Research Article

Promoter Variant of PIK3C3 Is Associated with Autoimmunity against Ro and Sm Epitopes in African-American Lupus Patients

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The PIK3C3 locus was implicated in case-case genome-wide association study of systemic lupus erythematosus (SLE) which we had performed to detect genes associated with autoantibodies and serum interferon-alpha (IFN-α). Herein, we examine a PIK3C3 promoter variant (rs3813065/-442 C/T) in an independent multiancestral cohort of 478 SLE cases and 522 controls. rs3813065 C was strongly associated with the simultaneous presence of both anti-Ro and anti-Sm antibodies in African-American patients [OR = 2.24 (1.34–3.73), P = 2.0 × 10⁻³]. This autoantibody profile was associated with higher serum IFN-α (P = 7.6 × 10⁻⁶). In the HapMap Yoruba population, rs3813065 was associated with differential expression of ERAP2 (P = 2.0 × 10⁻⁵), which encodes an enzyme involved in MHC class I peptide processing. Thus, rs3813065 C is associated with a particular autoantibody profile and altered expression of an MHC peptide processing enzyme, suggesting that this variant modulates serologic autoimmunity in African-American SLE patients.

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterized by involvement of multiple organ systems including the skin, musculoskeletal, renal, and hematologic systems. While the exact pathogenic mechanism of SLE is unknown, strong evidence exists for contributions from both genetic risk factors and environmental events which lead to an irreversible break in immunologic self-tolerance [1]. SLE is a devastating disease, typically affecting young women during the reproductive years, resulting in significant morbidity and mortality [2]. SLE is nine times more common in women than in men [3], and four times more common in people of African-American ancestry than those of European-American ancestry [1].

Interferon-alpha (IFN-α) is a pleiotropic type I interferon which can bridge the innate and adaptive immune systems and thus may set thresholds for self-tolerance. Serum IFN-α is elevated in many SLE patients [4]. Recombinant human IFN-α administered as a therapy for chronic viral hepatitis and malignancy is thought to cause SLE in some patients [5]. IFN-α-induced SLE typically resolves after the IFN-α is discontinued [6, 7], supporting the idea that IFN-α was causal. Serum IFN-α is also abnormally high in 20% of healthy first-degree relatives of SLE patients, and strong familial aggregation of high serum IFN-α has been observed in lupus families, supporting heritability of this trait [8]. The high IFN-α trait in SLE families is inherited in a complex fashion, suggesting polygenic inheritance which is not fully characterized currently [8–11].

Autoantibodies directed at double-stranded DNA (dsDNA) and RNA-binding proteins (anti-Ro, anti-La, anti-Sm, and anti-RNP, collectively anti-RBP) are characteristically found in SLE sera and are the strongest known predictors of high serum IFN-α in SLE patients [8]. Immune complexes formed by these autoantibodies can directly
stimulate IFN-α production in vitro, likely via the endosomal Toll-like receptors [12]. These data suggest that these SLE-associated autoantibodies are correlated with and likely mechanistically related to serum IFN-α. SLE-associated autoantibodies are also a heritable trait in SLE families [13], and a number of established SLE-risk loci have demonstrated associations with autoantibodies [14–16].

We have recently conducted a case-case genome-wide association study (GWAS) to determine the genetic factors associated with SLE-associated autoantibodies and high serum IFN-α (Kariuki et al., submitted). In this GWAS study, four SNPs which were all in very high LD (r-squared > 0.8) in the 5′ region near the PIK3C3 gene were in the top 200 SNPs which showed evidence for association with autoantibody traits and/or serum IFN-α. Phosphoinositide-3-kinase, class 3 (PIK3C3), is a member of the phosphatidylinositol 3-kinase family that maps to chromosome 18q12. The PIK3C3 protein, also known as hVps34, plays a role in IFN-α production in vitro, likely via the endosomal pathway [22].

