Evaluation of Systemic Sclerosis Risk Genes in the Turkish Population

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Background/Purpose: The use of high-throughput genotyping platforms has allowed a better understanding of the genetic background underlying systemic sclerosis (SSc). Sixteen non-HLA genes have been consistently associated with SSc at the genome-wide level of significance, with IRF5, STAT4, CD247, DNASE1L3, IL12A and ATG5 representing the top signals in the two most powered large-scale analyses on SSc performed to date (a genome-wide association study and an Immunochip study in Europeans). We aimed to evaluate for the first time the possible role of the above mentioned genes in SSc susceptibility in the Turkish population.

Methods: We genotyped a total of 355 SSc patients and 718 unrelated healthy controls from Turkey for the SSc-associated lead genetic variants IRF5 rs10488631, STAT4 rs3821236, CD247 rs2056626, DNASE1L3 rs35677470, IL12A rs77583790, and ATG5 rs9373839. The genotyping of the whole SSc group and part of the control group (219 samples) was performed by TaqMan assays, whereas the remaining control data (499 samples) was obtained using the Immunochip platform. To test for association, we compared the minor allele frequencies of every polymorphism between cases and controls by performing 2×2 contingency tables and x² tests.

Results: The overall analysis evidenced statistically significant associations of the global SSc with IRF5 (P=1.48E-05, OR=1.76, CI 95%=1.36-2.27) and CD247 (P=2.20E-03, OR=0.75, CI 95%=0.62-0.90). Trends of association were also suggested for STAT4 (P=0.066, OR=1.21, CI 95%=0.99-1.48), IL12A...
Trends of association were also suggested for STAT4 \((P=0.066, \text{OR}=1.21, \text{CI 95\%}=0.99-1.48)\), IL12A \((P=0.080, \text{OR}=4.06, \text{CI 95\%}=0.74-22.23)\), and DNASE1L3 \((P=0.100, \text{OR}=1.41, \text{CI 95\%}=0.93-2.11)\). Interestingly, the subphenotype analysis showed subtype- and autoantibody-specific associations, that is, CD247 was specifically associated with the diffuse form of the disease (diffuse SSc vs controls: \(P=4.91\times10^{-4}, \text{OR}=0.64, \text{CI 95\%}=0.49-0.82\); diffuse SSc vs limited SSc: \(P=0.065, \text{OR}=0.75, \text{CI 95\%}=0.55-1.02\)), and IRF5 with the presence of anti-topoisomerase autoantibodies (ATA+ SSc vs controls: \(P=8.84\times10^{-8}, \text{OR}=2.28, \text{CI 95\%}=1.68-3.11\); ATA+ SSc vs ATA- SSc: \(P=8.43\times10^{-3}, \text{OR}=1.70, \text{CI 95\%}=1.14-2.52\)).

**Conclusion:** We were able to replicate the associations of IRF5 rs10488631 and CD247 rs2056626 with SSc in the Turkish population, thus confirming the relevant role that these genes may have in the pathophysiology of this disease.

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