Published in final edited form as:

Lupus. 2011 October ; 20(10): 1095–1103. doi:10.1177/0961203311404915.

The United States to Africa lupus prevalence gradient revisited

GS Gilkeson¹, JA James², DL Kamen¹, TJ Knackstedt¹, DR Maggi³, AK Meyer¹, and NM Ruth¹

¹Department of Medicine and Pediatrics, Medical University of South Carolina, Charleston, SC, USA

²Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA

³West Africa Fistula Foundation, Bo, Sierra Leone

Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that has a significantly higher prevalence, morbidity and mortality in African Americans compared with Americans of European descent. The pathogenesis of lupus is unclear but appears to be a result of environmental factors interacting with a genetically susceptible host. Despite the high disease load of SLE in African Americans, there is the perception that lupus is relatively rare in Africa. This prevalence gradient suggests that comparative studies of related cohorts from the two continents may provide insight into the genetic/environmental interactions that result in the development of lupus. To define if a lupus gradient exists, we began a study of autoimmunity prevalence utilizing two unique cohorts. The first is the Gullah population of the Sea Islands of South Carolina, who are unique in their low genetic admixture and their known ancestral heritage. The second is the population of young women served by the West Africa Fistula Foundation in Bo, Sierra Leone. Anthropologic studies indicate a direct ancestral link between the Gullah population and Sierra Leoneans. Since it is impossible to perform an epidemiologic study of lupus in Sierra Leone at this time, we assessed the prevalence of lupus serum autoantibodies, serologic evidence of specific infections and levels of serum 25-OH vitamin D in young women in the two cohorts who have no known relatives with lupus. Our results indicate similar prevalence of serum antinuclear antibodies in the two cohorts, though there was a significantly increased prevalence of antiphospholipid and anti-Sm antibodies in the Sierra Leone cohort. Seropositivity to common viral infections was significantly higher in women from Sierra Leone, while serum 25-OH vitamin D levels were markedly lower in the Gullah population. These data suggest that the prevalence of autoimmunity is similar in the two populations, but that there are significant environmental differences that may impact progression to autoimmune disease. Further studies comparing these two cohorts is likely to provide important insight into the impact of environmental factors on development of lupus.

Keywords

African American; lupus; prevalence gradient; vitamin D

© The Author(s), 2011.

Correspondence to: Gary S Gilkeson, Medical University of South Carolina – Medicine, 96 Jonathan Lucas Street, Charleston, SC 29412, USA, gilkeson@musc.edu.

Conflict of interest

The authors declare that they have no conflicts of interest.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by immune complex mediated tissue damage. There are marked demographic differences in lupus prevalence, with women being 8–10 times more likely than men to develop lupus and African Americans being 3–4 times more likely than Caucasian Americans to develop disease.^{1–3} The mechanisms underlying these marked demographic differences are unclear at present. As in most autoimmune diseases, lupus is felt to occur secondary to an environmental event triggering pathogenic immune factors leading to development of disease. Lupus development is at least a two-stage process, with the development of autoantibodies occurring many years prior to expression of clinical disease.⁴ It is clear that some individuals develop autoantibodies, especially first-degree relatives of lupus patients, but never develop clinical disease.^{5,6} Defining autoantibody prevalence poses a much more attainable goal than determining actual prevalence of disease in a country such as Sierra Leone, where there is only a minimal health care system.⁷

Environmental triggers of lupus are difficult to identify as they likely occur years before disease onset and may be common environmental exposures.⁸ Different viruses (such as Epstein-Barr virus, EBV) and toxins (such as silica, insecticides) are implicated in epidemiologic studies of lupus.^{9,10} More recently there has been an increasing interest in the role of vitamin D as an immune system modulator, and that deficiency of vitamin D could potentially lead to development of autoimmune diseases, including lupus.^{11,12} Indeed, a number of studies reported associations of vitamin D deficiency with lupus and other autoimmune diseases, with additional evidence for higher rates of disease flare in deficient patients.¹³