The PIK3C3 locus which has previously been linked to schizophrenia susceptibility was chosen for our GWAS study by ancestry and the presence or absence of anti-RBP or anti-dsDNA antibodies. A study design incorporating multiple ancestral backgrounds was chosen as both autoantibodies and serum IFN-α levels are heritable pathogenic factors which are shared between all ancestral backgrounds. The top 200 SNPs were examined in detail using expert review of public databases, and the seven top SNPs chosen for replication all demonstrated strong associations with either serology or serum IFN-α in an independent cohort, as would have been expected based upon the initial GWAS study design (Kariuki et al., in revision). An SNP 5′ to the PIK3C3 gene was also noted as an SNP of interest among the top 200 SNPs in this GWAS study. Based upon the data presented in the introduction, the functional promoter variant 5′ of PIK3C3 was chosen for follow up in this study.

2.2. Validation Cohort. The independent validation cohort of 478 SLE patients was obtained from the University of Chicago Translational Research in the Department of Medicine (TRIDOM) registry and Rush University Medical Center and consisted of 252 African-American, 152 European-American, and 74 Hispanic-American SLE patients. All patients met the revised 1982 ACR criteria for the diagnosis of SLE [22]. Samples from 522 controls were obtained from the TRIDOM registry, including 361 African-American and 161 European-American subjects who were individually screened for the absence of autoimmune disease by medical record review. The subjects in this study were not related to each other. Informed consent was obtained from all subjects at each site, and the study was approved by the IRB at each institution.

2.3. SNP Genotyping of PIK3C3 rs3813065 in the Validation Cohort. Individuals in the validation cohort were genotyped at PIK3C3 rs3813065. Genotyping was performed using ABI Taqman Assays-by-Design primers and probes on an ABI 7900HT PCR machine with >98% genotyping success. Scatter plots were all reviewed individually for quality, and genotype frequencies did not deviate significantly from the expected Hardy-Weinberg proportions (P > .01 in all ancestral backgrounds).

2.4. Reporter Cell Assay for IFN-α. The reporter cell assay for IFN-α has been described in detail elsewhere [8, 23]. Reporter cells were used to measure the ability of patient sera to cause IFN-α-induced gene expression. The reporter cells (WISH cells, ATCC no. CCL-25) were cultured with 50% patient sera for 6 hours, and then lysed. mRNA was purified from cell lysates, and cDNA was made from total cellular mRNA. cDNA was then quantified using real-time PCR.

2. Methods

2.1. Initial GWAS Study Description. The initial cohort of SLE patients studied in the GWAS scan was obtained from the Hospital for Special Surgery Lupus Registries, and consisted of 104 SLE patients, including 20 African-American, 36 European-American, 32 Hispanic-American, and 16 Asian-American SLE patients. This study was designed as a case–case analysis to compare SNP frequencies in SLE patients with high versus low IFN-α and those with and without SLE-associated autoantibodies. Patients were selected in an extremes-of-phenotype design from the top 33% and bottom 33% of serum IFN-α activity and were additionally stratified for the GWAS study by ancestry and the presence or absence of anti-RBP or anti-dsDNA antibodies. A study design incorporating multiple ancestral backgrounds was chosen as both autoantibodies and serum IFN-α levels are heritable pathogenic factors which are shared between all ancestral backgrounds.
Table 1: Percent of SLE patients with a positive test for each SLE-associated autoantibody in each ancestral background.

<table>
<thead>
<tr>
<th></th>
<th>Ro</th>
<th>La</th>
<th>Sm</th>
<th>RNP</th>
<th>DNA</th>
<th>Ro and Sm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Af-Am</td>
<td>52</td>
<td>19</td>
<td>38</td>
<td>65</td>
<td>41</td>
<td>24</td>
</tr>
<tr>
<td>His</td>
<td>40</td>
<td>10</td>
<td>22</td>
<td>33</td>
<td>48</td>
<td>14</td>
</tr>
<tr>
<td>Eur-Am</td>
<td>33</td>
<td>9</td>
<td>13</td>
<td>20</td>
<td>43</td>
<td>4</td>
</tr>
</tbody>
</table>

Af-Am: African-American, His: Hispanic-American, and Eur-Am: European-American. Numbers indicate percent of subjects with a positive test in each category; “Ro and Sm” category indicates subjects with positive tests for both autoantibodies.

