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Impact of Genetic Ancestry and Socio-Demographic Status on the Clinical Expression of Systemic Lupus Erythematosus in Amerindian-European Populations

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Abstract

Objective—Amerindian-Europeans, Asians and African-Americans have an excess morbidity from SLE and higher prevalence of lupus nephritis than Caucasians. The aim of this study was to

analyze the relationship between genetic ancestry and socio-demographic characteristics and clinical features in a large cohort of Amerindian-European SLE patients.

Methods—A total of 2116 SLE patients of Amerindian-European origin and 4001 SLE patients of European descent with clinical data were used in the study. Genotyping of 253 continental ancestry informative markers was performed on the Illumina platform. The STRUCTURE and ADMIXTURE software were used to determine genetic ancestry of each individual. Correlation between ancestry and socio-demographic and clinical data were analyzed using logistic regression.

Results—The average Amerindian genetic ancestry of 2116 SLE patients was 40.7%. There was an increased risk of having renal involvement (P<0.0001, OR= 3.50 95%CI 2.63-4.63) and an early age of onset with the presence of Amerindian genetic ancestry (P<0.0001). Amerindian 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 by age, gender and age of onset. However, gender and age of onset had stronger effects on malar rash, discoid rash, arthritis and neurological involvement than genetic ancestry.

Conclusion—In general, genetic Amerindian ancestry correlates with lower socio-demographic status and increases the risk for developing renal involvement and SLE at an earlier age of onset.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organ systems and affecting women approximately nine times more than men. The severity of SLE varies widely among different ethnic groups. In African-Americans, Hispanics/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 of disease onset, and a higher occurrence of lupus nephritis than their European counterpart (4-9). The underlying nature of these disparities has not been defined, and differences in socio-economic status and genetic factors have been proposed (10, 11).

The contemporary Amerindian-European, also called Hispanics/Mestizo populations are a recently admixed population derived from the original Amerindian (Native American) 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 United States. The contribution of each parental population and the degree of admixture vary across regions in the Americas depending upon the local pattern of interaction amongst the different ethnic groups (12, 13). We have previously shown that an increased proportion of Amerindian genome correlates with the presence of an increased number of risk alleles (14). Also the role of socio-economic factors in increasing morbidity and mortality in SLE among Amerindian-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 ancestral estimates.

Ancestry informative markers (AIMs) 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 ethnicity alone might be sufficient to control for the confounding effect in genetic and epidemiologic studies. Furthermore, the understanding of the background

ancestries is essential to identifying genome-wide associations in complex traits (20). Understanding how genetic, social economic 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 Amerindian-European origin from different countries in the Americas, and to determine the relationship between genetic ancestry, socio-demographic characteristics and clinical features. We used a set of 253 highly informative AIMs to determine Amerindian, European, Asian and African genetic contributions in the sample. In general, we found that Amerindian genetic ancestry correlated with lower socio-demographic status. Clinically, there was an increased risk of having renal involvement with the presence of Amerindian genetic ancestry, which correlated with the self-reported or physician assessed Amerindian-European ethnicity. On the other hand, European genetic ancestry increased the risk (or Amerindian protected against the risk) for photosensitivity, oral ulcers, and serositis and to a lesser degree to malar and discoid rash and arthritis.

MATERIAL AND METHODS

Populations

Three groups of patients were included in the study. The first set is an Amerindian-European population with SLE that was recruited from five countries (Argentina, Mexico, Perú and Chile) through a multicenter collaboration within Latin America (GENLES consortium) and from the USA at the Lupus Family Registry and Repository in Oklahoma (LFRR) and assembled at the Oklahoma Medical Research Foundation (OMRF). This combined population includes 1384 SLE patients (Amerindian-European SLE set 1). The second set is a SLE Amerindian-European population including 732 non-overlapping SLE patients (Amerindian-European SLE set 2) from Colombia and different states in the USA (including LFRR, University of California, The PROFILE Study group and University of Southern California). Finally an additional SLE European population including 4001 SLE patients and recruited through a multicenter collaboration within the USA and assembled as well at the OMRF (European SLE set) was included. Therefore, the study includes a total of 2116 SLE patients of Amerindian-European origin and 4001 European SLE patients. All cases fulfilled the American College of Rheumatology (ACR) criterion for the classification of SLE (21). All subjects provided informed consent for this study. The study was approved by the various institutional review boards at each of the participating institutions.