One interesting approach to defining environmental effects is to define whether a disease differentially impacts a population that moves from one geographical area to another. Thus, defining if there are differences between the prevalence of lupus in native Africans versus African Americans would suggest that environmental factors are important in disease pathogenesis. There are numerous case reports of lupus developing in African individuals after they moved from Africa to Europe or North America.^{14,15} There are also small series suggesting that the prevalence of lupus in West Africa is low.^{16–19} These observations have led to the ‘gradient hypothesis’ that there is a significant difference in the prevalence of lupus between native Africans and African Americans.^{17,20} Most of the studies that looked at lupus prevalence in Africa were done in East Africa, Central Africa or Southern Africa, which are not the ancestral areas of origin of most African Americans.^{21–25} Thus significant genetic differences exist between Eastern Africans and Western Africans that likely impact diseases such as lupus. Significant genetic admixture in most African American populations further confounds attempts to separate environmental differences versus genetic variation.^{26,27}

The Gullah/Geechee population of African Americans, living on the Sea Islands of South Carolina and Georgia, are a unique cohort in their low genetic admixture and retention of cultural traditions (Figure 1).^{28–30} The Gullah are also unique in that their ancestral origin in Africa is known.^{28,29} During the slave trade era, Africans from Sierra Leone were captured and forcibly brought to the Charleston, South Carolina area due to their skill in rice farming (Figure 2). Rice, at that time, was the cash crop along the coast of South Carolina and Northern Georgia. The ‘founding population’ for the Gullah community is estimated to be between 3000–5000 individuals.³⁰ These slaves and their families were kept on the Sea Islands to raise rice. Due to the prevalence of malaria and yellow fever, as well as the heat and humidity, slave owners and slave foreman, for the most part, did not go to the islands. After the Civil War, most of the Gullah/Geechee population remained on the islands living

on subsistence farming and fishing. Again due to disease, climate and lack of access, they remained relatively isolated on the islands until the mid-1900s when roads and bridges were built to the islands and malaria and yellow fever were eliminated. The Gullahs' English-based creole language is strikingly similar to Sierra Leone Krio and contains such identical expressions as *bigyai* (greedy), *pantap* (on top of), *ohltu* (both), *tif* (steal), *yeys* (ear), and *swit* (delicious). As late as the 1960s, a Black American linguist found Gullahs in rural South Carolina and Georgia who could recite songs and fragments of stories in Mende and Vai, and who could do simple counting in the Guinea/Sierra Leone dialect of Fula. In fact, all of the African texts that Gullah people have preserved are in languages spoken within Sierra Leone and along its borders.³⁰

Due to their relative isolation for centuries, there is very little non-African genetic admixture in the Gullah population (3% admixture in those living on the Sea Islands) compared with other African American populations (18–24% admixture).^{28,29} In recent genetic analyses of lupus in the Gullah population, principal component analysis demonstrated that the Gullah are indeed genetically separable from other African American cohorts.^{28,29} This analysis also confirmed the continued low genetic admixture of the Gullah cohort reported herein to be 6%. The overall prevalence of lupus in the Gullah is unknown, although based on hospital data in South Carolina, it appears to be between 1/150–1/200 African American women (unpublished data).

Based on these factors, we believe that comparing the Gullah/Geechee population with a cohort in Sierra Leone provides a unique opportunity of comparing two populations with similar genetic makeup, but highly different environmental exposures. Due to the lack of an organized health care system in Sierra Leone, it is impossible at this time to establish the prevalence of lupus there. We therefore proposed to determine the prevalence of 'autoimmunity' in lupus-unaffected women in the two populations as determined by serologic measures. We also assessed the prevalence of seropositivity for viruses implicated in lupus pathogenesis and serum 25-OH vitamin D levels.

Methods

Cohorts

Unaffected female controls with no known relatives with lupus and no symptoms of lupus were selected from the Gullah 'SLEIGH' (**SLE** in **G**ullah **H**ealth) cohort ($n=107$) to match the age and gender of the Sierra Leone cohort.⁵ The specifics of recruitment and demographics of the SLEIGH cohort were previously described elsewhere.⁵ The Sierra Leone cohort is composed of women under the care of the West Africa Fistula Foundation at the Bo Government Hospital in Bo, Sierra Leone ($n=70$). The women are seen for care of vesicovaginal fistulas occurring as a result of obstructed labor. They had been tested for and were negative for HIV. Serum for this study was obtained from women while they were boarding in the hospital awaiting surgery. The women were questioned regarding symptoms related to lupus using the validated connective tissue disease questionnaire.³¹ They were all examined by a volunteer physician (GSG, DRM, or NMR) and assessed for symptomatic or physical evidence of connective tissue disease. This protocol was approved by the Research Ethics Committee of the Ministry of Health and Sanitation in Sierra Leone and by the Institutional Review Board of MUSC.

