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European population substructure is associated with mucocutaneous manifestations and autoantibody production in systemic lupus erythematosus

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Abstract

Objective—To determine whether genetic substructure in European-derived populations is associated with specific manifestations of systemic lupus erythematosus (SLE), including mucocutaneous phenotypes, autoantibody production, and renal disease.

Methods—SLE patients of European descent (n=1754) from 8 case collections were genotyped for over 1,400 ancestry informative markers that define a north/south gradient of European substructure. Based on these genetic markers, we used the STRUCTURE program to characterize each SLE patient in terms of percent northern (vs. southern) European ancestry. Non-parametric methods, including tests of trend, were used to identify associations between northern European ancestry and specific SLE manifestations.

Results—In multivariate analyses, increasing levels of northern European ancestry were significantly associated with photosensitivity (p_{trend}=0.0021, OR for highest quartile of northern European ancestry compared to lowest quartile 1.64, 95% CI 1.13–2.35) and discoid rash (p_{trend}=0.014, $OR_{high\text{-}low}$ 1.93, 95% CI 0.98–3.83). In contrast, northern European ancestry was protective for anticardiolipin ($p_{trend}=1.6 \times 10^{-4}$, $OR_{high\text{-}low}$ 0.46, 95% CI 0.30–0.69) and anti-dsDNA (p_{trend}=0.017, $OR_{high\text{-}low}$ 0.67, 95% CI 0.46–0.96) autoantibody production.

Conclusions—This study demonstrates that specific SLE manifestations vary according to northern vs. southern European ancestry. Thus, genetic ancestry may contribute to the clinical heterogeneity and variation in disease outcomes among SLE patients of European descent. Moreover, these results suggest that genetic studies of SLE subphenotypes will need to carefully address issues of population substructure due to genetic ancestry.

Introduction

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease and can affect virtually any organ system. The overall prevalence of SLE is approximately 1 in 2000 individuals, with a marked female predominance (female:male ratio of 6–10:1). Peak incidence occurs between ages 15 and 40 (1). Studies have shown that the prevalence of SLE manifestations varies between ethnic groups, with higher rates of severe disease manifestations in non-European populations. For example, higher rates of renal disease have

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been noted in Asians (2,3), African Americans (4–6), and Hispanics (6). In contrast, higher rates of photosensitivity have been observed in SLE cases of European descent (7). These differences in SLE manifestation rates are presumably due, in part, to differences in genetic factors between these continental groups.

Genetic population structure arises from the genetic differences between the major continental ethnic groups (e.g., European, African, Amerindian, East Asian and South Asian), and can lead to confounding in genetic association studies if cases and controls differ in ethnic background. In this situation, biased associations can be observed with genetic polymorphisms that are not related to disease, but instead have different frequencies in the continental ethnic groups that comprise the cases and controls (8). An example of this type of confounding has been observed between a human immunoglobulin G haplotype and diabetes mellitus among Pima Indians. Initially, the Gm3;5,13,14 haplotype was found to be protective for diabetes mellitus in this group. However, this haplotype was determined to be a marker for European ancestry, and Europeans have a lower prevalence of diabetes mellitus compared to the Pima Indians. The association between this haplotype and diabetes disappeared when only Pima Indians without any European ancestry were studied (9).

Recent advances in human population genetics have led to the identification of genetic polymorphisms whose frequencies differ between the continental ethnic groups. These markers, termed ancestry informative markers (AIMs), can be used to identify major continental contributions to an individual's ancestry. AIMs have also been used to study admixture between 2 or more major continental populations. More recently, genetic differences within the same major continental group (called population substructure) have also been identified. Studies of European-derived populations have shown clear evidence of substructure, with the largest genetic distinction occurring along a north/south (or northwest/southeast) gradient (10–13). As defined in these studies, Scandinavian, Western European, Eastern European (Poland and Ukraine) and Central European (German) are considered northern, whereas Spanish, Portuguese, Italian, Greek, and Ashkenazi Jewish are southern. [Note: For Ashkenazi Jewish the country of origin has been shown to be irrelevant (10,12).] Admixed individuals (e.g. two grandparents of Italian origin and two grandparents of Irish origin) appear in the intermediate region of this gradient. These studies have also identified EUROSTRUCTURE AIMs (ESAIMs), which can be used to identify European population substructure in genetic studies and assess the contribution of northern and southern European ancestry for a given individual (10,12).

