Identification of Novel Genetic Susceptibility Loci in African American Lupus Patients in a Candidate Gene Association Study

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Objective. **Candidate gene and genome-wide association studies have identified several disease susceptibility loci in lupus patients. These studies have largely been performed in lupus patients who are Asian or of European ancestry. This study was undertaken to examine whether some of these same susceptibility loci increase lupus risk in African American individuals.**

Methods. **Single-nucleotide polymorphisms tagging 15 independent lupus susceptibility loci were genotyped in a set of 1,724 lupus patients and 2,024 healthy controls of African American descent. The loci examined included *PTPN22*, *FCGR2A*, *TNFSF4*, *STAT4*, *CTLA4*, *PDCD1*, *PXK*, *BANK1*, *MSH5* (HLA region), *CFB* (HLA region), *C8orf13-BLK* region, *MBL2*, *KIAA1542*, *ITGAM*, and *MECP2/IRAK1*.**

Results. **We found the first evidence of genetic association between lupus in African American patients and 5 susceptibility loci (*C8orf13-BLK*, *BANK1*, *TNFSF4*, *KIAA1542*, and *CTLA4*; $P = 8.0 \times 10^{-6}$,**

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$P = 1.9 \times 10^{-5}$, $P = 5.7 \times 10^{-5}$, $P = 0.00099$, and $P = 0.0045$, respectively). Further, we confirmed the genetic association between lupus and 5 additional lupus susceptibility loci (*ITGAM, MSH5, CFB, STAT4,* and *FCGR2A*; $P = 7.5 \times 10^{-11}$, $P = 5.2 \times 10^{-8}$, $P = 8.7 \times 10^{-7}$, $P = 0.0058$, and $P = 0.0070$, respectively), and provided evidence, for the first time, of genome-wide significance for the association between lupus in African American patients and *ITGAM* and *MSH5* (HLA region).

Conclusion. **These findings provide evidence of novel genetic susceptibility loci for lupus in African Americans and demonstrate that the majority of lupus susceptibility loci examined confer lupus risk across multiple ethnicities.**

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by autoantibody production, abnormalities of immune system function, and damage in several organs. Although the exact pathogenesis of SLE is unknown, there is strong evidence for contributions of both genetic risk factors and environmental events, which lead to a break in immunologic self tolerance (1). SLE is 9 times more common in women than in men (2), particularly during the childbearing years. There are also marked disparities in SLE incidence and prevalence worldwide; SLE prevalence varies among different ethnic and geographic populations (3). SLE is 4 times more common in people of African American ancestry than in those of European ancestry (4,5). In addition, African Americans have a markedly increased risk of developing lupus nephritis relative to European Americans (5). The ethnic and genetic heterogeneity of SLE may contribute to the complexity of its clinical manifestation.

Recent genome-wide association studies (GWAS) and candidate gene studies have identified >30 SLE risk alleles that are common in both populations of European ancestry and populations of Asian ancestry (6,7). These include genes encoding proteins important for adaptive immunity and the production of autoantibodies (HLA alleles, *BLK, BANK1,* and *PTPN22*) (8–10), proteins with roles in innate immunity and interferon (IFN) signaling (*ITGAM, STAT4,* and *IRF5*) (8,11–13), and genes involved in DNA methylation (*MECP2*) (14), among others.

In this study, we analyzed 3,462 African American patients with lupus and controls and 286 Gullah African American patients with lupus and controls for genetic association with polymorphisms within 15 confirmed lupus susceptibility loci (8,9,11–22). We con-

firmed that HLA, *STAT4, FCGR2A,* and *ITGAM* are associated with SLE and provided evidence of genome-wide significance of the association of HLA and *ITGAM* in African American patients with lupus. Further, we described, for the first time, genetic associations between *C8orf13-BLK, BANK1, TNFSF4, CTLA4,* and *KIAA1542* and lupus in African American patients.

