by HLA subtype alone. It also reveals that the previously validated associations at position 13 of HLA-DRB1 are also correlated with JIA in the polygous subtype suggesting that genetic risk factors will help refine risk within clinical subtypes. Consistency on DRB1 alleles reveals that the secondary independent DRB1 position association is also strongly associated in the polygous subset of this cohort. Together these results highlight the potential future use of genetics risk factors for risk classification for uveitis in patients with JIA.

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OP0015 GENOMIC RISK SCORE FOR ADVANCED OSTEARTHRITIS IN OLDER ADULTS

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Background: Osteoarthritis (OA) is a major cause of disability, with treatment options mostly limited to advanced disease when joint replacement is indicated. Recent Genome-wide association analysis more than doubled the number of OA risk-associated alleles when compared to prior studies. Polygenic risk score (PRS) -a measure of the cumulative disease risk estimated from all the genetic variants associated with disease-has been proposed as an individualized risk assessment tool. The aim of this study was to evaluate the clinical utility of PRS in OA using a large population-based cohort of older adults.

Objectives: Including these variants, we calculated polygenic risk scores (PRSs) and performed validation in a well-characterised population of older individuals.

Methods: We calculated PRSs for knee and hip OA respectively, using joint replacement as surgical markers of advanced disease in 12,724 older individuals of European descent in the ASPREE trial. We considered in-trial joint replacement (hospitalizations during median 4.7 years follow-up) and pre-trial joint replacement from self-reported medical history. Multivariable models examined the effect of PRS as a continuous variable (per standard deviation [SD]) and categorical variable (low-risk [0-20%], medium-risk [21-80%], high-risk [81-100%]) groups, adjusting for sex, age, BMI, smoking, and smoking status.

Results: Mean population age at baseline was 75 years and 54.9% of participants were female. In total, 1478 (11.6%) participants had knee replacements and 1324 (10.4%) had hip replacements. Female sex, higher BMI and age were associated with higher risk of knee and hip replacements. PRSs as continuous variables per SD were associated with knee (odds ratio [OR] 1.11, 95% confidence interval [CI] 1.04-1.17) and hip (OR 1.18, 95% CI 1.11-1.25) replacements. We found meaningfully different rates of knee or hip joint replacement occurring between low-, medium- and high-risk PRS groups. Participants in the high-risk PRS group, compared with those in the low and medium group, had higher knee replacement rates (OR=1.35, CI 1.2-1.62) and hip replacement rates (OR 1.66, 95% CI 1.57-2.02). We found no interaction between PRS and sex, and no collinearity between PRS and BMI, suggesting PRS is an independent risk factor for OA.

Conclusion: Joint-specific genetic risk scores predict advanced OA in older adults, independent of age, sex and BMI. Stronger associations are observed for hip versus knee OA. Our study provides some of the first evidence of potential clinical utility of genomic risk prediction for OA, which may help identify individuals who would benefit most from targeted clinical management and preventive intervention.

References:


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OP0016 IDENTIFICATION OF FUNCTIONAL VARIANTS IN THE RHEUMATOID ARTHRITIS ASSOCIATED JAZF1 LOCUS IN SYNOVIAL FIBROBLASTS

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Background: Over the past decade, genome wide association studies (GWAS) have identified the JAZF1 locus as a risk locus for several autoimmune diseases, including rheumatoid arthritis (RA). However, the exact causal variants in the JAZF1 locus and their underlying regulatory events contributing to RA are still not known. Here, we focus on the effect of these variants on gene expression in synovial fibroblasts (SF).

Objectives: To characterize the functional consequences of RA-causal variants in the JAZF1 locus in SF.

Methods: Genetic fine-mapping of RA loci was conducted by computing sets of credible variants driving GWAS signals. These credible variant sets were integrated with DNA architecture (ChiP-seq), 3D chromatin interactions (3C, HiC and capture HiC), DNA accessibility (ATAC-seq) and gene expression (RNA-seq and CAGE-seq) datasets to select putative RA-causal variants in SF. Selected variants in the JAZF1 locus were tested for regulatory function by luciferase reporter assays and electrophoretic mobility shift assays (EMSA) in the fibrosarcoma cell line HT1080. The JASPAR2020 database was used to identify putative transcription factors (TF) binding to the selected variants. The expression of HOTPIP was measured by quantitative PCR in hand SF (n=23). Genotyping was done by pyrosequencing.

Results: Genetic fine mapping revealed 47 variants in the JAZF1 locus. Integration of these variants with the chromatin datasets prioritized rs2158624 (rs57585177 and rs186735825 as the top candidates (posterior probability of causality >0.1) in the JAZF1 locus. We found that rs2158624 and rs186735825 are located in the vicinity of enhancer elements in SF as determined by ATAC-seq. In addition, the region of rs2158624 exhibited strong chromatin interactions with the genomic region of HOT Pip and HOXA13. Both these transcripts were previously shown to be specifically expressed in SF isolated from hands and feet. Based on this, we selected rs2158624 as the most promising candidate in the JAZF1 locus. We found that the rs2158624-C allele (risk) is associated with lower expression of HOTPIP, but not HOXA13, in hand SF compared to the rs2158624-T allele (non-risk) (p<0.02). Luciferase assays in HT1080 cells demonstrated enhancer activity with both the rs2158624-C allele (p=0.006) and T allele (p=0.04), with no significant difference in enhancer activity between the rs2158624-C and T allele. EMSAs identified stronger specific binding of HT1080-cell nuclear extract for the rs2158624-T allele than for the C allele (risk). Based on the JASPAR2020 database, we identified NFAT5 as a potential TF that can bind to rs2158624 and may regulate the expression of HOTPIP.

Conclusion: We were able to substantially narrow down the potential functional variants in the JAZF1 locus using our data integration approach and functional assays. We suggest that the risk allele of rs2158624 influences the binding of TFs controlling the expression of the long non-coding RNA HOTPIP in SF, which might confer specific risk to develop RA in hands.

References:


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OP0017 VALIDATION OF GWAS-IDENTIFIED VARIANTS FOR ANTI-TNF DRUG RESPONSE IN RHEUMATOID ARTHRITIS: A META-ANALYSIS OF THREE LARGE COHORTS

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