Differences in SLE manifestations among SLE patients from different continental groups are likely due, in part, to the genetic differences between these groups (population structure). Therefore, we hypothesized that differences in SLE manifestations among SLE patients from the same major continental group may be due to differences in genetic ancestry within that group (population substructure). To examine this hypothesis, we conducted this study to determine if population substructure among SLE cases of European descent, specifically northern vs. southern European ancestry, is associated with particular subphenotypes of SLE.

Material and Methods

Subjects and clinical data

SLE patients (n=1891) were obtained from the following independent case collections:

1. University of California, San Francisco Lupus Genetics Project (UCSF, n=579) (14)
2. Autoimmune Biomarkers Collaborative Network (ABCoN, n=312) (15)

3. Pittsburgh Lupus Registry (n=297) (16)
4. University of Minnesota SLE cohort (UMN, n=251) (17)
5. Lupus Family Registry and Repository at the Oklahoma Medical Research Foundation (OMRF, n=231) (18)
6. Multiple Autoimmune Disease Genetics Consortium (MADGC, n=103) (19)
7. University of California, Los Angeles (UCLA, n=81) (20)
8. Collection of European SLE patients based at Uppsala University (Uppsala, n=37) (21–23)

All subjects were of self-described European descent and confirmed as having SLE by fulfilling 4 or more of the American College of Rheumatology (ACR) classification criteria for SLE (24) as determined by medical record review. The Institutional Review Board of all investigative institutions approved these studies, and all participants provided written informed consent.

Phenotypes of interest for this study were the 11 SLE manifestations that comprise the ACR classification criteria (24)—malar rash, discoid rash, photosensitivity, oral ulcers, serositis, arthritis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, and a positive anti-nuclear antibody (ANA)—as well as six autoantibodies associated with SLE: anti-dsDNA, anti-SSA/Ro, anti-SSB/La, anti-Sm, anti-RNP, and anti-cardiolipin autoantibody. Clinical data for the SLE manifestations for all subjects were obtained from medical record review performed at the individual institutions. Autoantibody status was determined by medical record review and/or serologic testing of banked serum. A subject was considered “positive” for an autoantibody if he/she had a positive test result for that autoantibody documented at least once. Additional information was collected on gender and disease duration, if available.

Genotyping and estimation of European ancestry

The primary genotyping data for this study were obtained from two genome-wide association scans of SLE (25,26). The UCSF, ABCoN, Pittsburgh, and MADGC collections were genotyped using the Illumina HumanHap500 BeadChip as described previously (26). The UMN, OMRF, UCLA, and Uppsala collections were genotyped on the Illumina HumanHap300 BeadChip as described previously (25).

Genotyping data for a minimum of 1400 AIMs was obtained on all subjects. These AIMs were informative for both continental ancestry and north-south European substructure (12,27). All subjects and AIMs were removed from analysis that had greater than 10% missing genotypes or did not meet a Hardy Weinberg equilibrium criterion ($p<1 \times 10^{-5}$), two common quality control criteria for genotyping data. A set of 128 AIMs was used to estimate percent European ancestry, using the model based non-hierarchical clustering approach applied in the STRUCTURE program (v2.1, http://pritch.bsd.uchicago.edu/structure.html) as previously described (27). For those subjects with > 90% European ancestry (n=1754, see Supplemental Table 1 for the final sample sizes of each case collection), another set of 1250 north-south EUROSTRUCTURE AIMs (n-sESAIMs) was used to estimate percent northern versus southern European ancestry. This set was derived from a panel of 1440 n-sESAIMs (12) that were common to all genotype sets and met quality filters.

For continental ancestry, population structure was examined using STRUCTURE v2.1 (28,29). Each STRUCTURE analysis was performed without any prior population assignment, employed the same parameters as analyses previously described (12), and used

100,000 replicates and 100,000 burn-in cycles. The analyses included 80 subjects from each of the following continental or sub-continental groups: European, Amerindian, East Asian, African and South Asian (27). Four independent runs demonstrated nearly identical results under these parameters.

For the European substructure analysis, the same parameters were utilized in STRUCTURE runs with the exception that the number of replicates and burn-in cycles were reduced to 50,000 each. Runs were performed including 150 southern and 150 northern European subjects determined from previous studies (12). Four independent runs demonstrated nearly identical results under these parameters.