PATIENTS AND METHODS

Patients and controls. Two independent SLE case–control cohorts were recruited through a multicenter collaboration within the US and assembled at the Oklahoma Medical Research Foundation. The study included a total of 3,462 African American samples (1,569 SLE patients and 1,893 healthy controls) and 286 Gullah African American samples (155 SLE patients and 131 healthy controls) (23). Gullah subjects have a considerably lower level of non-African genetic admixture when compared to other African American populations. All cases fulfilled the American College of Rheumatology criteria for the classification of SLE (24). Informed consent was obtained from all subjects. The study was approved by the institutional review boards at each of the participating institutions.

Genotyping. Genotyping was performed using the Illumina Custom Bead system on an iSCAN instrument as part of a large lupus candidate gene association study, in order to reduce the cost of genotyping and maximize the sample size. The following single-nucleotide polymorphisms (SNPs) within 15 confirmed susceptibility loci for SLE were used: rs2476601 (*PTPN22*), rs1801274 (*FCGR2A*), rs2205960 (*TNFSF4*), rs7574865 (*STAT4*), rs231775 (*CTLA4*), rs11568821 (*PDCD1*), rs6445975 (*PXK*), rs10516487 (*BANK1*), rs3131379 (*MSH5* within the class III major histocompatibility complex [MHC] region), rs1270942 (*CFB* within class III MHC), rs13277113 (*C8orf13-BLK* region), rs1800450 (*MBL2*), rs4963128 (*KIAA1542*), rs1143679 (*ITGAM*), and rs17435 (*MECP2/IRAK1*) (8–22,25). *IRF5*, a known SLE susceptibility gene, was not examined in the present study because it was extensively studied in an African American cohort with lupus that included some of the samples included in this study (26). Similarly, the genetic association between *IL21* and lupus in African American patients has recently been demonstrated (27). These SNPs were selected because they tag independent lupus susceptibility loci in lupus patients of European ancestry. In addition, 161 admixture informative markers were genotyped and evaluated in our samples. The admixture informative markers were selected to distinguish 4 continental ancestral populations: Africans, Europeans, American Indians, and East Asians (28–32).

Data analysis. Samples with a genotype success rate of <90% were excluded from the analysis. A total of 19 African American samples and 1 Gullah sample were removed due to a low genotype success rate. The remaining samples were then evaluated for duplicates or related individuals, and one individual from each pair was removed if the proportion of alleles with shared identity by descent was >0.4 in African American samples or >0.35 in Gullah samples (resulting in the exclusion of 57 African American and 8 Gullah samples). Samples with
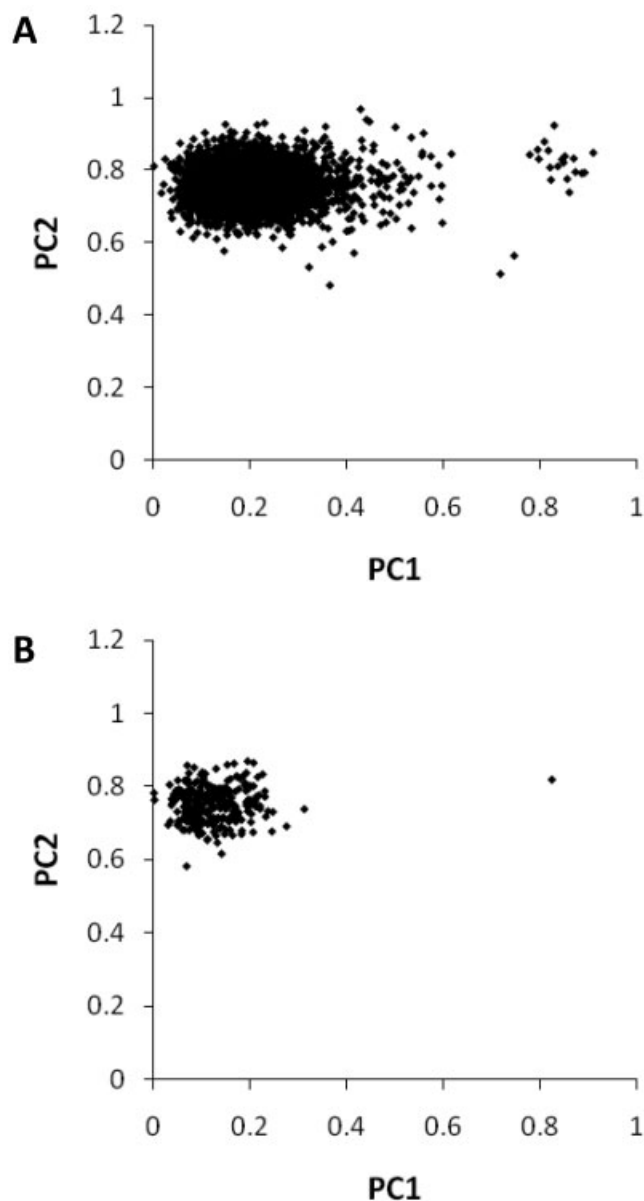
Figure 1. Scatter plots generated by the first 2 components of a principal components analysis of the African American samples (**A**) and the Gullah samples (**B**). The x-axis shows principal component 1 (PC1), and the y-axis shows principal component 2 (PC2).

