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From genetics through epigenetics to proteomics: understanding disease mechanisms

OP0291 IDENTIFICATION OF NOVEL SUSCEPTIBILITY LOCI IN A LARGE UK COHORT OF JUVENILE IDIOPATHIC ARTHRITIS (JIA) CASES

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Background: Juvenile idiopathic arthritis (JIA) is a group of chronic arthropathies of unknown cause affecting children under 16yrs, and is the most common childhood inflammatory rheumatic diagnosis. In recent years great advances in dissecting the genetic basis of JIA have been made. In a landmark study, conducted on the two most common subtypes (oligoarthritis and RF-negative polyarthritis), 17 susceptibility loci were identified at genome-wide significance (p-value $<5x10^{-08}$) and a further 11 reaching suggestive significance (p-value $<1x10^{-06}$). These findings were the results of a large international collaboration using the ImmunoChip array, targetting 186 known loci in 12 autoimmune diseases. However, a limitation to the afore-mentioned study was that the analysis is limited to the selected loci; large genome-wide studies are now needed.
Objectives: The aim of this work is to identify novel genetic loci associated with disease susceptibility using a large cohort of UK JIA cases
Methods: Whole-genome genotyping data was generated using four platforms (Illumina). Following stringent quality control common variants to all four platforms were extracted from the individual datasets before merging together. Imputation was performed using the Haplotype Reference Consortium panel on the Michigan Imputation Server using Minimac3 software. SNPs with imputation accuracy ($r^2>0.5$), minor allele frequency >1% and Hardy-Weinberg p-value$>1x10^{-03}$ were retained for analysis. Association was conducted using logistic regression; using the top three principal components as covariates. Bioinformatics analysis was performed using in-house Capture Hi-C data, to study long-range interactions, to elucidate the potential function of the associated SNPs
Results: Post-QC, 2,585 cases and 5,181 controls were available for analysis with ~7.4 million SNPs. Analysis conducted within oligoarthritis and RF-negative polyarthritis cases, (n=1,617) confirmed 13 previously identified JIA risk loci and identified more than 20 potentially novel regions above suggestive significance ($2.25x10^{-05}$). Of these, rs7874896, an intergenic SNP located between *TNFSF15* and *TNFSF8* on chromosome 9 was one of the most strongly associated (p-value $3.67x10^{-07}$). *TNFSF15* is particularly interesting as by homology and function, is very similar to TNFα. Furthermore, in Crohns disease, it has been found that *TNFSF15* drives expression of pro-inflammatory cytokines (IFNγ) and TNFα from CD4+CD161+ T-cells, yet these cells were found to be resistant to anti-TNF treatment; suggesting that blockade of *TNFSF15* may possess therapeutic benefit. Further investigation of SNPs within the *TNFSF15/TNFSF8* gene region using Capture Hi-C data yielded potentially interesting interactions both within this region and with nearby genes within T- and B-cell lines
Conclusions: This study represents the largest GWAS conducted in JIA to date and our preliminary results have identified novel associations with the most common subtypes of the disease and may have highlighted a potentially novel therapeutic target
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OP0292 GENETIC VARIATION ASSOCIATED WITH CARDIOVASCULAR RISK IN AUTOIMMUNE DISEASES