Using an Applied Biosystems 7900HT PCR machine with the SYBR Green fluorophore system. Forward and reverse primers for the genes MX1, PKR, and IFIT1, which are known to be highly and specifically induced by IFN-α, were used in the reaction [8]. GAPDH was amplified in the same samples to control for background gene expression.

The amount of PCR product of the IFN-α-induced gene was normalized to the amount of product for the housekeeping gene GAPDH in the same sample. The relative expression of each of the three tested IFN-induced genes was calculated as a fold increase compared to its expression in WISH cells cultured with media alone. Results from the IFN-α assay were standardized to a healthy multiancestral reference population as previously described, and a serum IFN-α activity score was calculated based upon the mean and SD of the reference population [8]. This assay has been highly informative when applied to SLE as well as other autoimmune disease populations [8, 24, 25].

2.5. Measurement of Autoantibodies. Antibodies to anti-Ro, anti-La, anti-Sm, and anti-RNP were measured in all samples by ELISA methods using kits from INOVA Diagnostics (San Diego, CA), and anti-dsDNA antibodies were measured using Crithidia luciliae immunofluorescence, with detectable fluorescence considered positive. All samples were assayed in University of Chicago clinical laboratory by the same personnel that test clinical samples. For the ELISA assays, the standard cutoff points for a positive test designated by the manufacturer were used to categorize samples as positive or negative. Autoantibody prevalences in SLE patients of each ancestral background are shown in Table 1.

2.6. Statistical Analysis. All subjects in the study had genotype data available for 13 SNPs, and principal component analysis was performed on 12 of these 13 SNPs excluding the PIK3C3 rs3813065 SNP, using the PCA option in the Cluster program by Eisen et al. [26]. The first two principal components are shown plotted on the X and Y axes, respectively, in Figure 1, and the first component provides a strong separation of those subjects of self-reported African-American ancestry from those of self-reported European-American ancestry. If the zero point on the X-axis of Figure 1 was used to categorically split the population, 84.4% of self-reported European ancestry subjects fell in the positive range for the first principal component, and 74.3% of self-reported African-American subjects had a negative value for the first principal component (P-value for departure from a random distribution of these two ancestral populations on the X-axis = 2.8 × 10^{-83}). We included the first principal component as a covariate in all subsequent association analyses to provide control for differences in proportional ancestry in both cases and controls.

Logistic regression models were used to detect associations between the presence of autoantibodies and genotype at rs3813065 using the PLINK program v1.07 [27] (http://pngu.mgh.harvard.edu/~purcell/plink/). All logistic regressions incorporated the first principal component as a covariate to provide some control for genetic ancestry at the individual level. Testing for homogeneity of odds ratios obtained in the study was performed using PLINK with the partitioning of the chi-square test statistic method. The IFN-α data was nonnormally distributed, and nonparametric Mann-Whitney U was used to compare quantitative IFN-α data between two genotype subgroups. When more than two columns of quantitative data were compared, the nonparametric one-way ANOVA (Kruskall-Wallis test) was used to test the hypothesis that the distribution in at least one column was significantly different from the distribution in the other columns. Chi-square test was used to compare allele frequency data between cases and controls. P-values shown in the paper are uncorrected for multiple comparisons. When testing differences in allele frequencies between different patient groups defined by autoantibodies, a P-value of .0071 is sufficient to control the family-wise type I error rate at 0.05. For the serum IFN-α studies in African-American SLE patients, P values <.0056 would withstand a Bonferroni correction for the number of comparisons possible between the different autoantibody states and genotypes presented on the graph.
correction for the number of specificities analyzed. There were similar nonsignificant trends in the Hispanic-American and European-American cohorts ($P = .23$ and .32, resp., data not shown).

