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.

REFERENCES:

- [1] Tachmazidou I, Hatzikotoulas K, Southam L, et al. 2019. Identification of new therapeutic targets for osteoarthritis through genome-wide analyses of UK Biobank data. *Nat Genet*, 51, 230-236
- [2] Zengini E, Hatzikotoulas K, Tachmazidou I, et al. 2018. Genome-wide analyses using UK Biobank data provide insights into the genetic architecture of osteoarthritis. *Nat Genet*, 50, 549-558

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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.

REFERENCES:

- [1] Okada Y et al. Genetic of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 2014;506:376.
- [2] Frank-Bertoncelj M et al. Epigenetically-driven anatomical diversity of synovial fibroblasts guides joint-specific fibroblast functions. *Nat Commun* 2017;8:14852.

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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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Background: The interplay between genetics and drug response in rheumatoid arthritis (RA) has shown that response to biologics varies between individuals and that a large proportion of patients show no clinical improvement (Plenge and Bridges, 2011). Despite the disappointing scenario, to date, only a few genetic markers have been consistently identified and we are far from being able to optimize drug dosing or prioritize drug combinations based on genetic findings.

Objectives: With this background, we sought to validate the association of GWAS-identified variants for response to TNF inhibitors (TNFi) in a two-stage case control association study and to shed some light into the functional role of the most interesting markers.

Methods: The discovery population consisted of 1361 RA patients ascertained through the REPAIR consortium and the DANBIO registry. RA patients fulfilled the 1987 revised American College of Rheumatology (ACR) and the ACR/EULAR 2010 classification criteria. The validation cohort included 706 Dutch RA patients from the DREAM registry. The study followed the Declaration of Helsinki and study participants gave their written informed consent to participate in the study, which was approved by the ethical review committee of participant institutions. Twenty-seven single-nucleotide polymorphisms (SNPs) were selected through a literature search of relevant GWAS. Linear regression analysis adjusted for age, sex and country of origin was used to determine the association between GWAS-identified SNPs and changes in DAS28 (Δ DAS28) after 3 or 6 months of treatment. The meta-analysis of both populations was performed using a fixed effect model. Correction for multiple testing was performed using the Bonferroni method but also considering the number of inheritance models tested ($P=0.0009$). To assess the role of the most interesting markers in modulating immune responses, stimulation experiments in whole blood, peripheral mononuclear cells (PBMCs) and monocyte-derived macrophages using a large number of pathogens and microbiome bacteria were performed in 408 subjects from the Human Functional Genomic Project cohort. We also evaluated the correlation of these SNPs with plasmatic levels of 108 inflammatory proteins, 7 serum steroid hormones and counts of 91 blood-derived immune cell populations.

Results: The meta-analysis of the discovery cohort and DREAM registry including 2067 RA patients treated with TNFi revealed an overall association of the *LINC02549*^{rs7767069} SNP with a decreased drop in DAS28 that remained significant after correction for multiple testing (per-allele $OR_{Meta}=0.83$, $P_{Meta}=0.000077$; $P_{Het}=0.61$). In addition, the meta-analysis of these large cohorts showed that each copy of the *LARRC55*^{rs1711717G} allele significantly decreased the drop in DAS28 in RF-positive patients (per-allele $OR_{Meta}=0.67$, $P=0.00058$; $P_{Het}=0.06$) whereas an opposite but not significant effect was found in RF-negative subjects (per-allele $OR_{Meta}=1.38$, $P=0.10$; $P_{Interaction}=0.00028$; $P_{Het}=0.45$). Interestingly, the meta-analysis also showed potentially interesting but not statistically significant overall and RF-specific associations for the *MAFB*^{rs6071980} and *CNTN5*^{rs1813443} SNPs with Δ DAS28 (per-allele $OR_{Meta,rs6071980}=0.84$, $P=0.0059$; $P_{Het}=0.63$ and $OR_{Meta,rs1813443,RF}=0.81$, $P=0.0059$; $P_{Het}=0.69$ and $OR_{Meta,rs1813443,RF}=1.00$, $P=0.99$; $P_{Interaction}=0.032$). Although analysis of functional data is ongoing, so far, we found that carriers of the *LARRC55*^{rs1711717G} allele showed decreased levels of IL6 after stimulation of PBMCs with *Borrelia burgdorferi* and *Escherichia coli* bacteria ($P=0.00046$ and 0.00044), which suggested a reduced IL6-mediated anti-inflammatory effect of this marker to worsen the response to TNFi.

Conclusion: This study confirmed the influence of the *LINC02549* and *LARRC55* loci to determine the response to TNFi in RA patients and a weak effect of the *MAFB* and *CNTN5* loci that needs to be further investigated.

REFERENCES:

[1] Plenge RM et al 2011. Arthritis Rheum 63, 590-3.

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OP0018

PREDICTING RESPONSES TO ANTI-TNF TREATMENTS IN RHEUMATOID ARTHRITIS PATIENTS FROM GENETIC AND CLINICAL DATA USING A MACHINE LEARNING APPROACH

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Background: Tumor necrosis factor (TNF) inhibitors are key therapies in rheumatoid arthritis (RA). However, a third of patients fail to respond to these agents, and there are no reliable predictors for response. Predictive models, potentially based on clinical and genomic data, are vital to personalizing therapy. The Dialogue for Reverse Engineering Assessments and Methods (DREAM) RA Responder Challenge invited research teams to create models for patient response to anti-TNF therapy. The winning model relied heavily on limited genetic input and was unable to correctly predict responses in a large number of individuals.

Objectives: We compared non-linear and linear analytic methods to predict response and non-response to anti-TNF treatment for RA patients in the DREAM database, using both clinical variables and a large number of potential genome-wide predictors.

Methods: DREAM data on anti-TNF treated RA patients were accessed through Synapse (synapse.sagebase.org). Analogously to the DREAM challenge, we were provided with the clinical and genomic data of 2706 patients with at least moderate disease activity according to their composite disease activity scores for 28 joints (DAS28). In contrast to the previous analysis that focused on single nucleotide polymorphisms (SNPs) based on existing knowledge of RA, we used the full genome-wide dataset of 2.5 million SNPs. We first reduced this to 284 SNPs by considering the marginal p-value of 0.001 for each SNP based on whether or not it predicted response. Then, we removed SNPs with borderline significant p-values if they were in linkage disequilibrium with the most significant SNPs. Instead of predicting a binary outcome of responder or non-responder, we trained both linear (e.g. least absolute shrinkage and selection operator, or LASSO) and non-linear models (e.g. Random Forest) to predict a continuous outcome, the change in DAS28 from baseline to 3-12 months after initiation of anti-TNF therapy. We split the patients into training (N=2031) and testing (N=675) subsets and used the predicted response scores to evaluate the true binary response labels for the test patients.

Results: The best performing method was Random Forest (RF), a non-linear model that uses decision trees to progressively separate subjects into groups based on the most predictive features. Support Vector Regression (SVR) also out-performed linear methods. Compared to only clinical covariates such as age and sex, adding SNPs improved the prediction from an area under the receiver operating curve (AUROC) of 0.63 to 0.67, i.e., 0.04 improvement. This AUROC of 0.67 was 0.046 greater than the DREAM challenge winner.

Conclusion: Non-linear methods such as RF and SVR gave larger predictive improvements compared to linear methods. This may imply some interaction between SNPs and clinical covariates as potential predictors of response to anti-TNF therapy in RA. We are further investigating these 284 SNPs and their interactions in this regard.