Genetic variation contributes to response to biologics: initial findings of the Psoriasis Stratification to Optimise Relevant Therapy (PSORT) consortium

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Biologic therapies, which target specific components of key pro-inflammatory immune pathways, can be highly effective in the treatment of moderate-to-severe psoriasis. However, failure to respond carries a high cost, both economically and in terms of patient care. The PSORT consortium therefore aims to identify predictors of treatment response in psoriasis patients.

To date we have genotyped 3,320 patients enrolled in the British Association of Dermatologists Biologic Interventions Register (BADBIR) using the Illumina OmniExpressExome BeadChip. We further imputed HLA status for key alleles, including HLA-C*06:02, using SNP2HLA software. For all patients the BADBIR register includes detailed records of treatments, psoriasis area and severity index (PASI) disease severity scores, and additional demographic and clinical measurements.

In an initial cohort of 2,467 patients we examined associations with biologic response reported in previous candidate variant studies. These investigations have focused on genes implicated in psoriasis susceptibility, biologic response in other diseases or drug target pathways but are yet to form a clear picture of how genetic variants contribute to treatment response. For anti-TNF (adalimumab, etanercept and infliximab) and anti-IL12/23 (ustekinumab) drugs we tested these variants for association with response in severe disease patients (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.

We find modest evidence to support opposing roles for HLA-C*06:02 under the two mechanisms of action, with presence of the allele being positively associated with early response to ustekinumab (PASI 75 and 90 at 3m; $p<0.01$) but negatively associated with excellent longer-term response to anti-TNFs (PASI 90 and 100 at 12m; $p<0.01$). We also validate 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). However, our initial genome-wide results indicate the presence of previously unreported genetic loci that display stronger association with biologic response.

As our unique datasets continue to accrue we expect our statistical power to identify novel genetic associations to improve. We will subsequently examine in detail the interplay between genetics and patient-specific clinical/demographic factors, with the aim of predicting response and stratifying patients according to their most likely effective biologic.

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Psoriasis Stratification to Optimise Relevant Therapy