

Localization of Psoriasis Susceptibility Variants with Family-Based Association Methods

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Abstract

Psoriasis is a complex inflammatory skin disease with an underlying genetic component. The HLA class I region (PSORS1) is known to harbor alleles associated with psoriasis, but extensive linkage disequilibrium (LD) in the region has made it difficult to identify the susceptibility allele. HLA-Cw*0602 has historically shown repeated association with psoriasis, but it is believed to be in LD with the susceptibility variant. To refine the location of PSORS1, we performed family-based association tests using 25 markers within a 300 kb region in 242 Northern European psoriasis families. Three different family-based association tests confirmed that the region of strongest association fell around two SNPs lying 8.5 kb from the start of HLA-C. Haplotype analysis revealed a consistent over-transmission of a haplotype which carried the associated variants upstream of HLA-C and frequently harbored the HLA-Cw*0602 allele as well. The associated upstream alleles were the only alleles that were consistently present on all over-transmitted haplotypes and consistently absent from all under-transmitted haplotypes. This association is in agreement with an independent report of SNPs associated with psoriasis in UK families, confirming that an upstream variant that regulates the expression of HLA-C is the major risk factor for psoriasis. Families were also stratified for the presence of the PSORS1 risk variant in offspring. Association to PSORS2 increased significantly when only risk families were used, while associations to PSORS2 (RAPTOR) decreased significantly when only non-risk families were used. This implies that the penetrance of PSORS1 may be regulated in part by variants within RAPTOR.