Alleles of interferon (IFN) regulatory factor 8 (IRF8) are associated with susceptibility to both systemic lupus erythematosus (SLE) and multiple sclerosis (MS). Although high-type I IFN is thought to be causal in SLE, type I IFN is used as a therapy in MS. We investigated whether IRF8 alleles were associated with type I IFN levels or serologic profiles in SLE and MS. Alleles that have been previously associated with SLE or MS were genotyped in SLE and MS patients. The SLE-associated rs17445836G allele was associated with anti-double-stranded DNA (dsDNA) autoantibodies in SLE patients (meta-analysis odds ratio = 1.92). The same allele was associated with decreased serum IFN activity in SLE patients with anti-dsDNA antibodies, and with decreased type I IFN-induced gene expression in peripheral blood mononuclear cell from anti-dsDNA-negative SLE patients. In secondary progressive MS patients, rs17445836G was associated with decreased serum type I IFN. Rs17445836G was associated with increased IRF8 expression in SLE patient B cells. In summary, IRF8 rs17445836G is associated with human autoimmune disease characterized by low-type I IFN levels, and this may have pharmacogenetic relevance as type I IFN is modulated in SLE and MS. The association with autoantibodies and increased IRF8 expression in B cells supports a role for rs17445836G in humoral tolerance.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease characterized by involvement of the skin, musculoskeletal, renal and hematologic systems and formation of autoantibodies directed at components of the cell nucleus. There is a strong genetic predisposition to SLE, as first degree relatives have a 20-fold increased risk of developing SLE as compared with the general population. Some of the genetic factors underlying SLE have been identified, and many SLE-susceptibility genes function within the type I interferon (IFN) pathway. In particular, the IFN regulatory factor (IRF) family of genes is important in SLE pathogenesis, as genetic variations in the IRF5, IRF7 and IRF8 genes have all been associated with risk of SLE.

High levels of circulating IFN-α are common in SLE patients. We have previously demonstrated that serum IFN-α levels are abnormally high in SLE family members, supporting the idea that high circulating IFN-α is a heritable risk factor for SLE. Many of the SLE-associated variants of IFN pathway genes such as IRF5, IRF7, STAT4, IFIH1(ref. 14) and UBE2L3(ref. 15) are gain-of-function in nature, resulting in increased circulating IFN-α or increased sensitivity to IFN-α in SLE patients in vivo. In addition, a number of novel genes have been discovered, which impact IFN-α levels in SLE patients.

In the case of IRF5 and IRF7, we have shown that the allele associated with risk of SLE was also associated with increased serum type I IFN activity, and that in each case this association was dependent upon the presence of particular autoantibodies. We have recently shown that IRF5 alleles are associated with anti-Ro autoantibodies in otherwise healthy individuals, further supporting the role of IRF family members in serologic autoimmunity. Common variants in the IFN regulatory factor 8 (IRF8) gene are associated with susceptibility to SLE, multiple sclerosis (MS) and systemic sclerosis. In addition, functional IRF8 deficiency is associated with a form of immunodeficiency characterized by decreased circulating plasmacytoid dendritic cells, the cells that are major producers of type I IFN.

It is interesting that alleles of IRF8 have been associated with both SLE and MS, as high type I IFN is a causal factor in human SLE, whereas type I IFN in the form of recombinant IFN-β is an effective treatment for MS. Serum levels of type I IFN are elevated in approximately 50% of adult SLE patients, but in MS circulating levels of type I IFN are significantly lower than those observed in healthy control populations, an effect that cannot be accounted for by functional inhibitors. We sought to explore this potential paradox, in which alleles of the same gene, IFN regulatory factor IRF8, were associated with both SLE and MS, two autoimmune diseases in which type I IFNs are thought to exert opposite effects.