Laboratory measures

Autoantibody tests were performed at the Oklahoma Medical Research Foundation serology laboratory using standard techniques.⁵ Antinuclear antibodies (ANA) were measured by Hep2 indirect immunofluorescence, anti-cardiolipin and anti- β 2 glycoprotein 1 antibodies

by ELISA, anti-DNA by Crithidia and ENA by Ouchterlony. Viral seroconversion was tested by standard ELISAs.³² 25-hydroxyvitamin D (25-D) levels were tested by radioimmunoassay (RIA) in both cohorts in the Hollis laboratory at the Medical University of South Carolina.³³

Subsequently, serum samples were analyzed for autoantibody levels using the Bio-Rad BioPlex 2200 Analyzer and ANA kits. Sera were screened by this multiplexed bead-based assay for 13 distinct autoantibody specificities including: dsDNA, chromatin, ribosomal P, 60 kD Ro (SSA-60), 52 kD Ro (SSA-52), La (SSB), Sm, Sm/RNP, nRNP A, nRNP 68, Scl-70, centromere B, and Jo-1.⁶ Syphilis positivity was assessed via standard RPR methods.

Results

We initially assessed ANA positivity in the two cohorts to determine overall level of autoimmunity. As shown in Table 1, a significant percentage of individuals in both cohorts tested positive for ANA at a 1/40 titer, with positivity being more prevalent, but not significantly, in the Gullah cohort. As the titer requirement increased to 1/120, approximately 20% of the Gullah and 16% of the Sierra Leoneans tested positive. Even at a 1/1080 titer 3% versus 4% of unaffected individuals had a positive ANA. In both cohorts the primary pattern was nuclear speckled, with a smaller percentage having cytoplasmic positivity. None of the differences in ANA positivity were significantly different. To define the specificity of the ANA-positive serum, anti-dsDNA by Crithidia and anti-ENA antibodies by Ouchterlony were performed. No individual in either group had detectable anti-dsDNA antibodies, while one Gullah participant tested positive for anti-RNP antibodies and two Sierra Leone sera were positive for anti-Ro antibodies.

A significant number of sera tested positive for IgG (37.1%) and IgM (10%) antiphospholipid (aPL) in the Sierra Leoneans compared with the Gullah (4.9% and 0%, respectively), as demonstrated in Table 1. No individual was positive for IgA aPL. To further define this positivity, we performed assays for serum anti-β2GPI that measures IgG, IgA and IgM antibodies. There were no individuals that tested positive for anti-β2GPI and those with the highest reactivity, though still within the normal range, were not the individuals that tested positive for aPL antibodies. Due to the possibility of false positive aPLs with treponemal infections, we performed RPR assays on all samples. Only two individuals showed low reactivity to RPR and both were ANA negative; one was aPL and anti-β2GPI negative, and one was low positive only for aPL IgG, but otherwise negative.

The sera were subsequently run on the Bioplex assay to detect 11 different autoreactivities. The Bioplex assay has higher sensitivity and allows multiple assays to be run simultaneously on the same sample. Results are shown in Table 2. There are a number of differences between the results from the two Ouchterlony and Bioplex assays, with there being more positives in the Bioplex assay. Most notably, 10% of the Sierra Leone samples were positive for anti-Sm activity compared with none of the Gullah ($p<0.001$) in the Bioplex assay. No sera in either group was positive for anti-Sm antibodies using immunodiffusion. Similarly, a number of individuals in both cohorts were antibody positive for Sm/RNP and RNP A antigen, with single patients positive for a number of the other antigens. In almost all instances the titers were low, and only one Sierra Leonean patient had multiple positivities (Sm and RNP A). Overall rates of Bioplex positivity were not significantly different in the two groups, other than the 10% of Sierra Leone women testing positive for anti-Sm antibodies.

We then assessed the two cohorts for differences in measurable environmental factors linked with lupus in the current literature.³⁴ We first assessed for seropositivity for common viral pathogens. This testing revealed that the Sierra Leoneans had significantly increased numbers of seropositive individuals for all the viruses tested including EBV, cytomegalovirus (CMV), and Herpes Simplex viruses (HSV1 and HSV2 (Table 3), though none of the Sierra Leonean women had evidence of active infection at the time serum was obtained. Only two Sierra Leonean women were negative for HSV2 and they were ANA negative, while the single woman negative for Epstein-Barr virus was also ANA negative. All Sierra Leonean ANA-positive individuals were seropositive for all four infections assessed. As noted above, none of the women in the Sierra Leone cohort were HIV positive. We have not systematically assessed for HIV infection in the Gullah cohort. Thus the infections linked to disease development in American lupus cohorts are more common in the Sierra Leonean population compared with the Gullah, although autoantibody positivity rates are similar, other than aPL antibodies. It is perhaps not surprising that infection rates would be higher in Sierra Leone where there is essentially no clean water or sewage system.

