HLA-DQA1 and HLA-DRB1 have been associated with immunogenicity in inflammatory bowel disease 1, 2 and RA 3, 4, respectively.

Objectives: The aims of this study were to identify associations between HLA alleles and immunogenicity to TNFi in an observational cohort of RA patients and to replicate findings from previous studies.

Methods: Anti-drug antibody titres were measured using radioimmunoassay in serum samples from RA patients participating in Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS). An anti-drug antibody titre of ≥12 AU/mL following six months on treatment was used to define positive immunogenicity. Genotype data were generated using Illumina HumanCoreExome Arrays. Standard quality control (QC) was applied prior to HLA imputation using SNP2HLA software before low minor allele frequency markers were removed. Logistic regression was used to study the association between HLA alleles and immunogenicity, whilst the omnibus test was applied to amino acid positions; sex and concurrent conventional synthetic D-MARD use were included as a covariate in all the models.

Results: In total, 445 RA patients were analysed, 377 patients (70 immunogenicity events) were undergoing adalimumab therapy and 68 certolizumab (30 immunogenicity events) therapy. Following QC, 162 HLA alleles and 361 amino acid positions were available for analysis. The strongest HLA allele association was observed for HLA-DQA1*0103 when all patients were analysed (OR = 0.61; 95% CI = 0.43 – 0.86; p-value = 5e-3) and 26 (p-value = 5e-3) within the HLA-DQA1 gene were significantly associated with immunogenicity events. When both drugs were analysed separately, they produced similar effect size for HLA-DQA1*0103 association; patients treated with adalimumab (OR = 0.59; 95% CI = 0.38 – 0.88; p-value = 1e-2) and certolizumab (OR = 0.52; 95% CI = 0.24 – 1.1; p-value = 1e-1). Another strong association was found for A-DRB1*1402 with TNFi therapy (OR = 6.56; 95% CI = 0.44 – 0.88; p-value = 7e-3) and the amino acid position of 180 (p-value = 7e-3) and 33 (p-value = 7e-3) of HLA-DRB1 gene. Additionally, the similar protective effect between the two presented alleles suggested possibility of linkage disequilibrium, upon investigation the r^2 between the 2 alleles is 0.69.

Conclusion: The current study increases the evidence for association between immunogenicity development with HLA-DQA1 and HLA-DRB1 alleles in patients receiving monoclonal antibody derived TNFi therapy. Further well powered studies are now required to determine the utility of HLA markers as a potential tool to aid the clinical management of RA.

REFERENCES:

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Methods: 951 individuals were divided into three cohorts: 281 children with JIA (mean age 9.1±4.8), 214 children with articular syndrome in case of another joint pathology (post-infectious, post-traumatic and reactive arthritis, osteochondrophy and polyarthralgia; mean age 9.5±4.7); and 456 healthy controls (mean age 14.3±6.25). The JIA patients were divided into subgroups according to IAR classification criteria. 9 SNPs of 8 genes (IL6 (rs1800795), IL6R (rs2228145 and rs4845618), STAT4 (rs7574865), TRAF1/C5 (rs3761847), RUNX1 (rs9979383), PTNP2 (rs2542151), PTNP22 (rs2476601), FOXP3 (rs2232365)) were genotyped using Real-time PCR or PCR-RFLP.

Results: The allele frequencies of the polymorphic loci of the FOXP3 (rs2232365), RUNX1 (rs9979383), PTNP2 (rs2542151), PTNP22 (rs2476601) genes in all three groups were comparable, indicating no association with the risk of development of joint pathology in children. It was shown that CC genotype at the rs1800795 locus of the IL6 gene is associated with JIA (OR 1.49 [1.05–2.13], p = 0.026), while the GC genotype revealed protective effect (OR 0.69 [0.51–0.93], p = 0.014). In addition, a weak association of GG genotypes at the TRAF1/C5 locus (rs3761847) with the risk of developing JIA was found (OR 1.47 [1.00–2.16], p = 0.05). Homozygous GG genotype at the rs3761847 TRAF1/C5 and CC at the rs1800795 IL6 loci, as well as the corresponding G and C alleles, were associated with early JIA onset (under the age of 6 years).

At the same time, CC homozygotes (OR 2.45 [1.50–3.97], p = 0.0003) and C allele (OR 1.33 [1.05–1.69], p = 0.02) at the rs2228145 locus, as well as TT homozygotes (OR 1.54 [1.06–2.23], p = 0.026) at the rs4845618 locus of the IL6R gene were associated with joint pathology except JIA. Moreover, minor alleles, as well as the corresponding homozygous genotypes of polyporphic IL6R loci were significantly more common among children with other articular pathology when compared with the JIA cohort.

Conclusions: The association revealed for the CC genotype at the rs1800795 locus of the IL6 gene in the general JIA group preserved in the group of oligoarticular JIA (OR 1.59 [1.04–2.41], p = 0.033) while GG genotype at rs3761847 locus of the TRAF1/C5 gene was associated with systemic JIA (OR 2.82 [1.29 – 6.15], p = 0.013), and rheumatoid-favor-negative polyarthritis was characterized by higher frequency of GT/TT genotypes at the STAT4 rs7574865 locus (OR 1.85 [1.06–3.24], p = 0.03).

Methods: CD4+ and CD8+ T cells were isolated from peripheral blood of 10 healthy controls and 48 PsA patients and from 6 PsA synovial fluid samples. We performed RNA-seq and ATAC-seq on these two cell types to analyse the global patterns of gene expression and chromatin activity.

Results: We find subtle differences between PsA patients and healthy controls in cells isolated from blood. RNA-seq analysis identified only a handful of differentially expressed genes whilst ATAC-seq analysis identified only 28 differential loci. On the other hand, T cells isolated from synovial fluid showed significant differences compared to T cells isolated from patient’s blood. Interestingly, we find that CD4+ T cells show substantially more differentially expressed genes compared to CD8+ T cells (1168 vs 346 Log2FoldChange > 1, FDR < 0.01). Genes overexpressed in synovial CD4+ T cells are more strongly enriched for immune pathways such as cytokine signaling and T cell proliferation compared to synovial CD8+ T cells.

Conclusions: This preliminary analysis suggests that T cells isolated from peripheral blood do not seem to differ significantly between PsA patients and healthy controls. In contrast, cells isolated from synovial fluid are highly specialized and activated. Moreover, these cells do not resemble canonically activated T cells which means that this state cannot be easily emulated in vitro. This study indicates the importance of not only studying GWAS loci in relevant primary cells from patients, but also that attention needs to be given to cells isolated from the affected site.

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