RESULTS

IRF8 rs17445836 G is associated with dsDNA autoantibodies in SLE patients across multiple ancestral backgrounds

We studied serum and genomic DNA samples from 627 SLE patients, including 252 African-American, 143 European-American
and 232 Cretan subjects. The American SLE patients were genotyped at the IRF8 single-nucleotide polymorphisms (SNPs) rs8058904, rs439885, rs4843868, rs12444486 and rs17445836. These SNPs were chosen because they had previously been associated with either SLE or MS.\textsuperscript{6,24,25} Because of the strong precedent for the association of IRF variants with serologic profiles in SLE patients,\textsuperscript{11,12,23} we first analyzed our data for associations between IRF8 alleles and autoantibodies in our American cohort of SLE patients. Using logistic regression models, we tested each SNP individually, and we also tested a haplotype in these models that was reported in a recent study to be associated with SLE.\textsuperscript{24} As shown in Figure 1, the linkage disequilibrium between the SNPs genotyped was generally low. In these logistic regression models, we found an association between IRF8 rs17445836 G and anti-dsDNA autoantibodies (odds ratio = 2.14, P-value = 0.032). No other SNPs demonstrated significant association with serologic parameters. We then replicated this association in the samples from Crete, and the association data are shown for each ancestral background separately and in meta-analysis in Table 1. The odds ratios for association are strikingly similar across populations, and thus the meta-analysis presumes a fixed effect. The allele that is associated with anti-dsDNA antibodies (rs17445836 G) is one that has been associated with MS in previous large case–control studies.\textsuperscript{25}

**Figure 1.** Diagram of the IRF8 gene and linkage disequilibrium (LD) plots. Each SNP studied is indicated by a colored line on the diagram, with the SNP rs number color-coded to the line which represents its location. The number before each rs number (1, 2, 3, etc) corresponds to the number used to designate the SNP in the LD plots below. The LD plots show pairwise correlations between the SNPs studied, with increasing red shading indicating increasing correlation between the two alleles. Numbers represent the D’ statistic.

|                   | African–American | European–American | Crete |
|-------------------|-----------------|------------------|-------|
| rs17445836 G allele frequency |                  |                  |       |
| Cases             | 0.959           | 0.847            | 0.856 |
| Controls          | 0.938           | 0.803            | 0.798 |
| dsDNA +           | 0.949           | 0.813            | 0.839 |
| dsDNA –           | 0.975           | 0.889            | 0.897 |

**Table 1.** Association of rs17445836 with anti-dsDNA autoantibodies in SLE patients

**Case–case**

|                   | African–American | European–American | Crete |
|-------------------|-----------------|------------------|-------|
| OR: dsDNA + vs dsDNA – SLE patients |                  |                  |       |
| OR                 | 2.17            | 1.85             | 1.96  |

**Meta-analysis: dsDNA + vs dsDNA – SLE patients**

|                   | African–American | European–American | Crete |
|-------------------|-----------------|------------------|-------|
| OR (95% CI)       | 1.92 (1.4–3.0)  | 0.019            | 0.97  |
| P-value           |                 |                  |       |
| Cochran’s Q       |                 |                  |       |

Abbreviations: dsDNA, double-stranded DNA; dsDNA +, SLE patients with a positive anti-dsDNA antibody test; dsDNA –, SLE patients with a negative anti-dsDNA antibody test; OR, odds ratio; SLE, systemic lupus erythematosus; 95% CI, 95% confidence interval. Meta-analysis performed under the assumption of a fixed effect, with the Cochran’s Q statistic indicating homogeneity of effect between ancestral groups.
observed in those who also had anti-dsDNA autoantibodies. The same pattern was observed in patients of both European and African-American ancestral backgrounds. This is somewhat parallel to our previous findings with SLE-associated alleles of both the IRF5 and IRF7, in which the effect of the allele upon serum type I IFN was only observed in the presence of the specific associated autoantibody. This situation differs from the SLE-associated IRF5 and IRF7 alleles in that the IRF8 allele in this study is associated with lower serum type I IFN, whereas the other SLE-associated IRF variants have been associated with higher serum type I IFN activity to date.10–12

IRF8 rs17445836 G is associated with lower serum IFN-α in secondary progressive MS
In our European-ancestry MS patients, we observed an increased frequency of the G allele of rs17445836 similar to that reported in large-scale genetic association studies of this allele25 (rs17445836 G = 0.830 in cases, 0.803 in controls). When we examined serum type I IFN in MS patients stratified by this allele, we found that rs17445836 G was associated with lower serum type I IFN activity in patients with secondary progressive MS (Figure 3), similar to the data presented above in SLE. Interestingly, patients with relapsing-remitting MS did not show this pattern, and the number of patients with primary progressive MS was not sufficient to make any comment.

