

Genetics of psoriasis

Francesca Capon, Division of Genetics and Molecular Medicine, King's College London, UK

Psoriasis is an immune-mediated, disfiguring skin disorder, which affects approximately 2% of the general population. Familial clustering of the disease being well established, psoriasis has long been regarded as a common and complex trait, resulting from gene-gene and gene-environment interactions.

Searches for disease susceptibility genes were initially undertaken by means of genome-wide linkage analysis. These studies, carried out by us and others on a wide range of Caucasian populations, provided overwhelming evidence for the existence of a major psoriasis susceptibility locus (PSORS1), lying within the class I region of the Major Histocompatibility Complex (MHC). Despite the robustness of these findings, the identification of the PSORS1 gene proved considerably more challenging, owing to the conservation of linkage disequilibrium across the MHC. To overcome this difficulty, we have carried out highly powered analyses of dense SNP maps and deep re-sequencing data. Although the results of these studies point to HLA-C as the most likely PSORS1 candidate, they cannot conclusively identify the underlying susceptibility allele. With genetic studies having now reached their maximal resolution, the identification of the PSORS1 variant will have to rely on the functional analysis of candidate SNPs.

Outside of the MHC, the performance of linkage studies has been poor, mostly owing to lack of statistical power. Conversely, the advent of genome-wide association scans (GWAS) has had a profound effect on the field, resulting in a dramatic acceleration in the pace of gene discovery. As the number of validated susceptibility genes continues to increase, important insights into disease pathogenesis have been emerging. Association results obtained by us and others have highlighted the critical involvement of IL23/IL17 and NF- κ B signalling. Moreover, the follow-up of GWAS hits, which we have pursued by integrating the use of functional experiments with that of bioinformatic tools, has demonstrated an important role for innate immune pathways. Finally, our studies have documented a significant genetic overlap between psoriasis and other immune-mediated conditions, such as Crohn's disease. In particular, we have observed a complex pattern of allelic heterogeneity, with independent variants conferring risk to clinically distinct disorders.

The next few years are expected to witness even more progress in our understanding of psoriasis genetics, as computational advances (e.g. the development of methods for SNP imputation, which allow the meta-analysis of GWAS carried out on different genotyping platforms) and technological breakthroughs (e.g. the advent of next-generation sequencing, which can be used for the systematic identification of rare penetrant mutations and structural variants) are exploited by researchers.