Statistical analysis

Associations between the SLE phenotypes of interest and the primary predictor of percent northern European ancestry were assessed first using Spearman rank correlations since the primary predictor was not normally distributed (see Figure 1). P-values for the Spearman rank correlation coefficients were determined using Monte Carlo permutation testing. Each analysis consisted of 10,000 repetitions and permuted the SLE phenotype of interest.

Phenotypes whose correlation with northern European ancestry had a permutation p-value of less than 0.05 were further analyzed using multivariate, non-parametric techniques. Since the distribution of percent northern European ancestry was highly skewed, we transformed this variable into a 4 level ordinal variable based on the quartiles of percent northern European ancestry. For each phenotype of interest, multivariate logistic regression analyses adjusting for gender were performed for each quartile and case collection. Of note, disease duration was not available for the UMN cases (n=241) or most of the Uppsala cases (n=30). Therefore, disease duration (dichotomized at the median) was also included in the multivariate models when it was a statistically significant term ($p<0.05$). When disease duration was not a statistically significant term, it was not included in the multivariate models in order to maximize the available sample size.

Odds ratios (OR) for a particular quartile were then combined across the case collections using the Cochran-Mantel-Haenszel method. Score tests were used to assess evidence of trend across the quartiles. We used these non-parametric methods since they are more conservative and do not rely on the linearity assumptions used in regression models.

Of note, the phenotypes investigated in this study are not independent. For example, the immunologic disorder criterion is based on the subject testing positive for one of the following three autoantibodies included in this study: anti-dsDNA, anti-Sm, or the anticardiolipin autoantibody. In addition, subjects who produce anti-SSA/Ro autoantibodies are more likely to produce anti-SSB/La autoantibodies (Pearson $r= 0.56$, $p<0.00005$), and subjects who produce the anti-dsDNA autoantibody are more likely to have renal disease (Pearson $r=0.24$, $p<0.00005$). Therefore, principal components analysis was performed for the 11 ACR criteria as well as the six autoantibodies to determine if northern European ancestry was associated with an unmeasured factor underlying the correlated phenotypes.

Since 17 phenotypes were analyzed (11 ACR criteria and 6 autoantibodies), the issue of multiple testing must be considered. However, these phenotypes are not independent, as described above. Given the lack of independence among phenotypes, a simple Bonferroni correction of $\alpha=0.05/17=0.0029$ is clearly overly conservative. However, an unadjusted $\alpha=0.05$ is clearly liberal. We present unadjusted p-values so that they may be directly interpreted by the reader.

All statistical analyses were conducted using Stata/SE 9.0 (College Station, TX, USA).

Results

Clinical characteristics for the 1754 analyzed SLE subjects in this study are provided in Table 1, including the overall prevalence of the 11 ACR criteria and autoantibody frequencies (the SLE phenotypes under study). As expected, over 90% of the subjects were women. The average age at onset of SLE was 33 years, and the median disease duration of the participants was approximately 7 years. The frequency of the 11 ACR criteria and autoantibodies for each case collection are presented in Supplemental Table 2.

We first estimated the continental ancestry for each subject in the study. All subjects with less than 90% European ancestry were removed from analysis (n=137, see Supplemental Table 1). European substructure analysis was then performed for the remaining subjects (n=1754). The median percent northern European ancestry in the entire sample was 94% (Table 1). For almost all of the case collections, the majority of participants had over 90% northern European ancestry (see Supplemental Table 2). Individuals of different European ancestry were generally dispersed among the different USA collection sites. The distribution of percent northern European ancestry was substantially skewed, as shown in Figure 1. Supplemental Figure 1 displays the confidence intervals around the estimated percent northern European ancestry for each subject.

Next, we examined the association between northern European ancestry and the phenotypes defined by the ACR classification criteria for SLE using Spearman rank correlations for univariate analyses. These analyses showed that northern European ancestry was associated with discoid rash (permutation p=0.0009), photosensitivity (permutation p=<0.0001), and the immunologic criterion for SLE (permutation p=<0.0001) (Table 2). The associations remained statistically significant in multivariate models with tests of trend (Tables 3 and 4). After using the Cochran-Mantel-Haenszel method to account for the effects of gender, case collection, and disease duration (if appropriate), increasing northern European ancestry was significantly associated with photosensitivity (p_{trend}=0.0021, OR for highest quartile of northern European ancestry compared to lowest quartile 1.64, 95% CI 1.13–2.35) and discoid rash (p_{trend}=0.014, $OR_{high\text{-}low}$ 1.93, 95% CI 0.98–3.83). Conversely, increasing northern European ancestry was protective for the immunologic criterion (p_{trend}=0.0003, $OR_{high\text{-}low}$ 0.50, 95% CI 0.33−0.76) (Table 4). Although univariate tests suggested associations between northern European ancestry and arthritis and renal disorder, no associations were observed with these phenotypes in tests of trend (Table 3). The analyses were also conducted using multivariate logistic regression adjusting for gender, case collection, and disease duration (if appropriate), and similar results were observed (data not shown).