IFN-induced gene expression differs by rs17445836 genotype in anti-dsDNA-negative SLE patients
We next examined type I IFN-induced gene expression in peripheral blood mononuclear cells (PBMCs) from 27 European-ancestry SLE patients, who also had simultaneous serum type I IFN activity data available. As shown in Figure 4, anti-dsDNA-negative

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Table 2. Case–control association of IRF8 rs17445836 G with SLE across multiple populations

| Allele     | African–American | European–American | Crete | Meta-analysis |
|------------|------------------|-------------------|-------|---------------|
|            | Cases | Controls | OR    | Cases | Controls | OR    | Cases | Controls | OR | OR (95% CI) | P-value | Cochran’s Q |
| rs17445836 G | 0.959 | 0.938 | 1.56 | 0.847 | 0.803 | 1.35 | 0.856 | 0.798 | 1.68 | 1.59 (1.2–1.8) | 1.4 × 10⁻³ | 0.57 |

Abbreviations: OR, odds ratio; SLE, systemic lupus erythematosus; 95% CI, 95% confidence interval. Numbers under the ‘cases’ and ‘controls’ headings indicate the frequency of the rs17445836 G allele; meta-analysis performed under the assumption of a fixed effect, with the Cochran’s Q statistic indicating homogeneity of effect between ancestral groups.
SLE patients with the G allele of rs17445836 had reduced type I IFN-induced gene expression than those with the A allele. Subjects with anti-dsDNA antibodies in general had greater type I IFN-induced gene expression, but no difference was observed in type I IFN-related gene expression related to rs17445836 genotype. Figures 4d–f demonstrate that the ability of the serum taken from the same blood sample as the PBMCs to induce the same type I IFN-induced genes in our standardized reporter cell line. Serum type I IFN-induced gene expression was very similar in the anti-dsDNA-negative subjects with either genotype, despite the clear reduction in type I IFN-induced gene expression in these subjects with the rs17445836 G allele. These data suggest a potential downstream regulatory influence upon type I IFN-induced gene expression related to this IRF8 polymorphism.

rs17445836 G allele is associated with increased IRF8 mRNA expression in SLE patient B cells

The rs17445836 SNP is located downstream of the IRF8 gene, and we hypothesized that this SNP may impact a regulatory region to exert a biological function. As shown in Figure 5, the rs17445836 SNP is located in a region that is characterized by DNase hypersensitivity and H3K27Ac chromatin marks in the ENCODE data set, supporting the idea that this SNP is located in a regulatory region. The ENCODE cell line that demonstrates the H3K27Ac marks is the GM12878 cell line, which is a B-cell lymphoblastoid cell line immortalized by Epstein–Barr virus (EBV) transformation. In addition, ChIP-seq peaks from the ENCODE project are observed in the region, including peaks supporting binding of the transcription factors nuclear factor κB, early B-cell

Figure 4. Type I IFN-induced gene expression studies in SLE patients stratified by rs17445836 genotype. There were no minor allele homozygotes in the subjects analyzed for gene expression. (a–c) Gene expression in SLE patient PBMC for the IFIT1, MX1 and PKR transcripts, respectively. (d–f) Expression of the same genes in WISH cells stimulated with sera from these patients taken at the same blood draw as the PBMCs. Central tendency is indicated by the median, P-values calculated using the Mann–Whitney U-test.
factor (EBF) and myelocytomatosus viral oncogene homolog (c-Myc). Given these data, we looked for an impact of rs17445836 upon IRF8 gene expression in circulating blood cells. IRF8 is not expressed as uniformly in all immune cell types as some of the type I IFN-induced genes we measured above in whole PBMC. For our IRF8 expression experiments, we first sorted PBMC from SLE patients using flow cytometry for CD4, CD8, CD14 and CD20 high cells before constructing cDNA libraries from each of these lineages for gene expression. As shown in Figure 6a, IRF8 mRNA was not detectable in CD4 or CD8 T cells, but was expressed to some degree in CD14 monocytes, and most prominently in CD20 B cells. When we examined the B-cell expression data in the context of IRF8 rs17445836 genotype, we found that the G allele was associated with increased IRF8 mRNA expression (Figure 6b).

