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Identification of novel genetic markers associated with the clinical phenotypes of systemic sclerosis through a genome wide association strategy

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Purpose

The aim of this study was to determine the genetic components contributing to the different systemic sclerosis (SSc) clinical sub-phenotypes of limited (lcSSc) and diffuse (dcSSc) cutaneous involvement, and with the most common SSc-specific autoantibodies, anti-centromere (ACA) and anti-topoisomerase I (ATA) through a genome-wide association study (GWAS) and a large replication study stratified for these disease features.

Methods

In the discovery phase 2,296 SSc patients and 5,171 healthy controls were analyzed for genetic associations in lcSSc, dcSSc, ACA positive and ATA positive subgroups. The non-HLA SNPs associated with each subphenotype with a genomic control corrected *P* value lower than $1x10^{-5}$, not previously associated with SSc, were selected for replication in 9 independent cohorts from the US and Europe comprising an additional 3,175 SSc patients and 4,971 controls. In addition, meta-analyses including all patients and healthy controls were conducted for each subphenotype.

Results

Three out of the 18 non-HLA SNPs selected for replication showed evidence of association. Meta-analysis including GWAS and replication cohorts showed a strong association of *IRF8* rs11642873 polymorphism ($P = 2.32x10^{-12}$, OR = 0.75) and a suggestive but consistent association among populations of *GRB10* rs12540874 polymorphism ($P = 1.27x10^{-6}$, OR = 1.15) with the lcSSc subtype of the disease. Furthermore, significant association of *SOX5* rs11047102 polymorphism ($P = 1.39x10^{-7}$, OR = 1.36) with the ACA positive patients was detected. In the HLA region, specific patterns of SNPs associated with the ACA and ATA subgroups were observed, reflected by highly associated haplotype in the *HLA-DQB1* locus with ACA ($P = 1.79x10^{-61}$), and in the *HLA-DPA1/B1* loci allelic combination with ATA ($P = 4.57x10^{-76}$).

Conclusions

We have identified three new genes (*IRF8, GRB10,* and *SOX5*) associated with clinical manifestations of SSc, emphasizing the differential genetic component of each subphenotype of this disease. Within the HLA region, we have observed that *HLA-DQB1* and *HLA-DPA1/B1* associations with SSc are likely confined to specific auto-antibody positive patients.

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