Socio-demographic data

For the patients from the Amerindian-European SLE set 1, the following socio-demographic data was collected: physician assessed ancestry, gender, age of onset defined as date of presentation of the first ACR criteria, education in formal years, medical coverage, which could be public, Institutional partial or complete, private partial or complete or none; and socio-economic level as defined by the Graffar scale in low, medium, high and poverty (22). The socio-economic-status was determined by questionnaires including information on six 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 of one of six socio-economic 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

and this was reported as European, Amerindian-European, Amerindian, African, Asian or other.

Genotyping

A total of 253 of the 347 AIMs overlapping in two BeadChip experiments were selected on the basis of a large allelic frequency difference between continental populations (16, 17, 23). In the Amerindian-European SLE set 1 genotypes were extracted from an ongoing genome-wide association study (GWAS) on the Illumina HumanOMNI1Quadv1 while for the Amerindian-European SLE set 2 and the European set we extracted genotypes from an Illumina Custom Bead system as part of the lupus large association study 2 (LLAS2) used for replication of the SLEGEN GWAS (24). For initial analysis, we included as reference genotypes publicly available in HapMap (http://hapmap.ncbi.nlm.nih.gov/) from Europe (CEU: Utah residents with Northern and Western European ancestry from the CEPH collection and TSI: Tuscan in Italy), Amerindian-European (MEX: Mexican ancestry in Los Angeles, California), West African (YRI: Yoruban in Ibadan, Nigeria) and Asian (CHB: Han Chinese in Beijing, China and JPT: Japanese in Tokyo, Japan). In addition we included genotypes from 80 Native American individuals (Nahuas) from Ocotitlán, Mexico (25) that were genotyped for the Illumina HumanOMNI1Quadv1 and known to have been in relative isolation.

Data analyses

Individual ancestry proportions were estimated using a model-based clustering method by grouping data for the total sample in four ancestral populations (K= 4) with the software STRUCTURE v2.2 (26). The individual ancestry proportions were also independently estimated using the software ADMIXTURE v1.4 (27). Spearman's rank 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 χ^2 test using the GraphPad Prism v5.04 for windows (GraphPad Software, San Diego, CA, USA). A χ^2 test to compare clinical manifestations between Amerindian-European and European was performed. We used logistic regression as implemented by STATA/SE 10.1 software (Stata Cop LP, TX, USA), to test the association between ancestry and clinical characteristics, adjusting for age and gender. The same software was used to perform a linear regression analysis to assess the role of Amerindian ancestry and age at onset of SLE.

RESULTS

Ancestry estimation

The first Amerindian-European set includes 1384 SLE patients. The admixture proportions in this set were 47.6% Amerindian, 44.5% European, 4.6% West African and 3.3% Asian (Table 1). We found increased Amerindian ancestry proportions in females compared with males (45.2% in females vs. 38.7% in males, P= 0.006).

Our second set included 732 SLE Amerindian-European patients with the following admixture proportions 27.8% Amerindian, 57.8% European, 9.5% West African and 4.9% Asian (Table 1). We did not find differences in the Amerindian ancestry proportions between females and males in this second cohort (27.3% vs. 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 due to effects of socio-economic status. The total mean of ancestries for both Amerindian-European cohorts together (Amerindian-European set 1 + 2, n= 2116) are 40.7% Amerindian, 49.4% European, 6.2% West African and 3.7% Asian (Table 1). No differences

in Amerindian ancestry proportions between females and males (38.3% vs. 38.7%, respectively, $P = 0.9$) were found. The individual admixture proportions estimated with STRUCTURE showed a high correlation with those obtained with ADMIXTURE (Spearman's $r^2 = 0.994$, $P < 0.0001$; Spearman's $r^2 = 0.995$, $P < 0.0001$ for correlations of Amerindian and European ancestry, respectively). The additional European cohort that includes 4001 SLE patients present a total mean of ancestries of 2% Amerindian, 94.6% European, 1.6% West African and 1.8% Asian.

