

Psoriasis Stratification to Optimise Relevant Therapy (PSORT): Genome-wide study reveals genetic drivers of response to biologic therapy in psoriasis

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The PSORT consortium aims to identify predictors of treatment response in psoriasis patients. While biologics have revolutionised the treatment of moderate to severe psoriasis, a more targeted treatment approach should improve patient care and deliver substantial economic savings.

We genotyped 2,467 patients enrolled in the British Association of Dermatologists Biologic Interventions Register using the Illumina OmniExpressExome BeadChip, and imputed HLA alleles and amino acids using the SNP2HLA tool. Detailed longitudinal data were available for all patients covering treatments, psoriasis area and severity index (PASI) scores for disease severity, and additional demographic and clinical measurements. For adalimumab, etanercept (both anti-TNF) and ustekinumab (anti-IL12/23) we tested genetic association with response in patients with severe disease (baseline PASI > 10). Response was defined at 3, 6 and 12 months as a 50%, 75%, 90% or 100% reduction in PASI relative to baseline.

Previous genetic investigations into biologic response in psoriasis have focused on candidate variants in genes implicated in psoriasis susceptibility, biologic response in other diseases or drug target pathways. But a clear picture of how genetic variants contribute to treatment response is yet to emerge. Here we seek to replicate every previously reported association with biologic response in psoriasis patients. We confirm the presence of the HLA-C*06:02 allele to be positively associated with early response to ustekinumab (PASI 75, 90 and 100 at 3m; $p < 0.05$) but negatively associated with excellent longer-term response to anti-TNF drugs (PASI 90 and 100 at 6 and 12m). We validate other findings that link biologic response with established psoriasis susceptibility loci, such as *TRAF3IP2* in the IL-17 signalling pathway (adalimumab) and the *LCE3B/C* genes within the epidermal differentiation complex (anti-TNFs).

Our unique datasets continue to accrue and are expected to have sufficient statistical power to extend genome-wide our search for novel genetic associations, and to examine in detail the interplay between genetics and patient-specific clinical/demographic predictors of biologic response.