Another possible environmental factor impacting development of SLE is vitamin D status.³⁵ Serum 25-D levels were significantly higher in the equatorial Sierra Leonean samples compared with those obtained in the Gullah in Charleston ($p < 0.001$, Table 4). Compared with the 95% who are insufficient (< 30 ng/ml) and 50% who are deficient (< 20 ng/ml) in vitamin D among the Gullah, only one individual in Sierra Leone was insufficient and none were deficient. There was a trend towards higher 25-D levels in both the Sierra Leoneans and the Gullah who were ANA negative, although the difference was not statistically significant ($p = 0.617$ and $p = 0.145$ respectively).

Discussion

In this report, we present preliminary studies of autoimmunity prevalence in two unique cohorts of African descent, which we believe may provide important insight into the environmental/genetic interactions that result in the development of SLE. The first cohort is the Gullah population of the Sea Islands of South Carolina and Georgia. We initiated this cohort in 2003 to study the impact of lupus on this African American community.⁵ GIS mapping studies of hospitalizations for lupus in South Carolina indicated a significantly higher prevalence of lupus in African Americans along the coast of South Carolina compared with the mid-state and up-state (unpublished data). Those of Gullah heritage make up a significant percentage of African Americans living along the coast of South Carolina. We thus undertook this study to define prevalence and severity of lupus in the Gullah. We found lupus is prevalent in this population, with disease manifestations similar to other African American cohorts with the exception of the Gullah having more skin disease and less hematologic manifestations.⁵ We enrolled into this cohort patients with lupus, unaffected first-degree relatives, and unrelated controls. The Gullah cohort, due to their genetic homogeneity, have contributed significantly to the identification of genetic associations recently reported in lupus in African Americans.^{36–39}

The close relationship, culturally and genetically, between the Gullah and current residents in their ancestral home in Sierra Leone raised questions regarding differences in disease prevalence between the two populations. Prior to initiation of our studies, Project Sugar, led by Dr Tim Garvey and Dr Ida Spruill, asked similar questions regarding diabetes.^{29,30,40–44} They established a community advisory committee and, through their work, a trust developed between the community and investigators at the Medical University of South Carolina.³⁰ This trust and collaboration allowed us to successfully recruit individuals to the lupus study (SLEIGH) to begin to address the question of environment versus genetics in lupus. One difficulty in addressing a disease gradient is the comparative populations to

study. As noted above, African Americans are, for the most part, genetically distinct from African populations due to admixture.²⁹ In addition, most African populations studied to date are in Eastern Africa, where the horrors of the slave trade had minimal impact.²⁴ Most African individuals forcibly moved during slave trade days to the United States came from a limited area of Western Africa. The genetics of East African tribes differ significantly from the genetic makeup of West African tribes due to centuries of separation.

Medical studies in East Africa were possible due to the relative political stability in those countries, though no epidemiologic assessment of lupus is published. Such is not the case in West Africa, where civil wars have made any type of medical research difficult to impossible.^{45,46} This is especially true in Sierra Leone, which until 2003 was wracked by a brutal civil war based to some extent on 'blood diamonds'.⁴⁶ Due to the civil war, almost the entire infrastructure of the country was destroyed. Health care is minimal despite heroic selfless efforts of a number of individuals and agencies.⁴⁶ Dr Darius Maggi, a retired Texas obstetrician, to help women with gynecologic fistulas that develop during obstructed childbirth, established the West Africa Fistula Foundation. The Foundation is headquartered at the Bo Government Hospital in Bo, Sierra Leone. Dr Maggi visits three to four times a year, operating on hundreds of women, repairing their fistulas so that they become continent and able to return to their homes without shame. Since his patients are young-to-middle-aged women, they could be readily matched in age and gender to the SLEIGH lupus patients and controls. Dr Maggi began collecting serum samples 2 years ago, which were expanded during a recent visit to Sierra Leone by two of the other coauthors. Care for children and adults is primarily provided by dedicated military trained medics, but not doctors. Upon questioning, none of the health care providers at the Bo Government Hospital were aware of the disease lupus, not unexpectedly as lupus is not a major health concern for the populace burdened with infectious diseases. Infrastructure and health care, especially for children, is improving in Sierra Leone. At this time, however, it is impossible to determine whether lupus is a prevalent disease or not given the limitations of the health care system.