Since the immunologic criterion for SLE is based on autoantibody production, we then examined the association between northern European ancestry and lupus-related autoantibodies. Associations were observed in univariate analyses between northern European ancestry and the anti-dsDNA and anti-cardiolipin autoantibodies (Table 2). No significant association was observed between northern European ancestry and antibodies to the nuclear antigens Ro/SSA, La/SSB, Sm, and RNP. In multivariate analyses using the Cochran-Mantel-Haenszel method to account for the effects of gender, case collection, and disease duration (if appropriate), northern European ancestry remained significantly protective for the anti-dsDNA antibody (p_{trend}=0.017, $OR_{high\text{-}low}$ 0.67, 95% CI 0.46−0.96), as shown in Table 4. The association with northern European ancestry was even stronger with the anti-cardiolipin antibody (p_{trend} =1.6 × 10^{-4}, $OR_{high\text{-}low}$ 0.46, 95% CI 0.30−0.69). These analyses were also conducted using multivariate logistic regression, and similar results were observed (data not shown).

Given the correlation between phenotypes, we conducted a principal components analysis to determine if northern European ancestry was more strongly associated with an unmeasured factor underlying the 11 ACR classification criteria than the individual criteria. Four principal components for the ACR criteria were identified, but the associations with northern European ancestry were not stronger than the associations with the individual criteria (data not shown). A similar analysis was performed using the 6 autoantibody phenotypes. Three principal components were identified, but once again, the associations with northern European ancestry were not stronger than the association with the individual autoantibodies (data not shown). Therefore, these findings do not suggest that northern European ancestry is more strongly associated with an unmeasured factor underlying these phenotypes.

Discussion

This study shows that genetic substructure within European-derived populations is associated with specific manifestations of SLE. Increased northern European ancestry is associated with an increased risk of photosensitivity and discoid rash (mucocutaneous manifestations), and a decreased risk of autoantibody production. These results support the hypothesis that differences in genetic background between subjects within the same major continental ethnic group (as reflected by northern vs. southern European ancestry in this study) can influence the development of specific SLE phenotypes. Of note, ancestry associations with autoantibody production are in some instances stronger than the associations with mucocutaneous manifestations. This finding also supports the theory that genetic factors may be more relevant to the production of autoantibodies (which are implicated in disease pathogenesis), than other SLE manifestations such as arthritis or serositis.

The associations between photosensitivity and discoid rash with increased northern European ancestry are particularly intriguing, since exposure to sunlight and ultraviolet radiation has been shown to precipitate various SLE manifestations, including cutaneous reactions (30–32). One can hypothesize an evolutionary mechanism for this finding. In general, populations in northern Europe are exposed to less sunlight than those in southern Europe. Over time, northern European populations may have developed increased capacity for sunlight absorption than their southern counterparts. However, this increased absorption may become detrimental if the person moves to a more sun-exposed region. The resulting additional sunlight absorption may lead to sun-induced damage (such as discoid rash) and photosensitive reactions. In addition, previous studies have shown that skin damage and inflammation from ultraviolet light exposure has been associated with skin and hair color (33,34), suggesting that the association between increased northern European ancestry and the mucocutaneous subphenotypes of photosensitivity and discoid rash may be related to these traits.

The mechanism for increased autoantibody production in those with less northern European (i.e., more southern European ancestry) is not known. This association is likely due, at least in part, to genetic differences between northern and southern Europeans. It is interesting to speculate that natural selection may play a role in explaining this result. Differential exposure to infectious agents in southern compared to northern European population groups may have resulted in selection of genetic variants with consequent differences in immune responses.