increased heterozygosity (>5 SD from the mean) were then removed from the analysis. Samples were assessed for mismatches between reported sex and genetic data, and individuals with sex discrepancies were removed from the analysis. Finally, genetic outliers were removed from further analysis as determined by principal components analysis (Figure 1) and admixture estimates using AdmixMap software (33–35). A total of 30 genetic outliers were removed from the African American sample set, and 1 genetic outlier was removed from

the Gullah sample set. After quality control, a total of 1,527 cases and 1,811 controls of African American descent and 152 cases and 123 controls of Gullah descent were included in subsequent analyses.

For each sample set analyzed, markers with a genotype success rate of <90%, Hardy-Weinberg equilibrium of <0.001, or minor allele frequency (MAF) of <0.01 were excluded from further analysis. All 15 markers were analyzed in the African American individuals, and 13 markers passed the inclusion threshold and were analyzed in the Gullah participants (2 SNPs were excluded due to MAF of <0.01).

To test for genetic association in SLE, we performed logistic regression, as implemented in Plink (36). Allele frequency differences between cases and controls were calculated with adjustment for the ancestry estimates provided by AdmixMap. Analysis was also performed separately with adjustment for the first 3 principal components. The results obtained by either method were very similar, and data adjusted for principal components are reported herein. Inflation factors (λ) were calculated using "null" ancestry informative markers. Pooled odds ratios (ORs) were estimated using StatsDirect, version 2.4.6. The meta-analysis was conducted using standard methods based on the Cochran-Mantel-Haenszel test (37). The Breslow-Day test (38) was performed for all SNPs to assess the heterogeneity of the ORs in different populations.

RESULTS

Population structure analyses showed that the African ancestry and European ancestry was 81.3% and 15.7%, respectively, among the African American samples, with an inflation factor λ of 1.32, and 90% and 7.2% among the Gullah samples, with an inflation factor λ of 1.10. Therefore, all results presented herein were adjusted for principal components.

We genotyped 15 SNPs, tagging 15 independent susceptibility loci previously established in patients of European ancestry with SLE, in 2 independent cohorts of African descent. After excluding SNPs and individuals that did not pass our quality control standards, a total of 15 and 13 SNPs were analyzed in the African American and Gullah samples, respectively, in a total of 1,679 SLE patients and 1,934 controls. Two SNPs in the Gullah samples were excluded after MAF quality control (*PDCD1* [rs11568821] and *PTPN22* [rs2476601]).