DISCUSSION

In this study, we find that an allele downstream of IRF8 (rs17445836 G) was associated with decreased activity of the type I IFN pathway in two different autoimmune diseases. Interestingly, this allele has been previously associated with susceptibility to MS in large case–control studies. In SLE patients, we find evidence for association of this allele with anti-dsDNA-positive SLE, and this finding is strikingly consistent across multiple different populations. Anti-dsDNA autoantibody immune complexes are thought to trigger the endosomal toll-like receptor (TLR) receptors, resulting in type I IFN and IFN-induced gene expression. An impact of this allele upon circulating type I IFN levels is only observed in those SLE patients who have anti-dsDNA antibodies, and somewhat surprisingly this allele is associated with lower serum type I IFN in those patients. IRF8 has a number of functions within the immune system, and may not be directly involved in type I IFN production, in contrast to IRF5 and IRF7, which can both induce the expression of type I IFN and IFN-induced genes. We have previously identified another gene associated with lower IFN in SLE patients, an allele of the MAVS gene. Although type I IFN is elevated in approximately 50% of SLE patients, the other 50% of patients do not have elevations in circulating type I IFN levels, and less is currently known about the molecular pathways involved in the pathogenesis of low IFN SLE. It seems that genetic variations in both MAVS and IRF8 contribute to pathogenesis in the low type I IFN SLE patient group. Our previous studies identifying genes associated with high type I IFN in SLE patients have shown that many factors have a role, and we would expect that similarly there will be many more genetic variations associated with low IFN SLE.
MS is characterized by lower circulating type I IFN levels than those observed in healthy control populations30,33 and recombinant IFN-β is an effective treatment for the disease. It is possible that low type I IFN levels could be a primary pathogenic factor in MS, and if so then alleles which are associated with lower IFN levels may predispose to MS. It would be interesting to see if this polymorphism demonstrated stronger evidence for association in the secondary progressive subgroup of MS patients, in which we saw the largest impact of the allele upon serum type I IFN activity. A previous study used publicly available gene expression data from EBV-transformed B cells to assess the impact of the rs17445836 allele upon IFN-induced gene expression.25 This allele was also associated with increased IFN-induced gene expression in EBV-transformed human B cell lines.25 This seems paradoxical, as MS is treated with type I IFN, and a susceptibility allele for MS, which results in augmented IFN signaling would not be expected. We did not observe this; instead in both MS and SLE patients the IRF8 allele linked to MS was associated with decreased type I IFN and decreased type I IFN-induced gene expression. We did not examine EBV-transformed B cells, and it is possible that the EBV transformation may be the cause for the difference between our results.

It is interesting that we see different effects of the same allele upon different type I IFN parameters in patients stratified by anti-dsDNA antibodies. In anti-dsDNA-positive SLE patients, the rs17445836 G allele is associated with decreased serum type I IFN activity, whereas in dsDNA-negative SLE patients, it is associated with decreased type I IFN-induced gene expression. This may indicate that the IFN system is activated in different ways in these two patient groups. In the anti-dsDNA-positive patients, we expect that anti-dsDNA immune complexes would cause TLR ligation that would prompt type I IFN production by dendritic cells, and it is possible that the IRF8 variant is tuning this response. In the anti-dsDNA-negative patients, the TLR system of type I IFN production may not be as relevant, and instead we see an effect of the same IRF8 allele upon type I IFN-induced gene expression. These findings demonstrate a conserved functional relevance of the IRF8 allele in two different human autoimmune diseases.

