).

In general, physician-assessed ancestry was only a visual and subjective estimation of the ancestry of the patient, based on skin color and other physical characteristics such as height. This was reported as European, American Indian–European, American Indian, West African, Asian, or other.

Genotyping. A total of 253 of the 347 ancestry-informative markers overlapping in 2 BeadChip experiments were selected on the basis of a large allelic frequency difference between continental populations (16,17,23). For the American Indian–European SLE set 1, genotypes were extracted from an ongoing genome-wide association study (GWAS) using the Illumina HumanOmni1-Quad version 1 BeadChip Kit, while for the American Indian–European SLE set 2 and the European SLE set, we extracted genotypes from an Illumina Custom Bead system as part of the Large Lupus Association Study 2 used for replication of the International Consortium on the Genetics of Systemic Lupus Erythematosus GWAS (24). For initial analysis, as reference we included genotypes, publicly available in HapMap (http://hapmap.ncbi.nlm.nih.gov/), from Europeans (CEU: Utah residents with Northern and Western European ancestry from the Centre d'Étude du Polymorphisme Humain collection and TSI: Tuscan in Italy), American Indian–Europeans (MEX: Mexican ancestry in Los Angeles, California), West Africans (YRI: Yoruban in Ibadan, Nigeria), and Asians (CHB: Han Chinese in Beijing, China and JPT: Japanese in Tokyo, Japan). In addition, we included genotypes from 80 American Indian individuals (Nahuas) from Ocotitlán, Mexico (25) who were genotyped using the Illumina HumanOmni1-Quad version 1 BeadChip Kit and who were known to have been in relative isolation.

Statistical analysis. Individual ancestry proportions were estimated using a model-based clustering method by grouping data for the total sample in 4 ancestral populations ($K = 4$) with Structure software, version 2.2 (26). The individual ancestry proportions were also independently estimated using Admixture software, version 1.4 (27). Spearman's rank

Table 1. Ancestry proportions (%) in each set of SLE patients*

Ancestry	American Indian–European SLE set 1 (n = 1,384)	American Indian–European SLE set 2 (n = 732)	American Indian–European SLE set 1 + SLE set 2 (n = 2,116)	European SLE set (n = 4,001)
American Indian	47.6	27.8	40.7	2
European	44.5	57.8	49.4	94.6
West African	4.6	9.5	6.2	1.6
Asian	3.3	4.9	3.7	1.8

* SLE = systemic lupus erythematosus.

correlation coefficient was calculated to compare the individual admixture estimates obtained with both programs. Comparisons of the individual ancestry estimates between females and males were performed by means of Student's *t*-test and chi-square test using GraphPad Prism software, version 5.04 for Windows. A chi-square test was performed to compare clinical manifestations between American Indian–Europeans and Europeans. We used logistic regression as implemented by Stata/SE software, version 10.1, to test the association between ancestry and clinical characteristics, adjusting for age and sex. The same software was used to perform a linear regression analysis to assess the role of American Indian ancestry and age at onset of SLE.

RESULTS

Ancestry estimation. American Indian–European SLE set 1 included 1,384 SLE patients. The admixture proportions in this set were 47.6% American Indian, 44.5% European, 4.6% West African, and 3.3% Asian (Table 1). We found increased American Indian ancestry proportions in females compared with males (45.2% versus 38.7%; $P = 0.006$).

American Indian–European SLE set 2 included 732 American Indian–European SLE patients with the following admixture proportions: 27.8% American Indian, 57.8% European, 9.5% West African, and 4.9% Asian (Table 1). We did not find differences in American Indian ancestry proportions between females and males in this second cohort (27.3% versus 30.1%, respectively; $P = 0.3$). The discrepancies in the admixture estimates in both cohorts could be explained by differences in the regional demographic history of each population and possibly by the effects of socioeconomic status. The means of admixture proportions for both American Indian–European cohorts together (n = 2,116) were 40.7% American Indian, 49.4% European, 6.2% West African, and 3.7% Asian (Table 1). No differences were found in American Indian ancestry proportions between females and males (38.3% versus 38.7%, respectively; $P = 0.9$). The individual admixture proportions estimated using Structure showed a high correlation with those obtained using Admixture ($r_s = 0.994$, $P < 0.0001$ and $r_s = 0.995$, $P < 0.0001$ for correlations of American Indian and European ancestry, respectively). The additional European cohort that included 4,001 SLE patients presented admixture proportions of 2% American Indian, 94.6% European, 1.6% West African, and 1.8% Asian.