Within the African American samples, we found evidence of significant genetic association between SLE and 10 loci after correction for the first 3 principal components. An association was observed for *ITGAM* ($P = 1.9 \times 10^{-9}$, OR 1.57), *MSH5* ($P = 4.1 \times 10^{-8}$, OR 1.65), *CFB* ($P = 7.1 \times 10^{-7}$, OR 1.63), *C8orf13-BLK* ($P = 6.4 \times 10^{-6}$, OR 1.36), *BANK1* ($P = 5.9 \times 10^{-5}$, OR 0.78), *TNFSF4* ($P = 0.00056$, OR 1.44), *KIAA1542* ($P = 0.0020$, OR 0.86), *FCGR2A* ($P = 0.012$, OR 0.88),

Table 1. Genetic associations between 15 lupus susceptibility loci and lupus in African Americans, adjusted for principal components*

Gene	SNP	Chromosome	Position†	Minor allele	MAF in cases (no. of minor alleles/ no. of major alleles)	MAF in controls (no. of minor alleles/ no. of major alleles)	OR (95% CI)	P
PTPN22	rs2476601	1	114179091	A	0.018 (56/2,996)	0.014 (50/3,568)	1.31 (0.90–1.92)	0.16
FCGR2A	rs1801274	1	159746369	A	0.429 (1,298/1,726)	0.460 (1,645/1,931)	0.88 (0.80–0.97)	0.012
TNFSF4	rs2205960	1	171458098	A	0.070 (213/2,839)	0.049 (179/3,441)	1.44 (1.17–1.76)	0.00056
STAT4	rs7574865	2	191672878	A	0.168 (505/2,503)	0.145 (512/3,022)	1.19 (1.04–1.36)	0.012
CTLA4	rs231775	2	204440959	G	0.392 (1,193/1,849)	0.363 (1,310/2,302)	1.14 (1.03–1.26)	0.013
PDCD1	rs11568821	2	242442585	A	0.026 (78/2,956)	0.020 (69/3,441)	1.31 (0.94–1.81)	0.11
PXK	rs6445975	3	58345217	A	0.429 (1,310/1,742)	0.441 (1,592/2,016)	0.95 (0.86–1.05)	0.32
BANK1	rs10516487	4	102970099	A	0.197 (599/2,435)	0.239 (859/2,741)	0.78 (0.70–0.88)	5.9×10^{-5}
MSH5	rs3131379	6	31829012	A	0.101 (308/2,744)	0.064 (231/3,389)	1.65 (1.38–1.98)	4.1×10^{-8}
CFB	rs1270942	6	32026839	G	0.085 (260/2,794)	0.054 (195/3,427)	1.63 (1.34–1.97)	7.1×10^{-7}
C8orf13-BLK	rs13277113	8	11386595	A	0.172 (520/2,506)	0.131 (467/3,111)	1.36 (1.19–1.55)	6.4×10^{-6}
MBL2	rs1800450	10	54201241	A	0.032 (98/2,952)	0.029 (104/3,514)	1.12 (0.84–1.48)	0.45
KIAA1542	rs4963128	11	579564	A	0.419 (1,260/1,746)	0.458 (1,621/1,917)	0.86 (0.78–0.95)	0.0020
ITGAM	rs1143679	16	31184312	A	0.153 (467/2,583)	0.104 (375/3,233)	1.57 (1.36–1.82)	1.9×10^{-9}
MECP2	rs17435	23	152965174	A	0.393 (1,151/1,778)	0.384 (1,166/1,873)	1.05 (0.95–1.17)	0.35

* Odds ratios (ORs) represent differences in the minor allele frequency (MAF) between cases and controls in each locus. SNP = single-nucleotide polymorphism; 95% CI = 95% confidence interval.
† Determined using Genome Build 36.3.

STAT4 ($P = 0.012$, OR 1.19), and CTLA4 ($P = 0.013$, OR 1.14) (Table 1).

