Family-based association mapping for the identification of PSORS4, a psoriasis susceptibility gene mapping to the Epidermal Differentiation Complex on human chromosome 1q21

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Abstract

Psoriasis vulgaris is a complex, inflammatory skin disease of the skin affecting 2% of Western populations. Genetic linkage analysis with extended U.S. and Italian families and gene expression studies implicate genetic variation at 1q21 (PSORS4) in conferring psoriasis susceptibility. A 2.5 Mb region on 1q21 harbors the gene rich Epidermal Differentiation Complex (EDC), whose genes have important functions in terminal differentiation of keratinocytes. In the present study, we employed family-based association mapping with a dense map of single nucleotide polymorphisms (SNPs) spanning 1.65Mb of the EDC. Two regions of association with psoriasis were detected, separated by 130kb. Strongest association was observed in the proximal region with markers spanning 37.3kb, which harbor LCE1F and a conserved intergenic region between LCE4A and LCE1F. Results suggest moderate evidence for a second psoriasis susceptibility locus in a distal, 370kb region flanked by SPRR1A and PGLYRP3. Long over and under-transmitted haplotypes harboring LCE genes (LCE3C, LCE3B, LCE3A, LCE2D, LCE2C and LCD2B) were found, which extend nearly 280kb. Haplotype blocks containing these extended haplotypes showed limited diversity (over and under-transmitted haplotypes account for 70-90% of all chromosomes). This study suggests that PSORS4 may lie in the LCE gene cluster, where extended risk haplotypes confer the greatest association. It is also possible that the EDC harbors more than one psoriasis susceptibility variant. Identification of functional variation this region will provide important insights into the role of EDC genes in altered cornified envelope formation observed in psoriasis and psoriasis pathogenesis.