Genes previously associated with SLE risk display evidence of geographic variation. One example is the R620W polymorphism of protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*). This polymorphism has been associated with multiple autoimmune diseases characterized by autoantibody production, including SLE (19,35). The allele frequency of

R620W in Europeans decreases substantially from northern Europe to southern Europe (36). However, the geographic variation seen in this polymorphism is not likely to explain the association between autoantibody production and European substructure seen in our results. The PTPN22 R620W polymorphism is more common in northern Europe, and we found that increased northern European ancestry was protective for autoantibody production. In addition, no associations between the PTPN22 R620W polymorphism and SLE-related autoantibodies have been published.

The human leukocyte antigen (HLA) region on chromosome 6p21 has also shown evidence of geographic variation. HLA alleles (specifically HLA-DRB1*0301 and HLA-DRB1*1501) were the first identified genetic susceptibility risk factors for SLE (37). In the United Kingdom, allele frequencies for genes in this region have been found to vary on a northwest-southeast cline (38). HLA class II alleles have also been associated with both anti-dsDNA (39) and anti-cardiolipin autoantibody production (40,41). Further studies are needed to determine the role of the HLA region in the associations between autoantibody production and European population substructure seen in this study.

The strengths of this study include its large sample size of subjects with well-characterized clinical features who were recruited from Europe and multiple sites across the United States. Analyses also adjusted for potential confounding factors such as SLE patient recruitment site, gender, and disease duration (when appropriate). The use of continental ancestry markers ensured that each participant in our study was truly of European ancestry. In addition, the detailed assessment of population substructure in European derived cases has not been previously applied to genetic studies of SLE manifestations.

This study does have limitations. The first limitation is the skewed distribution of the primary predictor, percent northern European ancestry. This skewing may reflect an overall predominately northern European ancestry of many North Americans of European descent. Ideally, the associations identified in this study should be further investigated in a sample of SLE subjects with more southern European ancestry. Secondly, while the north-south cline in Europe is the largest source of population substructure in European Americans (10), more subtle stratification due to ethnic or regional differences may influence specific phenotypes.

In addition, since these SLE cases are not part of a longitudinal cohort, misclassification of the outcomes may occur. SLE patients may develop additional manifestations as their disease progresses. Since these subphenotypes were not present at study enrollment, the subject would be misclassified as “negative” for this outcome. However, this misclassification error results in biasing our finding towards the null, and thus should not cause false positive results. Further, since most SLE patients in this study had well-established disease at study entry, with a median disease duration of ~7 years, the rate of misclassification should be relatively low.

Lastly, we had limited statistical power to detect association with certain SLE phenotypes (e.g., the neurologic disorder criterion) due to the low frequency in SLE subjects. To fully identify genetic predictors for the rare outcomes, one would need to enrich the case group for these manifestations to achieve a sample size adequate to study these outcomes.

In summary, this study emphasizes the concept that SLE cases descended from the same major continental ethnic group (e.g., European) have measurable genetic differences related to their geographic ancestry (e.g., northern Europe vs. southern Europe) that influence their risk of developing specific SLE manifestations. As an example, we have shown in this study that increased northern European ancestry is associated with photosensitivity and discoid rash, and protective for autoantibody production. These findings also indicate that geographic ancestry, likely reflecting genetic differences between those of northern and

southern European ancestry, may contribute to the clinical heterogeneity seen in SLE patients of European descent. Further detailed investigation of the genetic differences among SLE patients with more northern vs. southern European ancestry may provide insight into genetic mechanisms underlying photosensitivity, discoid rash, and autoantibody production. Given the association between SLE-related autoantibodies with potentially severe disease manifestations (e.g., anti-cardiolipin autoantibody with arterial and venous thrombosis), this study also suggests that genetic ancestry can influence life-threatening disease outcomes. Finally, the overall findings of this study also have substantial implications for case-control genetics studies of SLE. Future genetic studies of SLE subphenotypes, even if investigating only a single continental ethnic group, should include assessment for population substructure to avoid confounding by differences in genetic ancestry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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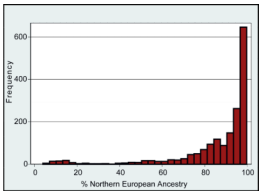

Figure 1.
Histogram of percent Northern European ancestry for all study participants (n=1754).

Table 1

Demographic and clinical disease characteristics of the study population.

