



HLA genes associate with response to multiple biologic therapies in psoriasis

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The PSORT consortium aims to identify predictors of response to biologic therapies in psoriasis patients.

We genotyped 3,320 patients enrolled in the British Association of Dermatologists Biologic Interventions Register (BADBIR) using the Illumina OmniExpressExome BeadChip, and imputed classical HLA alleles using SNP2HLA software. BADBIR includes longitudinal treatment and psoriasis area and severity index (PASI) data, and other demographic and clinical measurements. We defined treatment response at 3, 6 and 12 months as a 50%, 75%, 90% or 100% reduction vs baseline PASI (12 measures in total; permutation adjustment for multiple tests).

Presence of the key psoriasis risk allele HLA-C*06:02 has been associated with better early response to ustekinumab (anti-IL12/23). Our findings support this result (PASI90 at 3m; OR = 2.48; $P_{\text{adj}} = 0.0377$). We also found a clear trend for patients with two copies of HLA-C*06:02 to achieve higher rates of ustekinumab response than patients with a single copy (not statistically significant due to the small number of homozygotes).

In patients treated with anti-TNF therapy (adalimumab, etanercept, infliximab) we observed a previously unreported trend with opposite direction of effect. HLA-C*06:02 carriers were less likely to achieve PASI90 or PASI100 response at all timepoints, with nominal significance for PASI90 at 6m ($P = 0.0091$) and 12m ($P = 0.0327$).

However, the role of HLA-C in psoriasis susceptibility does not guarantee its relevance to biologic response. We thus examined alleles across the HLA region, which harbours extended haplotypes, and found class II alleles more strongly associated with response (ustekinumab: HLA-DQ with PASI90 at 3m; OR = 3.48; $P_{\text{adj}} = 0.0046$; anti-TNFs: HLA-DR with PASI50 at 6m: OR = 0.25; $P_{\text{adj}} = 0.0026$).

We have shown that while HLA-C*06:02 is associated with response to multiple biologics, the true underlying HLA signals remain to be determined. As our unique datasets accrue we anticipate greatly improved power to unpick the complex relationships between HLA genes. Robust HLA associations could form a key part of a stratification approach to minimise time spent by patients receiving suboptimal treatments.