### 3.2. Association of $rs3813065$ with Individual Autoantibodies

Logistic regression models were run to detect associations between $rs3813065$ C and each SLE-associated autoantibody individually and follow up models assessed associations with autoantibody combinations. Both anti-Ro and anti-Sm showed evidence for association with $rs3813065$ C allele in African-Americans, and the best fit model was achieved between the $rs3813065$ C and the combination of anti-Ro and anti-Sm antibodies in this background (Table 1, OR $= 2.24$, 95% CI $= 1.34–3.73$, and $P = 2.0 \times 10^{-3}$). This association clearly withstands Bonferroni correction for the number of comparisons in this study. A similar nonsignificant trend was observed for an association between $rs3813065$ C and the combination of anti-Ro and anti-Sm antibodies in Hispanic-American and European-American subjects (OR $= 3.30$, $P = .14$ and OR $= 2.22$, $P = .45$, resp., Table 2). While the direction and magnitude of the odds ratio for association was similar in each background, independent statistical significance was not observed in the Hispanic- and European-American subjects due to the low prevalence of the anti-Ro/anti-Sm serologic profile (Table 1). The odds ratios for association of the $rs3813065$ C allele with the anti-Ro/anti-Sm antibody profile in each individual ancestral background were not significantly different ($\chi^2 = 0.21$, $P = .90$). A meta-analysis across all three ancestral backgrounds supported a significant overall association (OR $= 2.26$, 95% CI $= 1.43–3.55$, and $P = 5.0 \times 10^{-4}$) although most of data supporting this meta-analysis association is derived from the African-American subjects in whom this antibody profile is the most prevalent.

### 3.3. Association of $rs3813065$ with Serum IFN-α Activity in African-Americans

Genetic variation at the $rs3813065$ SNP was not associated independently with differences in serum IFN-α, however the African-American SLE patients who had both anti-Ro and anti-Sm had higher serum IFN-α than those SLE patients who lacked this antibody profile (Figure 3, $P = 7.6 \times 10^{-6}$). These data support a secondary association with serum IFN-α, in which genetic variation is associated with the anti-Ro/anti-Sm antibody profile, and then the particular serologic profile is associated with increased serum IFN-α.

### 3.4. Case-Control Association Study of PIK3C3 $rs3813065$

There were no significant differences in allele frequencies between cases and controls in our cohort although the C allele trended toward enrichment in the African-American cases as compared to controls (Table 3, OR $= 1.07$, $P = .63$). $rs3813065$ C allele frequency in African-American cases lacking either anti-Ro or anti-Sm antibodies was similar to African-American controls (0.605 versus 0.620, resp.), supporting the idea that the C allele is specifically enriched with the subgroup of patients who have both anti-Ro and anti-Sm antibodies.

#### 2.7. SCAN Database Query

We searched $rs3813065$ in the SNP and CNV Annotation (SCAN) database ([http://www.scandb.org/](http://www.scandb.org/)) [28]. This database is a searchable index of genome-wide gene expression data linked to genome-wide SNP genotype data from the HapMap project. Gene expression data is derived from studies in which gene expression arrays were run on Epstein-Barr virus-transformed lymphoblastoid cell lines from individuals genotyped in the HapMap project. The SCAN database contains expression data from both European (Centre d’Etude du Polymorphisme Humain or CEPH) and West African (Yoruba or YRI) HapMap reference populations. We searched the database using $rs3813065$ as the query term, with a threshold $P$ value of $10^{-4}$.  

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**Figure 2:** Distribution of the number of different autoantibody specificities in African-American SLE patients stratified by $rs3813065$ genotype. no. of specificities = the sum of the number of positive test results for anti-Ro, anti-La, anti-Sm, anti-RNP, and anti-dsDNA for a given subject (thus every subject is assigned a number 0 through 5). The horizontal line in the middle of the box indicates the median, boundaries of the boxes indicate the interquartile range, and the error bars show the 10th and 90th percentile, respectively. The $P$ value for the Kruskall-Wallis test is shown.