Characteristic	Overall (n=1754)
Female, n (%)	1652 (94%)
Age at diagnosis, mean (SD)	33 (24–43)
Disease duration, median years (IQR)	7.3 (3–14)
ACR classification criteria for SLE, n (%)	
Malar rash	965 (56)
Discoid rash	176 (10)
Photosensitivity	1225 (70)
Oral ulcers	772 (44)
Arthritis	1447 (83)
Serositis	767 (44)
Neurologic disorder	211 (12)
Hematologic disorder	1077 (62)
Immunologic disorder	1209 (69)
Renal disorder	518 (30)
Anti-nuclear antibody (ANA)	1682 (97)
Autoantibodies, n positive/n total (% positive) *	
Anti-dsDNA	769/1565 (49)
Anti-SSA/Ro	449/1597 (28)
Anti-SSB/La	199/1598 (12)
Anti-Sm	184/1575 (12)
Anti-RNP	294/1589 (19)
Anti-cardiolipin	483/1415 (34)
% Northern European ancestry, median (IQR)	94 (83–98)
>90% Northern European ancestry, n (%)	1071 (61)

* Since autoantibody data was not available on all subjects, the total number of subjects for which data was available is provided.

Table 2

Associations between percent northern European ancestry and manifestations of SLE.

SLE phenotype	Spearman rank correlation	Permutation p-value*
ACR classification criteria for SLE		
Malar rash	0.025	0.31
Discoid rash	0.078	0.0009
Photosensitivity	0.10	<0.0001
Oral ulcers	−0.044	0.065
Arthritis	−0.075	0.0022
Serositis	−0.047	0.051
Neurologic disorder	0.0002	0.99
Hematologic disorder	−0.0039	0.87
Immunologic disorder	−0.12	<0.0001
Renal disorder	−0.057	0.015
Anti-nuclear antibody (ANA)	−0.043	0.073
Autoantibodies		
Anti-dsDNA	−0.050	0.046
Anti-Ro/SSA	0.019	0.47
Anti-La/SSB	0.027	0.28
Anti-Sm	−0.015	0.56
Anti-RNP	−0.029	0.25
Anti-cardiolipin	−0.10	0.0001

*Permutation p-value based on 10,000 replications. See Materials and Methods for further details.

Table 3

Tests of trend for discoid rash, photosensitivity, arthritis, and renal disorder using Cochran-Mantel-Haenszel combined odds ratios (OR) from multivariate analyses for each quartile.

	Discoid rash*		Photosensitivity†		Arthritis†		Renal disorder*	
Quartile (% N. European, no. of subjects)	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
1 (<83, n=439)	Ref.		Ref.		Ref.		Ref.	
2 (83–94, n=445)	1.68 (0.88–3.18)	0.11	1.25 (0.92–1.71)	0.15	0.78 (0.51–1.19)	0.24	0.98 (0.70–1.37)	0.90
3 (94–98, n=445)	2.36 (1.19–4.68)	0.011	1.90 (1.32–2.73)	0.0005	0.62 (0.40–0.97)	0.034	0.98 (0.64–1.47)	0.91
4 (>98, n=425)	1.93 (0.98–3.83)	0.054	1.64 (1.13–2.35)	0.0084	0.68 (0.44–1.06)	0.086	0.88 (0.59–1.33)	0.55
Test of trend p		0.014		0.0021		0.12		0.19

*adjusted for gender, case collection, and disease duration (see Materials and Methods)

†adjusted for gender and case collection (see Materials and Methods)

Table 4

Tests of trend for autoantibody-related phenotypes using Cochran-Mantel-Haenszel combined odds ratios (OR) from multivariate analyses for each quartile.

	Immunologic criterion*		Anti-dsDNA antibody*		Anti-cardiolipin antibody†	
Quartile (% N. European, no. of subjects)	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
1 (<83, n=439)	Ref.		Ref.		Ref.	
2 (83–94, n=445)	0.92 (0.63–1.33)	0.66	0.98 (0.72–1.36)	0.92	0.80 (0.57–1.11)	0.19
3 (94–98, n=445)	0.65 (0.43–0.99)	0.042	0.87 (0.60–1.25)	0.45	0.56 (0.38–0.83)	0.0034
4 (>98, n=425)	0.50 (0.33–0.76)	0.001	0.67 (0.46–0.96)	0.029	0.46 (0.30–0.69)	0.0001
Test of trend p		0.0003		0.017		1.6×10^{-4}

*adjusted for gender, case collection, and disease duration (see Materials and Methods)

†adjusted for gender and case collection (see Materials and Methods)