

Medical Update Memo

March 3, 2010

Genome-wide Association Study in a High-Risk Isolate for Multiple Sclerosis Reveals Associated Variants in STAT3 Gene

Summary

MS is a complex disease of unknown cause where both genes and environment seem to have a role in its pathogenesis. The authors have investigated the impact that some specific genetic variants - recently linked to MS - have on the risk of MS, in an extensive group of people with MS and healthy controls in Finland. They found a specific genetic variant which had a protective role in MS. Interestingly this gene was found to have been previously associated to another autoimmune disease, suggesting a significant role of this gene in immune system and autoimmune disease pathogenesis. *Am J Hum Genet.* 2010 Feb 12;86(2):285-291.

Details

Genetic risk for multiple sclerosis (MS) is thought to involve both common and rare risk alleles. Recent Genome-wide Association study (GWAS) and subsequent meta-analysis have established the critical role of the HLA locus and identified new common variants associated to MS. These variants have small odds ratios (ORs) and explain only a fraction of the genetic risk. To expose potentially rare, high-impact alleles, researchers conducted a GWAS of 68 distantly related cases and 136 controls from a high-risk internal isolate of Finland with increased prevalence and familial occurrence of MS. The top 27 loci with $p < 10^{-4}$ were tested in 711 cases and 1029 controls from Finland, and the top two findings were validated in 3859 cases and 9110 controls from more heterogeneous populations. SNP (rs744166) within the STAT3 gene was associated to MS ($p = 2.75 \times 10^{-10}$), OR 0.87, confidence interval 0.83-0.91). The protective haplotype for MS in STAT3 is a risk allele for Crohn disease, implying that STAT3 represents a shared risk locus for at least two autoimmune diseases. This study also demonstrates the potential of special isolated populations in search for variants contributing to complex traits.

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