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Background: Autoimmune diseases are highly disabling chronic disorders characterized by the activation of multiple immune and inflammatory pathways against self-components. Clinical studies have demonstrated that autoimmune diseases have a higher prevalence of cardiovascular events compared to the general population. Understanding the genetic and biological mechanisms underlying cardiovascular disease (CVD) risk in autoimmunity could therefore be fundamental to develop more efficient preventive and therapeutic strategies.
Objectives: The objective of this study was to characterize the genetic basis of CVD risk in autoimmune diseases.
Methods: A total of 6,485 patients from the six autoimmune diseases RA, PA, SLE, PS, CD and UC were recruited by the Spanish biomedical consortium IMID Consortium. All patients were Caucasian European from the Spain. CVD patients were defined as having ≥1 out of the 3 most frequent cardiovascular phenotypes: (i) ischemic heart disease (ii) cerebrovascular accident and (iii) peripheral arterial disease. In order to characterize the genetic basis of CVD risk in autoimmune diseases, we used genome-wide genotyping data from all autoimmune disease patients included in the study. First, we tested the association of established CVD risk variants within each autoimmune disease. Second, we analyzed the association of autoimmune disease risk variants with an increase in CVD risk. Finally, we used the cross-phenotype meta-analysis approach (CPMA) to perform a genome-wide meta-analysis and identify global genetic patterns associated with CVD risk in autoimmune diseases.
Results: A total of 17 loci previously associated with CVD risk in the general population were significantly associated with CVD risk in the autoimmune patient cohorts ($P<0.05$). From these, 4 loci were found to have significantly different genetic effects across autoimmune diseases ($P<0.05$). We also found that 6 risk loci for autoimmune diseases were associated with an increase in CVD risk, like the RA risk gene *CFLAR-CASP8*. The CPMA identified a total of 10 genetic patterns significantly associated with CVD risk across all autoimmune diseases. Two of these patterns showed a highly significant association with CVD risk in RA, PsA and SLE. The functional analysis of these two genetic patterns revealed a significant enrichment in key pathways related to the etiology of rheumatic diseases like TNFα ($FDR<0.05$) and IFNγ ($FDR<0.05$) cytokine pathways.
Conclusions: The results of the present study represent an important step towards the characterization of the genetic basis of CVD in autoimmune diseases. These findings contribute to explain the higher prevalence of cardiovascular events observed in patients with autoimmune diseases compared to the general population.
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OP0293 WEIGHTED GENE CO-EXPRESSION NETWORK ANALYSIS OF DMARD-NAÏVE EARLY RA PATIENTS ACHIEVING SUSTAINED DRUG-FREE REMISSION AFTER INITIATING TOCILIZUMAB THERAPY

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Background: Rapidly reducing disease activity is of major importance in the management of newly diagnosed rheumatoid arthritis (RA) patients as early response strongly correlates with long-term clinical outcomes. To select patients for whom it would be favourable to initiate a biological drug from start of therapy, it is crucial to study biological pathways and biomarkers involved in treatment response.
Objectives: To identify biological networks and signature genes among disease modifying anti-rheumatic drug (DMARD)-naïve early RA patients achieving sustained drug-free remission (sDFR) after initiating treatment with tocilizumab (TCZ).
Methods: Data was used from DMARD-naïve early RA patients in the U-Act-Early trial who had been randomized to initiate TCZ therapy. The study design and details have previously been described.[1] Briefly, TCZ (8 mg/kg) was given every 4 weeks and if remission was not achieved, methotrexate (oral) was added. When the target was achieved, therapy was tapered and subsequently discontinued provided remission persisted. sDFR was reached when patients remained ≥3 months in remission while being drug-free until the end of the two-year study period. Before the first dose of medication, whole blood samples were collected and RNA was isolated from CD4 cells and analyzed using RNA sequencing. The DESeq2 package was used to identify differentially expressed genes (DEGs) between responders (achieving sDFR, n=13) and non-responders (not able to taper medication, n=11). Subsequently, weighted gene co-expression network analysis (WGCNA) was used to study clusters (modules) within the 1000 most relevant DEGs.
Results: In total, eight modules with varying sizes (10–470 genes) were identified. The module best correlated (Pearson correlation coefficient 0.52, p=0.009) with achieving sDFR included 26 genes and was used for further functional analysis. Within this module, we found three significantly enriched pathways in the Kyoto Encyclopaedia of Genes and Genomes (KEGG) database. These were calcium signalling pathway ($p=5.81E^{-04}$), carbohydrate digestion & absorption ($p=4.46E^{-02}$), and neuroactive ligand-receptor interaction ($p=2.61E^{-02}$).