Socio-demographic characteristics of the analyzed sample

In our Amerindian-European population a total of 814 of 2116 patients had socio-demographic data. We observed differences between the physician-assessed ethnicity and genetic ancestry. Those individuals assessed as Europeans had 73.2% of European ancestry and 24.2% of Amerindian ancestry (Table 2). However, those individuals assessed as Amerindian-European had a higher Amerindian ancestry (57.2%) and lower European ancestry (37.4%) that those assessed as Amerindians (50.3% Amerindian ancestry and 46.5% European ancestry) (Table 2).

When we analyzed in this data set the socio-economic information, we found that the mean Amerindian admixture was higher in those individuals who had fewer years of education (less than 11 years of education, $P = 0.003$), those without medical coverage ($P = 0.0002$) and lower socio-economic status (less than 5 points in socio-economic level, $P = 0.006$) as measured using the Graffar scale.

Clinical characteristics of the patients studied

The clinical characteristics of Amerindian-European and European SLE patients in these datasets are summarized in Table 3. We first investigated the overall group of self-reported or physician assessed Amerindian-European and compared to data previously published by our group for Europeans from the LLAS2 study that overlap with our 4001 SLE European set (28). Similarly to previous studies we found higher prevalence of renal involvement in our complete set of Amerindian-European as compared to Europeans (48.7% vs. 34.7%, $P = 3.73 \times 10^{-25}$). In addition, an early age of onset was found in Amerindian-European as compared to European SLE patients (22.2 ± 13.1 years vs. 33.6 ± 13.7 years, $P < 0.0001$). In contrast, the presence of malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis and neurological involvement was higher in Europeans as compared to Amerindian-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 hematological involvement between Europeans and Amerindian-Europeans ($P = 0.29$) (Table 3).

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 Amerindian ancestry, age, gender and age of onset as independent variables are presented in Table 4. In a linear regression model, a significant correlation between individual genetic Amerindian ancestry and early age of onset ($P < 0.0001$) was observed. This finding confirms the early age of onset observation of SLE in so called Amerindian-European populations (29). We found an increased risk in the odds of having renal involvement (OR= 3.55) that also correlated with genetic Amerindian ancestry as Amerindian-European ethnicity did. In addition, Amerindian genetic ancestry was protective for 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 neurological involvement (OR= 0.68). No significant association with other clinical features such as hematological involvement was found (OR= 1.16). Importantly, malar rash (OR= 0.73),

discoid rash (OR= 0.51), arthritis (OR= 0.59) and neurological involvement (OR= 0.93) were confounded by age, gender status and age of onset, suggesting that age and gender have a stronger influence on those manifestations than genetic ancestry. In fact, neurological 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, gender and age of onset.

Discussion

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

Amerindian ancestry protected against photosensitivity, oral ulcers, and serositis while no relationship was observed with hematological or neurological involvement and Amerindian genetic ancestry. Malar rash, discoid rash and arthritis were strongly influenced by age, age of onset and gender. Our results are consistent with epidemiological studies suggesting that individuals of Amerindian descent have a higher risk for developing SLE at early age and also have more severe disease, with a higher prevalence of lupus nephritis compared to individual of European ancestry. The differences in SLE risk among individuals of Amerindian and European ancestry render this complex trait ideal for the designs of admixture mapping in the Amerindian-European population. This approach is most successful when the differences in susceptibility allele frequency and disease prevalence between two or more 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 towards an important difference between the 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 term “Hispanics” 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 Amerindian-European and their actual genetic ancestry, may be the lack of individuals of pure Native American ancestry represented in the sample. To assess this problem we have included genotypes from 80 Nahuas individuals as a reference panel of Native Americans. These Nahuas are a relative isolated population of Amerindian 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 as to their true ethnicity while others may identify with one ethnic group despite their admixed background, as well as 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 Amerindian-