In addition, we can demonstrate an effect of the rs17445836 G allele upon IRF8 mRNA expression in B cells from SLE patients. This is also supported by the ENCODE data set, in which the B cell–derived cell line expresses many chromatin marks associated with active regulatory elements surrounding the rs17445836 SNP. The fact that this allele is associated with anti-dsDNA autoantibodies and alters IRF8 mRNA expression in B cells suggests a role for this allele in humoral tolerance. The association with reduced type I IFN responses in human autoimmune disease is clinically relevant, as there are a number of drugs in late-stage development for SLE, which target type I IFN, and type I IFN is an important therapeutic for MS. Our data may explain some of the heterogeneity in treatment response between patients with each of these conditions.

Measurement of type I IFN-induced transcript and IRF8 expression in PBMC
PBMC were separated from whole blood using a standard Ficoll gradient, and blood was processed immediately following phlebotomy. For experiments measuring IFN-induced transcripts, the PBMC fraction was lysed, and CDNA was made from total cellular RNA. Type I IFN-induced CDNA transcripts were then quantified using real-time PCR with the same primers for the IFIT1, MX1 and PKR genes used above. Relative expression values for these transcripts were then log-transformed, and compared between patient subgroups. To facilitate direct comparisons between PBMC IFN-induced gene expression and serum type I IFN activity, we also tested serum from these patients from the same blood draw in the WISH assay described above. For this analysis, we treated the data from the three IFN-induced genes in the WISH cells the same way as the PBMC data, instead of combining the three genes into one score. This allows for a visualization of the gene expression in PBMC alongside the amount of IFN-induced gene expression the serum from that blood draw induced in the reference WISH cell line (a measure of serum type I IFN activity). See Kirou et al.48 for further details regarding PBMC transcript analysis. For the experiments analyzing IRF8 expression, PBMC from SLE patients were first sorted by flow cytometry using the surface markers CD4, CD8, CD14 and CD20 to identify CD4 T cells, CD8 T cells, monocytes and B cells, respectively. Then CDNA libraries were made from each of the sorted cell populations individually, and IRF8 expression was determined in each cell lineage.

Measurement of autoantibodies
Antibodies to anti-Ro, anti-La, anti-5m and anti-RNP were measured in all samples by ELISA methods using kits from INOVA Diagnostics (San Diego, CA, USA), and anti-dsDNA antibodies were measured using Crithidia luciliae immunofluorescence, with detectable fluorescence considered positive. All samples were assayed in the University of Chicago clinical laboratory. Standard cut-off points for a positive test designated by the manufacturer were used to categorize samples as positive or negative.
Statistical analysis

To account for potential differences related to proportional ancestry in admixed populations, we performed a principal component analysis on data from 12 SNPs, which confer information about genetic ancestry and which were genotyped in all cases and controls as described in Kariuki et al., similar to the approach outlined in Parra et al. The first principal component in this analysis provided strong separation of self-reported European vs African-American ancestry, and this component was included in logistic regression analyses as a covariate to control for any differences in the degree of admixture between cases and controls, which could otherwise potentially confound genetic association analyses.

Logistic regression models were used to detect associations between genotype at IRF8 SNPs and the presence or absence of each of the five tested autoantibodies in the SLE cases (case–case analysis). Meta-analysis was performed under the assumption of a fixed effect. Case–control analysis of the rs17445836 SNP in SLE patients vs controls was performed using a standard $\chi^2$ test statistic. The serum type I IFN data and the PBMC IFN-induced gene expression data were non-normally distributed, and non-parametric Mann–Whitney U-test was used to compare quantitative IFN data in SLE patients between genotype subgroups. $P$-values shown in the paper are uncorrected for multiple comparisons. To account for multiple comparisons, we used a threshold $P$-value of 0.01 or smaller to control the family-wise type I error rate at 0.05 using a Bonferroni correction when testing differences in allele frequencies between different patient groups defined by autoantibodies. For the IFN studies, $P$-values < 0.025 would withstand a Bonferroni correction for the number of statistical comparisons made on each graph. $P$-values that did not meet these thresholds were not considered significant in this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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