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FINAL RESEARCH MANUSCRIPTS
INTRODUCTION

Systemic SLE erythematous (SLE) is a chronic degenerative autoimmune disorder that affects multiple organ systems by such characteristics as increased production of antibodies and abnormal inflammation of organs.1 Bechet’s disease (BD) is a chronic inflammatory disease that is characterized by recurrent oro-genital ulceration, and uveitis.2 Though the complex pathogenesis of SLE and BD have yet to be fully understood, research suggests genetic and environmental factors influence susceptibility and disease progression.

Interleukin (IL)-18 is a pleotropic cytokine that can induce Th1 and Th2 responses, in the presence and absence of IL-12, respectively.3 Previous studies have shown that serum IL-18 levels in SLE and Behcet’s patients correlated with disease activity.4 A new putative functional IL-18 gene variant (rs360719) was reported by Sanchez et al in a Spanish population, and thus we were interested to see if their results would be consistent in our Turkish population. Because of the relation between IL-18 and BD, we investigated the possible association of that same SNP in our BD patients.

In addition, our lab found another gene associated with BD using a GWAS approach (KIAA1529). No research thus far has found a function for this gene and thus we have selected 14 tag SNPs to fine-map the genetic effect in KIAA1529. Our preliminary results have confirmed this association.

MATERIALS AND METHODS

Patients and controls. Our sample set consisted of 189 SLE patients, 156 Behcet’s disease patients, and 253 ethnically-matched normal healthy controls. All SLE patients and all Behcet’s disease patients fulfilled the 1997 American College of Rheumatology classification criteria for SLE.5, and the 1990 International Study Group classification criteria for Behcet’s disease6 respectively. Samples were received from Marmara University Medical School, Istanbul, Turkey. DNA was extracted from peripheral blood mononuclear cells using standard techniques and all protocols were approved by the institutional review boards of the research ethics committees at Marmara University, the University of Oklahoma Health Sciences Center, and the Oklahoma Medical Research Foundation. All patients provided written informed consent.

Genotyping. The IL 18 gene was chosen based on a previous reporting of a possible putative functional gene variant (rs360719) in a Spanish cohort in SLE (Sanchez); KIAA1529 was examined based on a previous reporting of a possible association between the putative functional genetic variant in the promoter region of IL18 (rs360719) and SLE. We attempted to replicate these results in an independent set of Turkish SLE patients and controls. Next we examined if the same IL18 polymorphism is associated with BD in Turkish patients. Our sample set consisted of 189 SLE patients, 156 BD patients, and 253 ethnically-matched normal healthy controls. The rs360719 SNP was genotyped using a TaqMan assay.

We did not find evidence for a genetic association between the putative functional IL18 SNP rs360719 and SLE in Turkish patients. This is in contrary to the findings by Sanchez et al in a Spanish sample set. These data suggest that the genetic association with IL18 might be limited to specific ethnicities, and perhaps contribute to the inter-ethnic clinical heterogeneity in SLE, rather than a general susceptibility to the disease.

We did not find genetic association between rs360719 and susceptibility to BD in Turkish patients. A genetic association between another SNP in IL18 (rs1946518; -607 C/A) was reported previously in a samples set of BD from Korea, and we are currently genotyping this SNP in our sample.

Furthermore, our lab found another gene that is associated with BD using a GWAS approach (KIAA1529). The function of this gene remains unknown. We have selected 14 tag SNPs to fine-map the genetic effect in KIAA1529. Our preliminary results confirmed this association, and our experiments in this locus are in progress.

RESULTS

We did not find evidence for a genetic association between the putative functional IL18 SNP rs360719 and SLE in Turkish patients (Table 1). This is in contrary to the findings by Sanchez et al in a Spanish sample set.1 Likewise, we did not find genetic association between rs360719 and susceptibility to Behçet’s disease in Turkish patients (Table 2).
DISCUSSION

Systemic SLE Erythematosus (SLE) and Behçet’s disease (BD) are characterized as chronic autoinflammatory disorders with an incompletely understood pathogenesis. Many studies have suggested genetic and environmental influences. In SLE patients, susceptibility increases within family, seen especially between monozygotic (34%) and dizygotic twins (3%). Likewise BD patients have been more commonly seen in populations along the old Silk Road trade route further suggesting this genetic factor. The most supported genetic association comes from HLA-B51, which is thought to trigger and excessive inflammatory response, but that only accounts for about 20% of susceptibility. Thus, many other novel genes have been studied in BD patients.

The proinflammatory cytokine, IL-18 has many biological functions such as mediating Th1 and Th2 responses in the presence and absence of IL12, respectively, which plays an important role in host immune defense against microbial infections. Studies have shown that overproduction of IL18 is seen in many other autoimmune diseases such as Crohn’s disease, rheumatoid arthritis, along with SLE. Studies have also shown that IL 18 serum levels were significantly higher in BD and SLE patients than healthy individuals in that same population, further suggesting a role IL18 may have in both SLE and BD.

We intended to investigate the role of IL-18 rs360719 variant in SLE and BD, but could not confirm the previous works suggesting a genetic association. However, it is to note, however that we used a Turkish population. It may be that the genetic association with IL18 might be limited to specific ethnicities, and perhaps contribute to the inter-ethnic clinical heterogeneity in SLE, rather than a general susceptibility to the disease.

A genetic association between another SNP in IL18 (rs1946518; -607 C/A) was reported previously in a samples set of Behçet’s disease from Korea, although this association was not found in another independent Korean sample set. In another independent study for this same SNP in a Turkish sample set reports results in agreement with Lee et al. We aim to see if we can find a genetic association with our own Turkish cohort that may confirm the results of Keshin et al and Lee et al.

Previously in an unbiased GWA study, several genes were identified as potential genetic loci in BD with KIAA1529 with the strongest association. Thus far, however, no report has mentioned the function of this gene. Thus we aimed to fine map the genetic effect in our Turkish cohort using 14 tag SNPs. Our preliminary analysis of KIAA1529 reports confirmatory results in 6 of our 14 tag SNPs. After conditional analysis, we hope to locate an independent effect causing SNP. To further verify these results it would be necessary to confirm our results in other cohorts followed by functional studies.
ACKNOWLEDGEMENT

I would like to thank Dr. Amr Sawalha for warmly opening his lab to me and allowing me this amazing research experience. A special thank you to the members of Dr. Sawalha’s lab—Travis Hughes, Ajay Nadig, Miranda Josey, and Travis Chapman—for making it amazing. Additionally, none of this would be possible without the funding from AT&T Oklahoma Foundation and Oklahoma Medical Research Foundation’s Fleming Scholar Program, so thank you!

REFERENCES


Figure 1. Linkage dissociation plot showing level of correlation between each SNP with each other.