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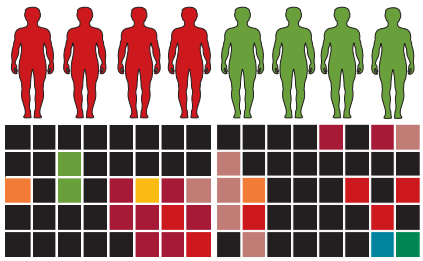
GENETICS

GWAS identifies *STAT4* as a susceptibility locus for Behçet disease in Han Chinese people

A genome-wide association study (GWAS) to identify risk factors for developing Behçet disease in Han Chinese people—by Peizeng Yang and colleagues from The First Affiliated Hospital of Chongqing Medical University, People's Republic of China—has identified a susceptibility locus for Behçet disease in the *STAT4* gene. The team also investigated the functional implications of their finding.

"Our previous candidate gene studies identified multiple Behçet disease associated genes; however, these genes don't fully explain disease pathogenesis," says Yang. "This prompted us to conduct the first GWAS to examine risk factors for Behçet disease in a population of Chinese descent, using the Affymetrix® Genome-Wide Human SNP Array 6.0."



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The GWAS and associated replication study included 149 and 554 patients with Behçet disease, and 951 and 1159 healthy controls, respectively. 3 single-nucleotide polymorphisms (SNPs) were identified in the *STAT4* locus; among them, rs7572482 has been described as associated with Behçet disease in Turkish people, whereas rs7574070 and rs897200 were new. As the association with Behçet disease was strongest for rs897200, the investigators studied this SNP further.

Individuals carrying the AA genotype of rs897200 expressed higher levels of *STAT4* mRNA in their peripheral blood mononuclear cells and skin than those with the GG genotype. Luciferase reporter gene assays showed that the increased mRNA expression of *STAT4* was likely to result from increased transcriptional activity of the *STAT4* promoter in patients carrying the AA allele compared with those carrying the GG allele of this SNP.

What functional significance does rs897200 have? Levels of IL-17 were higher in individuals carrying the AA genotype than those carrying the GG allele; levels of interferon-γ did not differ between these two groups. Individuals with the AA risk genotype of rs897200 also had more severe disease than those with the GG genotype.

"These findings strongly suggest that *STAT4* is a novel locus underlying Behçet disease," explains Yang. "We propose a model where upregulation of *STAT4* expression and subsequent STAT4-driven production of inflammatory cytokines, such as IL-17, is a potential pathway leading to Behçet disease."

Jenny Buckland

Original article Hou, S. *et al.* Genome-wide association study identifies susceptible locus in *STAT4* for Behçet's disease in Han Chinese. *Arthritis Rheum.* doi:10.1002/art.37708