Genetic association analysis of the Gullah samples revealed only 2 markers associated with SLE, TNFSF4 ($P = 0.0015$, OR 4.99) and ITGAM ($P = 0.0080$, OR 1.97) (Table 2). Notably, these 2 markers were also associated with SLE in the African American participants.

Next, a meta-analysis was performed using the African American and Gullah data sets and the 13 SNPs that could be evaluated in both sample sets (Table 3).

The meta-analysis of these genetic markers in the African American and Gullah data sets using the Mantel-Haenszel test under a fixed-effects model revealed a significant association with SLE for FCGR2A ($P_{meta} = 0.0070$, OR_{meta} 0.88), TNFSF4 ($P_{meta} = 5.7 \times 10^{-5}$, OR_{meta} 1.51), STAT4 ($P_{meta} = 0.0058$, OR_{meta} 1.20), CTLA4 ($P_{meta} = 0.0045$, OR_{meta} 1.15), BANK1 ($P_{meta} = 1.9 \times 10^{-5}$, OR_{meta} 0.78), MSH5 ($P_{meta} = 5.2 \times 10^{-8}$, OR_{meta} 1.63), CFB ($P_{meta} = 8.7 \times 10^{-7}$, OR_{meta} 1.60), C8orf13-BLK ($P_{meta} = 8.0 \times 10^{-6}$, OR_{meta} 1.34), KIAA1542 ($P_{meta} = 0.00099$, OR_{meta} 0.86), and ITGAM

Table 2. Genetic associations between lupus susceptibility loci and lupus in Gullah subjects, adjusted for principal components*

Gene	SNP	Chromosome	Position†	Minor allele	MAF in cases (no. of minor alleles/ no. of major alleles)	MAF in controls (no. of minor alleles/ no. of major alleles)	OR (95% CI)	P
FCGR2A	rs1801274	1	159746369	A	0.430 (129/171)	0.476 (117/129)	0.85 (0.60–1.18)	0.33
TNFSF4	rs2205960	1	171458098	A	0.092 (28/276)	0.020 (5/241)	4.99 (1.85–13.43)	0.0015
STAT4	rs7574865	2	191672878	A	0.150 (44/250)	0.107 (26/218)	1.39 (0.85–2.29)	0.19
CTLA4	rs231775	2	204440959	G	0.372 (113/191)	0.303 (74/170)	1.34 (0.94–1.91)	0.11
PXK	rs6445975	3	58345217	A	0.398 (121/183)	0.390 (96/150)	1.03 (0.73–1.44)	0.87
BANK1	rs10516487	4	102970099	A	0.211 (64/240)	0.262 (64/180)	0.74 (0.50–1.10)	0.14
MSH5	rs3131379	6	31829012	A	0.053 (16/288)	0.045 (11/235)	1.19 (0.55–2.60)	0.66
CFB	rs1270942	6	32026839	G	0.043 (13/291)	0.037 (9/237)	1.18 (0.50–2.75)	0.71
C8orf13-BLK	rs13277113	8	11386595	A	0.153 (46/254)	0.139 (34/210)	1.11 (0.68–1.80)	0.69
MBL2	rs1800450	10	54201241	A	0.016 (5/299)	0.016 (4/242)	1.02 (0.27–3.90)	0.98
KIAA1542	rs4963128	11	579564	A	0.389 (115/181)	0.438 (105/135)	0.82 (0.58–1.15)	0.25
ITGAM	rs1143679	16	31184312	A	0.191 (58/246)	0.110 (27/219)	1.97 (1.19–3.26)	0.0080
MECP2	rs17435	23	152965174	A	0.308 (89/200)	0.333 (76/152)	0.85 (0.57–1.27)	0.42

* Two of the 15 single-nucleotide polymorphisms (SNPs) examined in the study were not included in this analysis due to low minor allele frequencies (MAFs) in the Gullah subjects. Odds ratios (ORs) represent differences in the MAF between cases and controls in each locus. 95% CI = 95% confidence interval.
† Determined using Genome Build 36.3.

