by ILAR subtype alone. It also reveals that the previously validated associations at position 13 of HLA-DRB1 are also correlated with JIAU in the polygo subtype suggesting that genetic risk factors will help refine risk within clinical subtypes. Conditioning on DRB1 alleles reveals that the secondary independent DRB1 position 69 association is also strongly associated in the polygo 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 OSTEOARTHRITIS 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-associated variants identified (1, 2), extending the feasibility of identification of high-risk individuals.

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 surgeries as 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 age, sex and BMI.

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 the low, had a higher risk of knee replacements (OR=1.35, CI 1.12-1.62), and hip replacements (OR 1.66, 95% CI 1.37-2.02). 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 genomic 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.

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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)¹. 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 HOTTIP 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, rs57585717 and rs186735625 as the top candidates (posterior probability of causality >0.1) in the JAZF1 locus. We found that rs2158624 and rs186735625 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 HOTTIP and HOXA13. Both these transcripts were previously shown to be specifically expressed in SF isolated from hands and feet². 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 HOTTIP, 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 HOTTIP.

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 HOTTIP in SF, which might confer specific risk to develop RA in hands.

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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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