Sociodemographic characteristics of the analyzed sample. In our American Indian–European population, we had sociodemographic data for 814 of 2,116 patients. We observed differences between physician-assessed ethnicity and genetic ancestry. Of those individuals assessed as Europeans, 73.2% had European ancestry and 24.2% had American Indian ancestry (Table 2). However, those individuals assessed as American Indian–Europeans had higher American Indian ancestry (57.2%) and lower European ancestry (37.4%) than

Table 2. Average genetic ancestry by physician-assessed designations in a portion of the American Indian–European systemic lupus erythematosus set 1 cohort (recruited through the Genoma de Lupus Eritematoso Sistemico Network [GENLES] consortium)

Physician-assessed ethnicity (n)	Genetic ancestry, %			
	European	American Indian	West African	Asian
European (54)	73.2	24.2	1.3	1.3
American Indian–European (Mestizo) (597)	37.4	57.2	4.2	1.2
American Indian (132)	46.5	50.3	1.5	1.7
Other (31)	44.1	51.8	2.0	2.1

Table 3. Clinical characteristics of the self-reported or physician-assessed American Indian–European and European SLE patients*

Characteristic	American Indian–European SLE patients (n = 2,116)	European SLE patients (n = 4,001)	*P*	OR (95% CI)
Age at onset, mean ± SD years	22.2 ± 13.1	33.6 ± 13.7	<0.0001	–
Malar rash	1,243/2,110 (58.9)	2,262/3,583 (63.1)	0.002	1.19 (1.07–1.33)
Discoid rash	252/2,109 (11.9)	617/3,376 (18.3)	4.29×10^{-10}	1.64 (1.40–1.92)
Photosensitivity	1,218/2,106 (57.8)	2,512/3,793 (66.2)	1.50×10^{-10}	1.43 (1.28–1.59)
Oral ulcers	861/2,107 (40.9)	1,673/3,538 (47.3)	2.70×10^{-6}	1.30 (1.16–1.45)
Arthritis	1,524/2,111 (72.2)	3,211/3,911 (82.1)	3.56×10^{-19}	1.77 (1.56–2.00)
Serositis	551/2,057 (26.8)	1,455/3,587 (40.6)	2.31×10^{-25}	1.86 (1.66–2.10)
Renal involvement	1,017/2,088 (48.7)	1,226/3,533 (34.7)	3.73×10^{-25}	1.79 (1.60–2.00)
Neurologic involvement	303/2,109 (14.4)	606/3,330 (18.2)	0.0002	1.32 (1.14–1.54)
Hematologic involvement	1,310/1,940 (67.5)	2,213/3,348 (66.1)	0.29	1.07 (0.95–1.20)

* Except where indicated otherwise, values are the number/total number (%) of patients. SLE = systemic lupus erythematosus; OR = odds ratio; 95% CI = 95% confidence interval.

those assessed as American Indians (50.3% American Indian ancestry and 46.5% European ancestry) (Table 2). When we analyzed the socioeconomic information in this data set, we found that the mean American Indian admixture was higher in those individuals who had fewer years of education (<11 years of education; $P = 0.003$), those without medical coverage ($P = 0.0002$), and those with lower socioeconomic status (<5 points in socioeconomic level; $P = 0.006$) as measured using the Graffar scale.