Due to these limitations, we elected to study the first phase of lupus disease development, that of circulating serum autoantibodies in asymptomatic individuals. We sought to determine if there was a difference in autoantibody prevalence between unaffected SLEIGH controls versus unaffected women in Sierra Leone. As noted, there were more similarities than differences between the two populations in autoantibody positivity except for anti-Sm and anti-cardiolipin reactivity. This is a preliminary study with small numbers, so noted differences may not hold up as we expand the sample size in both groups. The overall similarity of ANA positivity between the two groups suggests that if there is a gradient in lupus, it is not at the stage of development of autoantibodies, but at the stage of progression to clinical disease. From the serologic studies, the one unexpected finding was the high prevalence of seropositivity for anti-cardiolipin antibodies in the women in Sierra Leone. None of the women had suffered blood clots by history. It would be impossible to determine history of fetal loss since most pregnancies do not end successfully there. Given that the anti- β 2GPI antibodies were negative in the Sierra Leonean women, we do not believe these represent true positives, but rather likely reflect cross-reactivity from other infections. It was previously reported that individuals infected with malaria have a high positivity rate for anti-cardiolipin antibodies similar to the 30% we report.⁴⁷ In these reports the serum was not reactive with β 2GPI, and thus likely represents cross-reactive binding to phospholipids induced by the malaria parasite. The clinical significance of these antibodies in malaria infection is unknown.⁴⁸ Given the endemic nature of malaria in Bo, Sierra Leone, we believe that the aPL positivity is secondary to malaria infection. Since essentially everyone in Bo is infected with malaria, it is not clear why only 30% of the women were positive. The seropositivity for specific antigens such as Sm in the Sierra Leone populations is interesting,

but given that they are all low titer and do not score on the Ouchterlony assays suggests they are likely not clinically relevant.

As expected, when environmental factors were assessed, there were multiple highly significant differences between the two populations. Common viral infections present in one-half to two-thirds of the SLEIGH population are almost universally present in the women in Sierra Leone. The low number of seronegative individuals in Sierra Leone made it impossible to derive any conclusions regarding the role of viral infections in inducing positive ANAs. Vitamin D deficiency, present in the vast majority of SLEIGH patients, is essentially non-existent in Sierra Leone. Again due to the limited number of individuals, it is difficult to determine what role vitamin D deficiency or sufficiency is playing, other than the trends towards lower 25-D levels in individuals with positive ANAs in both populations.

In summary, we have established two unique cohorts of individuals of African heritage. There are unique cultural and ancestral links between the Gullah of South Carolina and the people of Bo, Sierra Leone. In preliminary studies, we demonstrated that the overall prevalence of autoantibodies is similar in unaffected controls from both groups. Antibody specificity varied between the two groups, but small sample size may explain these differences. Ongoing genetic studies, that include samples from both groups, along with further enrollment and environmental analysis in these cohorts will provide important insight into not only the presence or absence of an Africa to US lupus gradient, but also insight into gene–environment interactions in lupus.

Acknowledgments

The authors thank Jennifer B. Lessard for her assistance with the scientific artistry of Figures 1 and 2 and the authors are indebted to the members of the Sea Island Families Project Citizen Advisory Committee, the staff of the West Africa Fistula Foundation clinic, and the study participants from the Sea Islands of South Carolina and Bo, Sierra Leone.

Funding

This publication was supported by the South Carolina Clinical & Translational Research (SCTR) Institute, with an academic home at the Medical University of South Carolina, NIH/NCRR Grant number UL1 RR029882