European ethnicity as such while strongly correlated with poor socio-economic level (7, 10), leads to an increased risk of developing a more florid disease with several ACR criteria than European individuals from the United States or Europe, but the actual genetic ancestry is not. Unfortunately, our study design has several limitations. The samples size for the individuals with socio-demographic data is too small to assess the relative effects or highly correlated of potentially confounding variables. A previous study from LUMINA suggested that both ethnicity and admixture accounted for the risk observed in non-European populations (34, 35). 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 Amerindian genetic ancestry have a higher risk for disease.

Using genetic ancestry our results confirm that the increased Amerindian 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 epidemiological 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 Amerindian origin, as well as genes that may be associated with early age of onset, renal disease, oral ulcers, photosensitivity and serositis, manifestations not influenced by gender or age.

However, our findings cannot rule out the possibility that lower socio-economic factors 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 socio-economic factors including genetic ancestry in the model.

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Table 1

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

Ancestry	Amerindian-European SLE Set 1	Amerindian-European SLE Set 2	Amerindian-European Set 1+2	European SLE Set
No. Subjects	1384	732	2116	4001
Amerindian	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

Table 2

Average genetic ancestry by physician assessed designations in a portion of the set 1 cohort (GENLES).

	Genetic ancestry			
Physician-Assessed Ethnicity	**% European**	**% Amerindian**	**% African**	**% Asian**
European (n= 54)	73.2	24.2	1.3	1.3
Amerindian-European (Mestizo) (n= 597)	37.4	57.2	4.2	1.2
Amerindian (n= 132)	46.5	50.3	1.5	1.7
Others (n= 31)	44.1	51.8	2.0	2.1

Table 3

Clinical characteristics between self-reported or physician assessed Amerindian-European and European SLE patients.

Characteristic	Amerindian-European	European[22]	*P* value	OR (95%CI)
No. Individuals	2116	4001		
Age of onset	22.2 ± 13.1	33.6 ± 13.7	< 0.0001	
Malar Rash	1243/2110 (58.9%)	2262/3583 (63.1%)	0.002	1.19 (1.07-1.33)
Discoid rash	252/2109 (12.0%)	617/3376 (18.2%)	4.29×10^{-10}	1.64 (1.40-1.92)
Photosensitivity	1218/2106 (57.8%)	2512/3793 (66.2%)	1.50×10^{-10}	1.43 (1.28-1.59)
Oral Ulcers	861/2107 (40.9%)	1673/3538 (47.3%)	2.70×10^{-6}	1.30 (1.16-1.45)
Arthritis	1524/2111 (72.2%)	3211/3911 (82.1%)	3.56×10^{-19}	1.77 (1.56-2.00)
Serositis	551/2057 (26.8%)	1455/3587 (40.6%)	2.31×10^{-25}	1.86 (1.66-2.10)
Renal involvement	1017/2088 (48.7%)	1226/3533 (34.7%)	3.73×10^{-25}	1.79 (1.60-2.00)
Neurological involvement	303/2109 (14.4%)	606/3330 (18.2%)	0.0002	1.32 (1.14-1.54)
Hematologic Involvement	1310/1940 (67.5%)	2213/3348 (66.1%)	0.29	1.07 (0.95 -1.20)

Table 4

Logistic and linear regression analysis of individual clinical lupus phenotypes with Amerindian genetic ancestry.

	P value	OR (95% CI)	Age of onset, gender adjusted *P* value	OR (95% CI)
Age of 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)
Neurological involvement	0.016	0.68 (0.50-0.93)	0.71	0.93 (0.64-1.35)
Hematological involvement	0.22	1.16 (0.91-1.47	0.89	1.02 (0.76-1.37)

* Linear regression

OR= Odds Ratio
NA= not applicable