Clinical characteristics of the patients studied. The clinical characteristics of American Indian–European and European SLE patients in these data sets are summarized in Table 3. We first investigated the overall group of self-reported or physician-assessed American Indian–Europeans and compared our findings with data previously reported by our group for Europeans from the Large Lupus Association Study 2 that overlap with data for our European set of 4,001 SLE patients (28). Similar to previous studies, we found a higher prevalence of renal involvement in our complete set of American Indian–Europeans as compared to Europeans (48.7% versus 34.7%; $P = 3.73 \times 10^{-25}$). In addition, an early age at onset was found in American Indian–European SLE patients as compared to European SLE patients (mean ± SD 22.2 ± 13.1 years versus 33.6 ± 13.7 years; $P < 0.0001$). In contrast, the presence of malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, and neurologic involvement was higher in Europeans as compared to American Indian–Europeans ($P = 0.002$, $P = 4.29 \times 10^{-10}$, $P = 1.50 \times 10^{-10}$, $P = 2.70 \times 10^{-6}$, $P = 3.56 \times 10^{-19}$, $P = 2.31 \times 10^{-25}$, and $P = 0.0002$, respectively) (Table 3). However, no significant differences were observed for the presence of hematologic involvement between Europeans and American Indian–Europeans ($P = 0.29$) (Table 3).

Table 4. Logistic and linear regression analysis of individual clinical lupus phenotypes with American Indian genetic ancestry*

	P	OR (95% CI)	Adjusted *P*†	OR (95% CI)
Age at onset	<0.0001‡	—	NA	NA
Malar rash	0.001	0.68 (0.55–0.85)	0.03	0.73 (0.56–0.96)
Discoid rash	<0.0001	0.35 (0.24–0.49)	0.001	0.51 (0.34–0.76)
Photosensitivity	<0.0001	0.35 (0.28–0.44)	<0.0001	0.58 (0.44–0.76)
Oral ulcers	<0.0001	0.51 (0.41–0.64)	<0.0001	0.55 (0.42–0.72)
Arthritis	<0.0001	0.34 (0.27–0.43)	0.001	0.59 (0.43–0.80)
Serositis	<0.0001	0.35 (0.27–0.45)	<0.0001	0.56 (0.41–0.75)
Renal involvement	<0.0001	3.55 (2.84–4.44)	<0.0001	3.50 (2.63–4.63)
Neurologic involvement	0.016	0.68 (0.50–0.93)	0.71	0.93 (0.64–1.35)
Hematologic involvement	0.22	1.16 (0.91–1.47)	0.89	1.02 (0.76–1.37)

* OR = odds ratio; 95% CI = 95% confidence interval; NA = not applicable.
† Adjusted for age, sex, and age at onset.
‡ Linear regression.

We then investigated the correlation between genetic ancestry and clinical features. The results of the linear and logistic regression analyses using the individual clinical manifestations as dependent variables and American Indian ancestry, age, sex, and age at onset as independent variables are presented in Table 4.

In a linear regression model, a significant correlation was observed between individual genetic American Indian ancestry and early age at onset ($P < 0.0001$). This finding confirms the observation of early age at SLE onset in so-called American Indian–European populations (29). We found an increased risk of renal involvement (odds ratio [OR] 3.55) that also correlated with genetic American Indian ancestry as did American Indian–European ethnicity. In addition, American Indian genetic ancestry was protective against malar rash (OR 0.68), discoid rash (OR 0.35), photosensitivity (OR 0.35), oral ulcers (OR 0.51), arthritis (OR 0.34), serositis (OR 0.35), and neurologic involvement (OR 0.68). No significant association was found with other clinical features, such as hematologic involvement (OR 1.16). Importantly, malar rash (OR 0.73), discoid rash (OR 0.51), arthritis (OR 0.59), and neurologic involvement (OR 0.93) were confounded by age, sex, and age at onset, suggesting that age and sex have a stronger influence on those manifestations than does genetic ancestry. In fact, neurologic involvement was no longer significantly correlated with genetic ancestry ($P = 0.71$) (Table 4). On the other hand, photosensitivity, oral ulcers, serositis, and renal involvement were not influenced by the adjustment for age, sex, and age at onset.