References

1. Fernandez M, Calvo-Alen J, Alarcon GS, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXI. Disease activity, damage accrual, and vascular events in pre- and postmenopausal women. *Arthritis Rheum.* 2005; 52:1655–1664. [PubMed: 15934092]
2. Ruiz-Irastorza G, Khamashta MA, Castellino G, Hughes GR. Systemic lupus erythematosus. *Lancet.* 2001; 357:1027–1032. [PubMed: 11293608]
3. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Baltimore).* 2003; 82:299–308. [PubMed: 14530779]
4. Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med.* 2003; 349:1526–1533. [PubMed: 14561795]
5. Kamen DL, Barron M, Parker TM, et al. Autoantibody prevalence and lupus characteristics in a unique African American population. *Arthritis Rheum.* 2008; 58:1237–1247. [PubMed: 18438839]
6. Ramos PS, Kelly JA, Gray-McGuire C, et al. Familial aggregation and linkage analysis of autoantibody traits in pedigrees multiplex for systemic lupus erythematosus. *Genes Immun.* 2006; 7:417–432. [PubMed: 16775618]

7. Kushner AL, Kamara TB, Groen RS, Fadlu-Deen BD, Doah KS, Kingham TP. Improving access to surgery in a developing country: experience from a surgical collaboration in Sierra Leone. *J Surg Educ.* 2010; 67:270–273. [PubMed: 20816367]
8. Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS. Risk factors for development of systemic lupus erythematosus: allergies, infections, and family history. *J Clin Epidemiol.* 2002; 55:982–989. [PubMed: 12464374]
9. Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Parks CG, Gilkeson GS. Hormonal, environmental, and infectious risk factors for developing systemic lupus erythematosus. *Arthritis Rheum.* 1998; 41:1714–1724. [PubMed: 9778212]
10. Harley JB, James JA. Epstein-Barr virus infection may be an environmental risk factor for systemic lupus erythematosus in children and teenagers. *Arthritis Rheum.* 1999; 42:1782–1783. [PubMed: 10446885]
11. Kamen DL, Aranow C. The link between vitamin D deficiency and systemic lupus erythematosus. *Curr Rheumatol Rep.* 2008; 10:273–280. [PubMed: 18662506]
12. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. *Exp Biol Med (Maywood).* 2004; 229:1136–1142. [PubMed: 15564440]
13. Kamen DL, Barron M, Hollis BW, et al. Correlation of vitamin D deficiency with lupus disease measures among Sea Island Gullah African Americans (abstract). *Arthritis Rheum.* 2005; 52:S180.
14. Molokhia M, McKeigue PM, Cuadrado M, Hughes G. Systemic lupus erythematosus in migrants from west Africa compared with Afro-Caribbean people in the UK. *Lancet.* 2001; 357:1414–1415. [PubMed: 11356443]
15. Greenwood B, Corrah T. Systemic lupus erythematosus in African immigrants. *Lancet.* 2001; 358:1182. [PubMed: 11597702]
16. Bae SC, Fraser P, Liang MH. The epidemiology of systemic lupus erythematosus in populations of African ancestry: a critical review of the “prevalence gradient hypothesis”. *Arthritis Rheum.* 1998; 41:2091–2099. [PubMed: 9870865]
17. Symmons DP. Frequency of lupus in people of African origin. *Lupus.* 1995; 4:176–178. [PubMed: 7655486]
18. Monnier A, Delmarre B, Peghini M, et al. Acute disseminated lupus erythematosus in Ivory Coast (apropos of 9 cases). *Med Trop (Mars).* 1985; 45:47–54. [PubMed: 2985908]
19. Westlake SL, Edwards CJ. Anti-malarials and Lupus in West Africa use and lupus in Africans. *Lupus.* 2009; 18:193–195. [PubMed: 19213855]
20. George A, Ogunbiyi A. Systemic lupus erythematosus: a rarity in West Africa, or a yet to be investigated entity. *Lupus.* 2005; 14:924–925. [PubMed: 16335588]
21. McGill PE, Oyoo GO. Rheumatic disorders in Sub-saharan Africa. *East Afr Med J.* 2002; 79:214–216. [PubMed: 12625680]
22. Dessein PH, Gledhill RF, Rossouw DS. Systemic lupus erythematosus in black South Africans. *S Afr Med J.* 1988; 74:387–389. [PubMed: 3055356]
23. Davis P, Stein M. SLE in Zimbabwean patients: a review of clinical and serologic features and evaluation of criteria for classification. *Cent Afr J Med.* 1991; 37:282–285. [PubMed: 1807806]
24. Adelowo OO, Oguntola SA. Pattern of systemic lupus erythematosus among Nigerians. *Clin Rheumatol.* 2009; 28:699–703. [PubMed: 19242770]
25. Kanyerezi BR, Lutalo SK, Kigonya E. Systemic lupus erythematosus: clinical presentation among Ugandan Africans. *East Afr Med J.* 1980; 57:274–278. [PubMed: 7389618]
26. Molokhia M, Hoggart C, Patrick AL, et al. Relation of risk of systemic lupus erythematosus to west African admixture in a Caribbean population. *Hum Genet.* 2003; 112:310–318. [PubMed: 12545274]
27. Molokhia M, McKeigue P. Risk for rheumatic disease in relation to ethnicity and admixture. *Arthritis Res.* 2000; 2:115–125. [PubMed: 11094421]
28. Parra EJ, Kittles RA, Argyropoulos G, et al. Ancestral proportions and admixture dynamics in geographically defined African Americans living in South Carolina. *Am J Phys Anthropol.* 2001; 114:18–29. [PubMed: 11150049]

