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Genetics, epigenetics and immunity

OP6189 GENETICS OF JUVENILE IDIOPATHIC ARTHRITIS: THE IDENTIFICATION OF A NOVEL RISK LOCUS AND CLINICAL SUBGROUP ANALYSIS

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Background: Juvenile idiopathic arthritis (JIA) is a clinically heterogeneous group of childhood onset inflammatory joint diseases with strong evidence to support a genetic contribution to susceptibility. JIA is divided into seven clinical subgroups based on observed patterns of clinical symptoms using the International League of Associations for Rheumatology (ILAR) classification system. The genetic overlap between these groups is not completely understood and this lack of knowledge typically leads to the different ILAR groups being analysed as discrete entities and reducing the overall power of genetic association studies. Objectives: The aim of this study was to conduct a large case-control association study on susceptibility to JIA to identify novel susceptibility loci and to investigate differences of these associations between the ILAR groups.

Methods: JIA participants were genotyped on the Illumina Infinium CoreExome or OmniExpress arrays at The University of Manchester. UK population control genotypes were obtained from the Understanding Society Longitudinal Study. Quality control of data was performed conforming to conventional standards based on call rate, cryptic relatedness and ancestry outliers. Imputation was performed using the HaploType Reference Consortium panel on the Michigan Imputation Server followed by exclusion of SNPs with low imputation accuracy (\( \hat{\theta} < 0.5 \)) and low minor allele frequency (MAF < 1%). Association testing of all SNPs was performed with an additive model incorporating imputation uncertainty using SNPTEST. A subset of SNPs independently associated with all JIA (p-value < 5x10^{-8}) were tested to evaluate if they were specific to a particular ILAR group or shared across multiple ILAR groups using Bayesian multinomial regression and model selection methods implemented in the Trinculo software package.

Results: Following quality control the dataset consisted of > 7.4 million SNPs for 3305 JIA cases and 9196 controls. Association testing in a combined dataset of all ILAR groups identified seven SNPs associated at genome-wide significance (5x10^{-8}); six of these have previously been reported for JIA while one is a novel association. The novel association (rs497523, p-value = 7.12x10^{-9}, OR 0.85, 95% CI 0.8:0.9) maps to chromosome 16p11 and is located within intron one of the CCDC101 gene. In a subset of 44 independently associated SNPs we found no strong evidence to support association of any SNP to a specific ILAR group with the majority of the SNPs showing evidence for sharing across multiple groups.

Conclusion: In the largest case control association study for susceptibility to JIA performed to date, we identified a novel association to a SNP in the intron of CCDC101. This gene is involved in transcriptional regulation through histone acetylation. CCDC101 may be the causal gene at this locus; however introns contain enhancer elements that regulate other genes in the transcriptional domain. Therefore fine mapping with the integration of genomic data is currently being performed for this locus. The results provide little evidence to support ILAR subgroup specificity for any of the associated variants; on the contrary the results support a general model of sharing across multiple groups. The combined analysis of data across subgroups, informed by model sharing, will maximise power to identify novel associations.

Disclosure of Interests: None declared.


OP0190 META-ANALYSIS OF IMMUNOCAP DATA OF FOUR AUTOIMMUNE DISEASES REVEALS NOVEL SINGLE-DISEASE AND CROSS-PHENOTYPE ASSOCIATIONS

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Background: In recent years, research has consistently proven the occurrence of genetic overlap across autoimmune diseases, which supports the existence of common pathogenic mechanisms in autoimmunity.

Objectives: The objective of this study was to further investigate this shared genetic component.

Methods: We performed a cross-disease meta-analysis of Immunochip data from 37,159 patients diagnosed with a seropositive autoimmune disease (11,489 celiac disease (CeD), 15,523 rheumatoid arthritis (RA), 3,477 systemic sclerosis (SSc), and 6,670 type 1 diabetes (T1D)) and 22,308 healthy controls of European origin using the R package ASSET.

Results: We identified 38 risk variants shared by at least two of the conditions analyzed, five of which represent new pleiotropic loci in autoimmunity. We also identified six novel genome-wide associations for the diseases studied. Cell-specific functional annotations and biological pathway enrichment analyses suggested that pleiotropic variants may deregulate gene expression in different subsets of T cells, especially Th17 and regulatory T cells. Finally, drug repositioning analysis evidenced several drugs that could represent promising candidates for CeD, RA, SSc and T1D treatment.

Conclusion: We have been able to advance in the knowledge of the genetic overlap existing in autoimmunity, thus shedding light on common molecular mechanisms of disease and suggesting novel drug targets that could be explored for the treatment of the autoimmune diseases studied.

REFERENCES:


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