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**3. Results**

**3.1. Association of $rs3813065$ with Autoantibody Specificities**

We detected an association between the C allele of $rs3813065$ and increasing number of autoantibody specificities in African-American SLE patients ($P = .0057$, Figure 2). The number of antibody specificities was calculated as the sum of the number of positive results for anti-Ro, anti-La, anti-Sm, anti-RNP, and anti-dsDNA antibody testing in a given SLE patient, for a maximum of 5 distinct antibody specificities. This $P$ value of .0057 would exceed a Bonferroni
Table 2: Association of the rs3813065 C allele with anti-Ro and anti-Sm positive patients in each ancestral background.

<table>
<thead>
<tr>
<th>Antibody profile</th>
<th>MAF</th>
<th>OR (C allele)</th>
<th>95 CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-american</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ro+ Sm+ SLE</td>
<td>0.245</td>
<td>2.24</td>
<td>1.34–3.73</td>
<td>2.0 × 10⁻³</td>
</tr>
<tr>
<td>All other SLE</td>
<td>0.395</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic-american</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ro+ Sm+ SLE</td>
<td>0.119</td>
<td>3.30</td>
<td>0.67–16.25</td>
<td>.14</td>
</tr>
<tr>
<td>All other SLE</td>
<td>0.248</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European-american</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ro+ Sm+ SLE</td>
<td>0.115</td>
<td>2.21</td>
<td>0.28–17.67</td>
<td>.45</td>
</tr>
<tr>
<td>All other SLE</td>
<td>0.160</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ro+ Sm+ SLE versus all other SLE</td>
<td>—</td>
<td>2.26</td>
<td>1.43–3.55</td>
<td>5.0 × 10⁻⁴</td>
</tr>
</tbody>
</table>

MAF: minor allele frequency, OR: odds ratio for association of the C allele with Ro+Sm+ patients as compared to all other SLE patients, and 95 CI = 95% confidence interval of the odds ratio.

Table 3: Case-control association of rs3813065 with SLE in African- and European-American subjects.

<table>
<thead>
<tr>
<th></th>
<th>MAF</th>
<th>OR (C allele)</th>
<th>95 CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA cases</td>
<td>0.320</td>
<td>1.07</td>
<td>0.82–1.38</td>
<td>.63</td>
</tr>
<tr>
<td>AA controls</td>
<td>0.380</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA cases</td>
<td>0.155</td>
<td>0.65</td>
<td>0.40–1.06</td>
<td>.09</td>
</tr>
<tr>
<td>EA controls</td>
<td>0.115</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAF: minor allele frequency, OR: odds ratio for association of the C allele in SLE cases as compared to controls in each ancestral background, and 95 CI = 95% confidence interval of the odds ratio.

3.5. Association of PIK3C3 rs3813065 with ERAP2 Expression in the SCAN Database. We next queried the SCAN database (http://www.scandb.org/) to determine whether genetic variation at the rs3813065 SNP was associated with any significant differences in global gene expression in EBV-transformed lymphoblastoid cell lines derived from HapMap individuals [28]. Interestingly, the rs3813065 SNP was associated with a highly significant difference in the expression of endoplasmic reticulum aminopeptidase 2 (ERAP2) in the HapMap cell lines derived from the African Yoruba population (P = 2 × 10⁻⁵). The ERAP2 gene is located on chromosome 5q15 and the molecular mechanism underlying this association is not known. ERAP2 is expressed in the endoplasmic reticulum, and is involved in precursor peptide processing prior to binding to HLA class I molecules in the endoplasmic reticulum [29]. No other transcript levels were associated with rs3813065, including PIK3C3 itself, in the Yoruba population. There were no associations between variation at rs3813065 and gene expression levels in lymphoblastoid cells from the representative European-derived CEPH HapMap population.