29. McLean DC Jr, Spruill I, Argyropoulos G, Page GP, Shriver MD, Garvey WT. Mitochondrial DNA (mtDNA) haplotypes reveal maternal population genetic affinities of Sea Island Gullah-speaking African Americans. *Am J Phys Anthropol.* 2005; 127:427–438. [PubMed: 15624208]
30. Spruill I. Project Sugar: a recruitment model for successful African-American participation in health research. *J Natl Black Nurses Assoc.* 2004; 15:48–53. [PubMed: 15853286]
31. Karlson EW, Costenbader KH, McAlindon TE, et al. High sensitivity, specificity and predictive value of the Connective Tissue Disease Screening Questionnaire among urban African-American women. *Lupus.* 2005; 14:832–836. [PubMed: 16304727]
32. McClain MT, Heinlen LD, Dennis GJ, Roebuck J, Harley JB, James JA. Early events in lupus humoral autoimmunity suggest initiation through molecular mimicry. *Nat Med.* 2005; 11:85–89. [PubMed: 15619631]
33. Kamen DL, Parker TM, Wagner CL, Hollis BW, Gilkeson GS. Correlation of vitamin D deficiency with skin pigment among African Americans with systemic lupus erythematosus. *Arthritis Rheum.* 2007;56S. Abstract#1949.
34. Parks CG, Cooper GS. Occupational exposures and risk of systemic lupus erythematosus: a review of the evidence and exposure assessment methods in population- and clinic-based studies. *Lupus.* 2006; 15:728–736. [PubMed: 17153843]
35. Kamen D, Aranow C. Vitamin D in systemic lupus erythematosus. *Curr Opin Rheumatol.* 2008; 20:532–537. [PubMed: 18698173]
36. Nath SK, Han S, Kim-Howard X, et al. A nonsynonymous functional variant in integrin- α (M) (encoded by ITGAM) is associated with systemic lupus erythematosus. *Nat Genet.* 2008; 40:152–154. [PubMed: 18204448]
37. Liu K, Li QZ, Delgado-Vega AM, et al. Kallikrein genes are associated with lupus and glomerular basement membrane-specific antibody-induced nephritis in mice and humans. *J Clin Invest.* 2009; 119:911–923. [PubMed: 19307730]
38. Harley JB, Alarcon-Riquelme ME, Criswell LA, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PTK, KIAA1542 and other loci. *Nat Genet.* 2008; 40:204–210. [PubMed: 18204446]
39. Jacob CO, Zhu J, Armstrong DL, et al. Identification of IRAK1 as a risk gene with critical role in the pathogenesis of systemic lupus erythematosus. *Proc Natl Acad Sci U S A.* 2009; 106:6256–6261. [PubMed: 19329491]
40. Divers J, Sale MM, Lu L, et al. The genetic architecture of lipoprotein subclasses in Gullah-speaking African American families enriched for type 2 diabetes: the Sea Islands Genetic African American Registry (Project SuGAR). *J Lipid Res.* 2010; 51:586–597. [PubMed: 19783527]
41. Johnson-Spruill I, Hammond P, Davis B, McGee Z, Loudon D. Health of Gullah families in South Carolina with type 2 diabetes: diabetes self-management analysis from project SuGar. *Diabetes Educ.* 2009; 35:117–123. [PubMed: 19244567]
42. Johnson-Spruill I, Riegel B. The quality of diabetes care to Gullah families of South Carolina. *J Natl Black Nurses Assoc.* 2008; 19:20–27. [PubMed: 19397050]
43. McLean DC Jr, Spruill I, Gevao S, et al. Three novel mtDNA restriction site polymorphisms allow exploration of population affinities of African Americans. *Hum Biol.* 2003; 75:147–161. [PubMed: 12943155]
44. Sale MM, Lu L, Spruill IJ, et al. Genome-wide linkage scan in Gullah-speaking African American families with type 2 diabetes: the Sea Islands Genetic African American Registry (Project SuGAR). *Diabetes.* 2009; 58:260–267. [PubMed: 18835935]
45. Allan R. Peace at all cost – the challenge of Sierra Leone. *Lancet.* 1999; 353:991. [PubMed: 10459921]
46. Betancourt TS, Brennan RT, Rubin-Smith J, Fitzmaurice GM, Gilman SE. Sierra Leone's former child soldiers: a longitudinal study of risk, protective factors, and mental health. *J Am Acad Child Adolesc Psychiatry.* 2010; 49:606–615. [PubMed: 20494270]
47. Consigny PH, Cauquelin B, Agnamey P, et al. High prevalence of co-factor independent anticardiolipin antibodies in malaria exposed individuals. *Clin Exp Immunol.* 2002; 127:158–164. [PubMed: 11882047]