Table 3. Meta-analysis of genetic associations in the African American samples and Gullah samples, adjusted for principal components*

Gene	SNP	OR (95% CI)	P_{meta}	$P_{heterogeneity}$	OR (95% CI) in European-derived populations (ref.)
FCGR2A	rs1801274	0.88 (0.80–0.96)	0.0070	0.81	0.86 (0.77–0.92) (67)
TNFSF4	rs2205960	1.51 (1.24–1.86)	5.7×10^{-5}	0.02	1.22 (1.15–1.30) (67)
STAT4	rs7574865	1.20 (1.06–1.37)	0.0058	0.54	1.57 (1.49–1.69) (67)
CTLA4	rs231775	1.15 (1.04–1.26)	0.0045	0.38	1.60 (1.01–2.53) (68)
PXK†	rs6445975	0.96 (0.87–1.05)	0.36	0.67	0.80 (0.74–0.86) (11)
BANK1	rs10516487	0.78 (0.76–0.87)	1.9×10^{-5}	0.78	0.72 (0.66–0.80) (9)
MSH5	rs3131379	1.63 (1.36–1.92)	5.2×10^{-8}	0.42	2.36 (2.11–2.64) (11)
CFB	rs1270942	1.60 (1.33–1.94)	8.7×10^{-7}	0.47	2.35 (2.10–2.63) (11)
C8orf13-BLK	rs13277113	1.34 (1.21–1.55)	8.0×10^{-6}	0.42	1.39 (1.28–1.51) (8)
MBL2	rs1800450	1.11 (0.85–1.47)	0.45	0.90	1.33 (1.08–1.65) (69)
KIAA1542	rs4963128	0.86 (0.77–0.94)	0.00099	0.80	0.83 (0.79–0.88) (67)
ITGAM	rs1143679	1.60 (1.37–1.83)	7.5×10^{-11}	0.40	1.78 (1.56–2.03) (17)
MECP2	rs17435	1.04 (0.94–1.16)	0.49	0.30	1.22 (1.07–1.38) (70)

* Only the 13 single-nucleotide polymorphisms (SNPs) that passed quality control measures in both sample sets were included in this analysis. Odds ratios (ORs) represent differences in the minor allele frequency between cases and controls in each locus. 95% CI = 95% confidence interval.
† The minor allele for the *PXK* polymorphism rs644975 is the C allele in populations of European ancestry and the A allele in African Americans.

$(P_{meta} = 7.5 \times 10^{-11}, \text{OR}_{meta} \ 1.60)$ (Table 3). Importantly, our data show that the risk alleles in the genetic associations we detected in lupus patients of African descent are the same as the risk alleles previously found in patients of European ancestry (Table 3).

DISCUSSION

The genetic heterogeneity between populations of different ethnicities has been suggested to be important in SLE risk (39), emphasizing the need for further studies in different populations. It has been consistently shown that patients of African descent have more severe lupus and a higher prevalence of lupus than those of European ancestry (4,5). In an attempt to determine whether some of the lupus susceptibility genes identified in patients of European ancestry also confer disease susceptibility in populations of African descent, we studied 2 independent African American populations from the US and genotyped common variants that represent 15 of the most established genetic susceptibility loci for lupus.

We found evidence of association between SLE and 10 genetic variants in American patients of African descent. A meta-analysis of both of the African-derived populations that were examined revealed associations with genome-wide significance at 2 loci, *ITGAM* and *MSH5* (in the HLA region).