4. Discussion

We find that genetic variation in the promoter region of the PIK3C3 gene is associated with a very particular serologic phenotype in African-American SLE patients. It is interesting that we find a primary association with serology and not with serum IFN-α levels, although autoantibodies may be more highly heritable than IFN-α. In SLE families, anti-Ro antibodies are characterized by a relative recurrence risk of 9.7 [13] while high IFN-α has a relative recurrence risk of 3.8 [8]. Relative recurrence risk for anti-Sm in SLE families is incalculable in the same large study [13], as none of the 877 controls had a positive result for anti-Sm. However, 0.2% of the 819 unaffected relatives of SLE patients had a positive anti-Sm test, supporting probable familial aggregation of this autoantibody trait as well.

The rs3813065 SNP has been associated with schizophrenia in multiple ancestral backgrounds [19, 20]. In the largest study to date in Chinese individuals, the rs3813065 C allele was associated with increased risk of schizophrenia (OR = 1.24, P = .017) [20], and a Chinese family-based
association study demonstrated similar findings (OR = 1.51, 
P = .0036 for association of the C allele) [30]. A study examining the rs3813065 allele in European ancestry populations did not find evidence for an association with schizophrenia while there was some evidence for association between the opposite allele (T allele) with risk of schizophrenia in a Jewish population [19]. Thus, while published data support an association between this locus and schizophrenia, there appears to be significant heterogeneity of association between different world populations. SNPs in or near the PIK3C3 locus have not been associated with SLE in genomewide studies to date; however these studies have only assessed European ancestry individuals and have not stratified by subphenotypes such as autoantibody traits.

Studies have implicated polygenic and environmental causes for both SLE [31] and schizophrenia [32, 33]. Infection with the Epstein-Barr virus (EBV) has been strongly implicated as an environmental risk factor for SLE [34], and the herpes virus family may play a role in the development of schizophrenia [35, 36]. Studies suggest that formation of the characteristic SLE-associated autoantibodies anti-Sm and anti-Ro can be triggered by antigenic cross-reactivity with anti-Epstein-Barr virus nuclear antigen-1 (EBNA-1) antibodies [31, 37]. Work in mice and rabbits demonstrated that immunization with EBNA-1 peptides can elicit the production of anti-Sm and anti-RNP autoantibodies [38]. Interestingly, in our study the C allele of the rs3813065 SNP was strongly associated with anti-Ro combined with anti-Sm antibodies in African-American SLE patients. Studies have shown that anti-Sm antibodies are also elevated in patients with schizophrenia and their healthy family members [21]; however it is not known whether this polymorphism is associated with anti-Sm antibodies in schizophrenia patients.

The strong association between the rs3813065 SNP and ERAP2 expression is of particular interest. ERAP2 is expressed in the endoplasmic reticulum and is involved in the processing of precursor peptides prior to their binding to HLA class I molecules in the endoplasmic reticulum [29]. HLA class I molecules present cytosolic peptides, including peptides derived from viruses, allowing presentation of antigens to the adaptive immune system and subsequent development of an immune response directed against the particular peptide. It is possible that dysregulation in ERAP2 expression due to variation in the PIK3C3 gene could lead to alternate peptide processing and presentation on MHC molecules. Improper peptide processing could enhance the chances of anti-self-immune response. Thus, the association of rs3813065 C with the formation of particular autoantibodies in SLE patients could be related to alternate ERAP2-mediated peptide processing prior to presentation on MHC molecules. This could begin to explain the curious finding of anti-Sm antibodies in schizophrenia patients and their family members although the data presented in this paper are only statistically significant in African-Americans, and the PIK3C3 SNP has not been definitively associated with schizophrenia in African-Americans [39]. Studies examining whether this polymorphism is related to anti-Sm serology in schizophrenia patients, and studies to determine whether there is any association between this variant and neuropsychiatric manifestations of SLE will be important areas for future work.

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