48. Soni PN, De Bruyn CC, Duursma J, Sharp BL, Pudifin DJ. Are anticardiolipin antibodies responsible for some of the complications of severe acute *Plasmodium falciparum* malaria? S Afr Med J. 1993; 83:660–662. [PubMed: 8310360]

Figure 1.
Map depicting the Sea Islands of South Carolina and Georgia. These islands are the home to the Gullah/Geechee African Americans.

Figure 2.
Slave trade routes depicting the Sierra Leone to Charleston route.

Table 1

Seropositivity for lupus-associated antigens in unrelated SLEIGH controls and unrelated Sierra Leone females. Data are presented as percent positive and statistics derived via student *t*-test

	SLEIGH Female Unrelated Controls (n=107)	Sierra Leone Females (n=70)	Age-adjusted p-value
ANA Positivity 1:40	35.2%	28.5%	NS
ANA Positivity 1:120	19.7%	15.7%	NS
ANA Positivity 1:1080	3.3%	4.2%	NS
Cardiolipin IgG >20	4.9%	37.1%	<0.01
Cardiolipin IgM >20	0.0%	10.0%	<0.01
dsDNA or Sm positive	0.0%	0.0%	NS
RNP positive	0.8%	0.0%	NS
Ro (SSA) or La (SSB) positive	0.0%	2.8%	NS

Table 2

Seropositivity as detected by the Bioplex assay. Results are presented as the percent of sera that were above the upper limits of normal

	SLEIGH unrelated controls (n=107) % Positive	Sierra Leone controls (n=70) % Positive	P value
dsDNA	0	1.4	NS
chromatin	1.9	0	NS
Ribosomal P	0	0	NS
60kD Ro	1.9	1.4	NS
52kD Ro	0	0	NS
La	0.9	1.4	NS
Sm	0	10	0.001
Sm/RNP	5.6	1.4	NS
RNP A	2.8	5.7	NS
Scl70	0	1.4	NS
Jo 1	0	0	NS
Cent B	0.9	2.8	NS

Table 3

Viral seropositivity in the SLEIGH compared to the Sierra Leone samples. Values presented are the percent of samples that were positive for anti-viral antibodies. *p*-values are comparing the positivity rates between the two groups

Virus	SLEIGH unrelated controls (n=107) % Positive	Sierra Leone controls (n=70) % Positive	<i>p</i>-value
CMV	59.8	100	<0.001
HSV1	70.1	100	<0.001
HSV2	47.7	95.7	<0.001
EBV	89.7	98.6	0.029

Table 4

Serum 25-OH vitamin D levels as detected by radioimmunoassay. Values are presented as the mean plus or minus the standard deviation. The *p*-values are comparing the differences in 25-D levels between the SLEIGH and the Sierra Leone samples

Serum Measure	SLEIGH unrelated controls (n=107)	Sierra Leone controls (n=70)	<i>p</i> -value
25-OH Vitamin D (ng/ml)	11.9 ± 7.7	36.2 ± 9.2	<0.001
25-D in ANA+at 1:120 serum titer	11.2 ± 6.7 <i>n</i> =21	34.6 ± 6.1 <i>n</i> =11	<0.001
25-D in ANA – at <1:120 serum titer	14.1 ± 8.4 <i>n</i> =86	36.2 ± 10.2 <i>n</i> =59	<0.001