DISCUSSION

We present here the largest set of American Indian–European SLE patients for whom we define correlations between genetic ancestry and individual clinical manifestations as defined by the ACR criteria and sociodemographic factors. In our study, we demonstrated for the first time a significant relationship between American Indian genetic ancestry and SLE. Our main findings are that American Indian genetic ancestry correlates with lower sociodemographic level and increases both the risk of developing SLE at an earlier age and the risk of developing renal disease. These results were not influenced by age, sex, or age at onset. Renal disease is a common and serious manifestation of SLE, the presentation of which can range from mild to severe. It would be of interest to try to correlate American Indian genetic ancestry with more severe nephritis. Unfortunately, and despite our effort to collect as much information as possible, we do not have enough detailed clinical data to address this point.

American Indian ancestry protected against photosensitivity, oral ulcers, and serositis, while no relationship was observed with hematologic or neurologic involvement. Malar rash, discoid rash, and arthritis were strongly influenced by age, age at onset, and sex. Our results are consistent with epidemiologic studies suggesting that individuals of American Indian descent have a higher risk of developing SLE at an early age and also have more severe disease, with a higher prevalence of lupus nephritis compared to individuals of European ancestry. The differences in SLE risk among individuals of American Indian and European ancestry render this complex trait ideal for the designs of admixture mapping in the American Indian–European population. This approach is most successful when the differences in susceptibility allele frequency and disease prevalence between ≥ 2 parental populations are large, and when the populations have been recently admixed (11,12).

The use of self-reported race or ethnicity in genetic and epidemiologic studies has been much discussed in the literature (13,18,19,30–33). Our results point toward an important difference between self-reported or physician-assessed ethnicity and the actual genetic ancestry of an individual. This result is not surprising given the current definition of the terms "Hispanic" or "Mestizo," which refer to a group of individuals who are culturally and genetically quite diverse. One factor that may explain the genetic heterogeneity detected among self-reported American Indian–Europeans and their actual genetic ancestry may be the lack of individuals of pure American Indian ancestry represented in the sample. To assess this problem, we included genotypes from 80 Nahua individuals as a reference panel of American Indians. The Nahuas are a relatively isolated population of American Indian origin (25), but it should be borne in mind that these represent primarily North American indigenous groups. Another factor of self-reported ethnicity errors can be a lack of awareness of one's true ethnicity, while others may identify with 1 ethnic group despite their admixed background; yet another factor is the subjectivity of the perception that a physician may have, possibly primarily based on skin or hair color or some particular facial features with dominant inheritance.

In any study of the relationship of disease risk to individual admixture, socioeconomic and demographic factors may confound the association. In fact, it may be that American Indian–European ethnicity as such, by virtue of being strongly correlated with poor socioeco-

nomic level (7,10), leads to an increased risk of developing a more florid disease with several ACR criteria than that found in European individuals from the US or Europe, while the actual genetic ancestry alone does not confer such increased risk. Unfortunately, our study has several limitations. The sample size for the individuals for whom we have sociodemographic data is too small to assess the relative effects or high correlations of potentially confounding variables. A previous LUpus in MInorities, NAture versus nurture (LUMINA) study suggested that both ethnicity and admixture accounted for the risk observed in non-European populations (5,34). Although we cannot exclude the contribution of environmental factors in our findings, the effect observed in the current study suggests that individuals with a high American Indian genetic ancestry have a higher risk of disease.

Using genetic ancestry, our results confirm that increased American Indian ethnicity is correlated with a disadvantageous outcome, particularly renal involvement. Our data also suggest that the use of self-reported ethnicity is not enough to control for the confounding effect in genetic and epidemiologic studies. Additionally, our findings suggest that this population is well suited for the identification and further characterization of genetic risk factors for SLE by means of admixture mapping for genes of American Indian origin, as well as genes that may be associated with early age at onset, renal disease, oral ulcers, photosensitivity, and serositis, manifestations not influenced by sex or age.

However, our findings cannot rule out the possibility that lower socioeconomic status may confound the association between, for instance, renal disease and ancestry. Many confounders may modulate the effects of ethnicity on disease expression and outcome, including insurance status, language barriers, time to referral, medication compliance, level of education, cultural differences, and others. Therefore, further studies should be carried out to try to elucidate the role of socioeconomic factors including genetic ancestry in the model.

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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. Alarcón-Riquelme 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.

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