The most significant effect was observed for a nonsynonymous SNP in the third exon of the *ITGAM*

gene (rs1143679 [$\text{OR}_{meta} \ 1.60$, $P_{meta} = 7.5 \times 10^{-11}$]). This variant was previously shown to be associated with SLE in populations of African descent (17) and has been hypothesized to disturb the interaction between ITGAM and its ligands. Another genetic association that was established with genome-wide significance in the present study was within the HLA region in the *MSH5* gene (rs3131379 [$\text{OR}_{meta} \ 1.63$, $P_{meta} = 5.2 \times 10^{-8}$]). It has previously been shown that the HLA region confers risk for lupus in African Americans (40–42), but this is the first study to establish this association with specific independent variants within this region and with genome-wide significance.

The next strongest associations were with 2 nonsynonymous polymorphisms (rs13277113 and rs10516487) located in the *C8orf13-BLK* locus and the *BANK1* gene, respectively ($\text{OR}_{meta} \ 1.34$, $P_{meta} = 8.0 \times 10^{-6}$ and $\text{OR}_{meta} \ 0.78$, $P_{meta} = 1.9 \times 10^{-5}$, respectively). *C8orf13-BLK* and *BANK1* are involved in B cell receptor–mediated signaling and B cell development (43,44). Although no functional variant has been identified in *C8orf13-BLK*, the risk alleles of the rs13277113 SNP correlate with low levels of messenger RNA for *BLK* and high levels of *C8orf13*, raising the possibility that either of these two effects could be related to SLE (8). In addition, it has been hypothesized that rs10516487 could potentially alter the affinity of BANK1 for inositol 1,4,5-trisphosphate receptor, altering B cell signaling in SLE patients (9). The *TNFSF4* gene also

showed a strong association with SLE in African American patients in the present study (OR_{meta} 1.51, P_{meta} = 5.7×10^{-5}). *TNFSF4* encodes the OX40 ligand, a costimulatory molecule involved in T cell activation. A similar association between *TNFSF4* rs2205960 and SLE has been reported in Chinese patients (45).

Two other genes that were previously found to be associated with SLE in populations of African ancestry, *STAT4* (rs7574865) and *FCGR2A* (rs1801274) (21,46,47), were also found to be associated with SLE in the present study (P_{meta} = 0.0058 for *STAT4* and P_{meta} = 0.0070 for *FCGR2A*). The *FCGR2A* gene is located in a region that was previously found to be associated with SLE through linkage studies in African Americans (1q41) (47) and has been described as a risk factor for lupus nephritis in this population (21). FCGR2A is an important receptor that mediates phagocytic functions in different cells, and there is evidence that *FCGR2A* alleles confer distinct functional capacities to phagocytes, providing a mechanism for heritable susceptibility to immune complex–mediated disease (48,49).

The association between *STAT4* and SLE risk was initially reported in 2007 (13). This was subsequently confirmed by several GWAS in Europeans and Asians (8,11,50,51) and in an African American cohort through high-density genotyping of *STAT4* in different racial groups (46). *STAT4* encodes a transcription factor that mediates the expression of genes in a number of key immunologic pathways and induces relevant cytokines, including type I IFNs, interleukin-12 (IL-12), and IL-23. STAT4 may also play a role in the differentiation of the potentially pathogenic Th17 T cell subset (52). Although no functional candidate polymorphism has yet been clearly established for *STAT4*, its roles in susceptibility to several autoimmune diseases and modulating immune functions suggest that it is an important gene in autoimmunity.

In previous studies, no association between *CTLA4* and *KIAA1542* genes and SLE in African Americans was found (53,54). However, both genes were found to be associated with SLE in this study (P_{meta} = 0.0045 and P_{meta} = 0.00099, respectively). The previous studies were underpowered to detect a significant association in these loci due to small sample sizes compared to the sample size in the present study. (The previous studies included 230 SLE patients and 276 controls [53] and 159 SLE patients and 115 controls [54].) Interestingly, the lupus-protective allele in rs4963128 (*KIAA1542*) has been associated with anti-Sm antibody in African American patients with lupus, and in the

presence of anti-Sm, this same allele is associated with increased serum IFNα activity levels (55).

