on smoking status, PSc was associated with RA among never-smoking women (HR 1.42; 95% CI [1.07 to 1.88]), but not among ever-smoking women (HR 1.10; 95% CI [0.83;1.46]).

In the whole population, PSa was also positively associated with the risk of RA in all three models (HR 1.19; 95% CI [1.02 to 1.40] in Model 3). In stratified analyses on the smoking status, PSa was associated with an increased RA risk only among never-smoking women (HR 1.27; 95% CI [1.02 to 1.57]) and not among ever-smoking women (HR 1.16; 95% CI [0.93;1.44]).

Conclusion: In this large population-based prospective cohort study of French women, we reported that passive exposure to smoking during childhood or adulthood increased the risk of RA. The association was principally observed among never smoking women. These results suggest that smoking by-products, whether actively or passively inhaled absorbed, could generate autoimmunity, at least towards antigens involved in RA pathogenesis.

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OP0013

SEX DIFFERENCES IN AUTOIMMUNE DISEASE SUSCEPTIBILITY; A MULTI-OMIC APPROACH

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Background: Males and females have altered immune responses resulting in variation in autoimmune and cardiovascular disease risk (CVR). Recently, these differences have played a role in the inflammatory response to COVID-19. Sex differences exist in the frequency and activity of immune-cell subsets but mechanisms underlying sexual dimorphism remain unknown. Juvenile-onset systemic lupus erythematosus (JSLE) is an autoimmune disorder that commonly emerges during puberty, has a strong female prevalence (female:male ratio, 4.5:1) and results in an increased CVR. JSLE is characterised by chronic inflammation and dyslipidaemia, where cardiovascular disease is a leading cause of mortality for patients. Our previous work identified a link between immune cell function and lipid metabolism in adult-onset SLE. We hypothesised that sex hormones could influence both lipid metabolism and immune cell function and this could determine sex-specific susceptibility to JSLE and associated CVR.

Objectives: We investigated the role of sex hormones in modifying systemic lipid metabolism and inflammation.

Methods: Nuclear magnetic resonance spectroscopy based serum metabolomics measuring over 130 lipoproteins (14-subsets with lipid compositions), flow cytometry measuring immune-cells, and RNA-sequencing were used to assess the metabolic and immune profile in young, pre/post-pubertal males (n=10/17) and females (n=10/23) and in individuals with gender-dysphoria (GD) under cross-hormone treatment (trans-male/female, n=26/25). This analysis was also performed on a cohort of post-pubertal male (n=12) and female (n=23) JSLE patients. Data was analysed by logistic regression, balanced random forest machine learning (BRF-ML), differential gene expression (DEG) and pathway analysis.

Results: Post-pubertal males had significantly reduced cardio-protective high-density lipoprotein (HDL) subsets (p<0.0001) and increased cardio-pathogenic very-low-density lipoprotein subsets (p<0.0001) compared to females. These differences were not observed pre-puberty and were reversed significantly by cross-hormone treatment in GD individuals, suggesting that sex hormones regulate lipid metabolism *in-vivo*.

BRF-ML (28 immune-cell subsets) identified an increased frequency of anti-inflammatory regulatory T-cells (Tregs) in post-pubertal males compared to females (p=0.0097). These Tregs were also more suppressive in males compared to females. Differences in Treg frequency were seen pre-puberty and were not altered by sex hormone treatment in GD individuals. However, Treg DEGs and functional transcriptomic pathways altered between post-pubertal males and females, including those involved in inflammatory signalling, overlapped with those altered by hormones in GD, suggesting hormones may also drive Treg functional changes. In addition, HDL metabolites modified by hormones showed differential associations with Treg phenotypes between post-pubertal males and females.

Strikingly, sex differences in lipoproteins and Tregs were lost in JSLE, suggesting hormone signalling could be dysregulated in the pathogenesis of autoimmunity and could increase CVR for patients.

Conclusion: Sex hormones drive altered lipoprotein metabolism and functional transcriptomic pathways in Tregs. Males have a lipoprotein profile associated with increased CVR, but a more anti-inflammatory immune profile compared to females. Together, this could explain sex differences in inflammatory disease susceptibilities and inform future sex-specific therapeutic strategies for the management of both JSLE and CVR.

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Genomics, genetic basis of disease and functional genomics

OP0014

HLA ASSOCIATIONS IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS ASSOCIATED UVEITIS AND CLINICAL SUBTYPES

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Background: Juvenile idiopathic arthritis (JIA) is a childhood onset rheumatic disease which is classified into seven different clinical subtypes based upon the ILAR classification criteria. The most common extra articular manifestation of JIA is its associated uveitis (JIAU); particularly chronic anterior uveitis (CAU). Uveitis is a serious complication with the potential to lead to visual impairment and blindness. The rheumatoid factor negative polyarthritis and oligoarthritis ILAR subtypes, often referred to as the “polygo” subgroup, are at a higher risk for developing JIAU, with up to 30% of polygos afflicted by CAU. The HLA region has long been reported as a genetic risk factor for JIA susceptibility, with evidence suggesting that different amino acids of HLA genes infer risk to different JIA subtypes.

Objectives: Investigate the association of amino acids and genetic variants in the HLA region with susceptibility to JIAU and the ILAR clinical subtypes.

Methods: Samples were genotyped using the Illumina Infinium CoreExome and Infinium Omniexpress arrays. Samples were excluded based on <98% call rate, discrepancy between genetically inferred sex and database records, inferred relatedness (identify-by-descent) and ancestral outliers based on principal component analysis (PCA). SNPs were excluded based on <0.01 minor allele frequency (MAF), and call rate <98%. SNP2HLA was used to impute HLA amino acids, SNPs and alleles. Analysis was then executed on markers with an information score >0.9 and MAF >.01 using logistic regression or an omnibus test for multiallelic markers, including 3 PCs as covariates. Independent associations were identified using forward stepwise logistic regression including previously identified variants as covariates. Comparison of regression models was performed using a likelihood ratio test (LRT).

Results: We analysed 7425 markers within the HLA region in 450 JIAU and 2024 JIA cases without uveitis. The most significant association was to amino acid positions 13 of HLA-DRB1 (p=2.9×10⁻³⁰). Conditional analysis on DRB1 position 13 revealed an independent signal at DRB1 position 67 (p=2.4×10⁻⁶). Conditioning on all DRB1 alleles revealed an independent signal at HLA-DPB1 position 69 (p=5.3×10⁻⁷). As expected, ILAR subtype was found to be associated with JIAU (p=1.58×10⁻⁶). We used LRT to test if genetics provided further information above ILAR subtype alone and found that including residues at DRB1 position 13 significantly improved the fit of a model based on ILAR subtype alone (LRT p = 3.6×10⁻²⁷). The reciprocal analysis, adding ILAR subtype to a model based on DRB1 position 13 alone, did not significantly improve the fit of a model (LRT p=0.83). Exploring associations in the polygo subgroup (n=1646) we found significant associations to the three previously described amino acids and JIAU (DRB1 position 13 p=3.4×10⁻²⁰, DRB1 position 67 p=3.3×10⁻⁴, DPB1 position 69 p=2.2×10⁻⁶).

Conclusion: This is largest analysis of HLA markers in JIAU patients to date and we identify two independent associations to amino acids in HLA-DRB1 and a further independent association to HLA-DPB1. This analysis demonstrates that including data on genetic risk factors adds further information to that captured

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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