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 radioimmunaoassay 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 HumanCore Exome Arrays. Standard quality control (QC) was applied prior to HLA imputation using SNP2HLA software to filter out 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 DMARD use were included as covariates in all 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 acids positions were available for analysis. The strongest HLA allele association was observed for HLA-DQA1*03 when all patients were analysed (OR = 0.61; 95% CI = 0.43 – 0.86; p-value = 5e-3). The amino acids positions 187 (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*03 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 PTPN22*232 (OR 0.62; 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 effective better between the two presented alleles suggested possibility of linkage disequilibrium, upon investigating the r2 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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Background: Juvenile idiopathic arthritis (JIA) is a multifactorial autoimmune disease and. JIA exhibits clinical heterogeneity and is divided into seven phenotype subtypes. The outcome of JIA is often difficult to predict, and differential diagnosis is significantly complicated by the variety of causes of joint pain and the similarity of the clinical picture of articular syndrome, especially in the early stages of disease development.

Objectives: To detect genetic markers, associated with the risk of developing JIA, its distinct subtypes and another joint pathology in children.

Methods: 951 individuals were divided into three cohorts: 281 children with JIA (mean age 9.1±4.8), 241 children with arthritic syndrome in case of another joint pathology (post-infectious, post-traumatic and reactive arthritis, osteochondrophy and artthritis; mean age 9.5±4.75) 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 (HLA (rs1800795), IL6 (rs2228145 and rs4845618), STAT4 (rs7574868), TRAF1/C5 (rs3761847), RUNX1 (rs9979383), PTPN2 (rs2542151), PTPN22 (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), PTPN2 (rs2542151), PTPN22 (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 CC 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=0.003) 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 IL6 gene were associated with joint pathology except JIA. Moreover, minor alleles, as well as the corresponding homozygous genotypes of polymorphic IL6R loci were significantly more common among children with other articular pathology when compared with the JIA cohort.

The association revealed by 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 factor-negative polyarthritis was characterized by higher frequency of GT/TT genotypes at the STAT4 rs7574868 locus (OR 1.85 [1.06–3.24], p = 0.03).

Conclusion: Thus, the IL6 gene polymorphism increases the sensitivity of the Belarusian population to JIA, while the IL6R gene polymorphism affects the development of other joint pathologies. It was found that JIA subtypes significantly differ from each other by the molecular profiles of non-HLA genes. This suggests that JIA is represented by a spectrum of genetically distinct subtypes that differ in clinical course and response to therapy.

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GENE REGULATION IN T-CELLS FROM PSA PATIENTS DIFFERS BETWEEN PERIPHERAL BLOOD AND THE INFLAMED JOINTS: IMPLICATIONS FOR THE INTERPRETATION OF GWAS FINDINGS

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Background: Genome-wide association studies (GWAS) have identified variants that are associated with complex diseases such as Psoriatic Arthritis (PsA). The majority of these variants do not affect the coding sequence of proteins but rather regulatory elements which are highly cell type and state specific, and can affect distally located genes via chromatin interaction mechanisms. We and others have previously analysed GWAS loci for multiple conditions (including PsA and Rheumatoid Arthritis) in cell lines using functional genomics techniques, providing putative mechanisms to many loci with previously unknown function [1]. However, multiple studies have identified large differences in gene regulatory mechanisms between cell lines and primary cells, which could significantly alter the proposed mechanisms. Differences between between samples from healthy volunteers and patients, in particular from the affected tissue, have although not been exhaustively investigated.

Objectives: To assess the impact of using primary cells derived from PsA patients compared to healthy volunteers in functional genomics studies.