The rs6445975 SNP in the *PXK* gene, rs2476601 in *PTPN22*, rs11568821 in *PDCD1*, and rs1800450 in the *MBL2* gene were not associated with SLE in the population examined in this study. The *PXK* and *MBL2* variants have been shown to be associated with SLE in different European cohorts (11,20); however, none of these associations has been replicated for other ethnic backgrounds (32,39,56–59). Previous studies of African American patients with SLE failed to show a significant genetic association between SLE and the *PTPN22* and *PDCD1* genes (60,61). Ethnic differences in *PTPN22* rs2476601 and *PDCD1* rs11568821 allele frequencies have been described (60,62). African Americans have much lower minor allele frequencies of rs2476601 (*PTPN22*) and rs11568821 (*PDCD1*) (2% and 3%, respectively) compared to individuals of European ancestry (8% and 13%, respectively) (62). Interestingly, neither of the minor alleles of these 2 SNPs is observed in populations of Asian descent (62–64). It is important to note that although we did not find an association between *PTPTN22* or *PDCD1* and SLE in African Americans, our study was underpowered to detect an association with an OR of 1.3 for *PTPTN22* or *PDCD1* (23% and 31%, respectively), probably due to the lower MAF of these polymorphisms in African Americans compared to populations of European ancestry. Therefore, we cannot rule out a possible role of these 2 genes in African American patients with lupus.
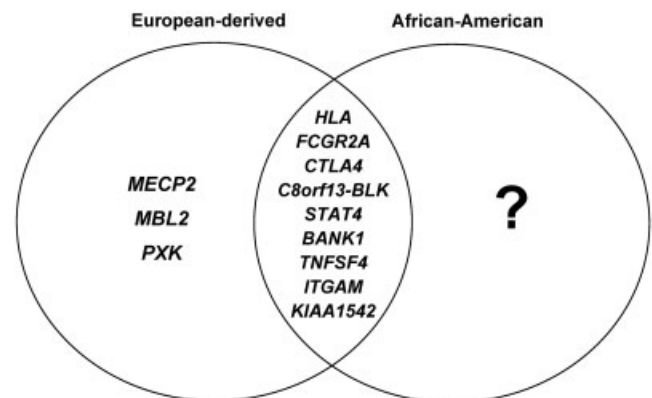

Figure 2. Lupus susceptibility loci that are unique to patients of European descent and those that are shared by patients of European descent and African American patients, determined based on the susceptibility loci included in this study and the results of the meta-analysis performed in the African American and Gullah sample sets. More genetic studies are needed to explain the higher prevalence and the more severe presentation of lupus in African Americans.

In addition, the genetic association with rs17435 within *MECP2,* which tags the *MECP2/IRAK1* susceptibility locus that has been well established in Asian patients and patients of European ancestry with lupus (14,65,66), was not replicated in the populations of African descent analyzed in the present study. However, fine-mapping and localization of the genetic effect in this locus in multiple ethnicities is under way (Kaufman KM, et al: unpublished observations).

The lack of genetic association between lupus in African American patients and some of the genetic susceptibility loci established in patients of European ancestry could be due to a different haplotype structure, given that causal variants for most of the genetic susceptibility loci have not been identified. Another possibility could be that some of the disease susceptibility loci operate in some, but not all, ethnicities. Figure 2 summarizes the unique and shared genetic susceptibility loci in SLE patients of European and African ancestry. Further studies of African American patients with lupus are needed to identify new and possibly unique SLE susceptibility loci in this population.

In summary, this is the first study to show a genetic association between lupus in African American patients and 5 loci (*C8orf13-BLK*, *BANK1*, *CTLA4*, *KIAA1542*, and *TNFSF4*). In addition, we established the genetic associations between SLE and the HLA region and between SLE and *ITGAM* with genome-wide significance in African Americans. We also confirmed the genetic association between SLE in African Americans and *STAT4* and *FCGR2A*.

AUTHOR CONTRIBUTIONS

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