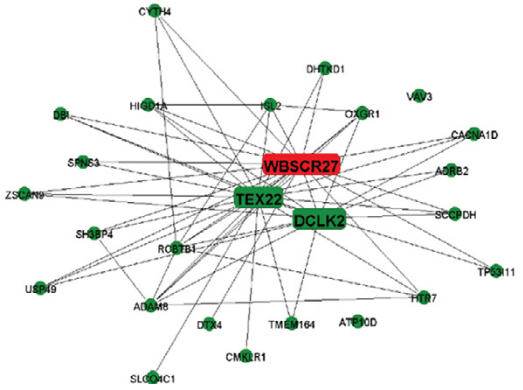
Fig. 1: Network visualization of the interaction of gene co-expression in the module best correlated with achieving sustained drug-free remission. Upregulated genes are expressed as green nodes and the down-regulate gene as red node. The three rounded rectangular nodes display the highest co-expressed genes within the module (>10 connections) when applying a weight cut-off of 0.01. The average number of nodes connected at this cut-off was 4.6 (correlation coefficient 0.82).



In addition, we identified 83 overrepresented Gene Ontology (GO) terms of which granulocyte migration (p=2.70E^{-04}), myeloid leukocyte migration (p=8.95E^{-04}) and G-protein coupled amine receptor activity (p=1.25E^{-03}) were most significant. The genes in the module of interest showing the highest connectivity were the upregulated testis expressed 22 (TEX22), doublecortin lie kinase 2 (DCLK2), and the downregulated Williams Beuren syndrome chromosome region 27 (WBSCR27) gene (Fig. 1).

Conclusions: When performing network analyses of the DEGs between responders and non-responders, TEX22 and DCLK2 were identified as signature genes for treatment response to TCZ therapy. WBSCR27 was found to be associated with less chance of achieving sDFR.

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OP0294 FRACTURE PREDICTION USING A GENETIC MARKERS ALGORITHM COMPARED TO FRAX IN THREE EUROPEAN COHORTS

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Background: Numerous genome-wide association studies (GWAS) and large meta-analyses have started to unravel the multiple gene polymorphisms associated with BMD and/or fragility fractures. However the clinical utility of these genetic markers for fracture prediction remains to be established.

Objectives: To develop a DNA genotyping tool for predicting osteoporotic fractures in postmenopausal women.

Methods: 768 SNPs previously associated with osteoporosis phenotypes were identified in silico through the NHGRI GWAS catalog and BoneKey Genetics website. They were genotyped on an Illumina GoldenGate assay in 1649 postmenopausal women aged 45+ yrs belonging to three osteoporotic fractures cohorts from Switzerland, Italy and France. SNPs potentially associated (p<0.10) with prevalent and incident clinical fragility fractures in one or more of the cohorts, or in the cohorts together, were then combined in a genetic risk score (GRS). GRS association with fragility fractures was tested by forward logistic regressions adjusting for age and FN BMD. The ability of GRS for fracture prediction was evaluated by the area under the ROC curve (AUC) in the three cohorts combined, as well separately (for internal replication). For comparison, fracture probabilities were computed using FRAX clinical risk factors (without BMD) without and with the addition of GRS.

Results: The average prevalence of fragility fractures in the three cohorts was 25% (range 22 to 28%), of which half were major fractures (FRAX definition). After QC filtering, 632 SNPs in 1625 individuals were correctly genotyped, of which 73 were potentially associated with fractures in one or more cohorts. In single and multiple regression models, GRS was significantly associated with fractures (OR 1.09, CI 1.07–1.12, p<0.0001). The GRS AUC for fracture prediction was significant (0.65) and highly consistent among the three cohorts. GRS predicted major fractures as well as FRAX clinical risk factors without BMD (AUC 0.63 vs 0.58, p=0.08), and when combined with clinical FRAX, the AUC was significantly improved (0.67, p=0.0106).

Conclusions: SNPs previously associated with osteoporosis phenotypes through large GWAS and meta-analyses can be replicated for association with fragility fractures in post-menopausal women from three European countries. Our results provide a proof-of-principle that a genetic risk score (GRS) based on these SNPs represents an independent risk factor for fractures and could be developed into a genetic algorithm to improve the prediction of fragility fractures, either alone or together with FRAX.

Disclosure of Interest: None declared

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OP0295 UNIQUE WHOLE BLOOD MICRORNA BIOSIGNATURE FOR RHEUMATOID ARTHRITIS

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Background: RA susceptibility risk is disproportionately high (~2–3fold) in Indigenous North American (INA) tribes compared to other populations[1,2]. Environmental, lifestyle & genetic factors account for <20% of observed disease variance suggesting contribution of additional risk determinants[3]. Emerging evidence suggests small non-coding microRNAs (miRs) e.g. miR-155, miR-146a, miR-26b are key contributors to RA pathogenesis[4]. In this project, we examined the role of miRs on RA incidence, and association with anti-citrullinated protein antibodies (ACPA), whose appearance precedes disease symptoms. We hypothesized that differential expression of specific miRs associated with disease symptoms will facilitate RA transition in genetically susceptible first-degree relatives (FDRs).

Methods: Whole blood and peripheral blood mononuclear cells (PBMCs) were obtained from age-matched ACPA+ RA patients (n=18), non-symptomatic ACPA+ FDRs (n=12) and ACPA- healthy controls (n=12), who belonged exclusively to INA Cree-Ojibway communities of Northern Manitoba, Canada. Total RNA was isolated using miRVANA kit (Ambion). Expression of selected 32 miRs based on the published literature, and associated downstream mRNA targets, were monitored by quantitative real-time PCR, RNU48 and 18sRNA were used for input normalization for miRNA and mRNA expression respectively.

Results: Whole blood expression profiling identified 10 differentially expressed miRs in RA patients compared to control subjects. Expression of miR-103a-3p was significantly up-regulated (~2.3-fold; p=0.0062), whereas that of imiR-16, miR-24, miR-29a, miR-125a-3p, miR-203, miR-222, miR-223, miR-150 and miR-346 were down-regulated in RA patients compared to controls. Increased miR-103a-3p expression was also confirmed in PBMCs from ACPA+ RA patients (~2 fold; p=0.0040) compared to controls. Further, miR-103a-3p expression was increased in ACPA+ FDRs (>4 fold) compared to controls (p=0.0005), and ACPA+ RA patients (p=0.0149). miR-103a-3p expression was consistently elevated in ACPA+ FDRs, when we analyzed samples obtained at two independent time points (1year apart). Consistent with this, expression of AGO1 and DAPK1 mRNA, downstream targets of miR-103a-3p, was decreased significantly (p<0.05) in ACPA+ FDRs compared to controls.

Conclusions: This study defines a unique signature of dysregulated miRs amongst RA patients and their related FDRs within the INA cohort. Our results suggest a potential role of miR-103a-3p as a prognostic biomarker for pre-clinical RA.

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OP0296 AUTOIMMUNE ASSOCIATED GENE PTPN22 NEGATIVELY REGULATES DECTIN-1 SIGNALLING IN DENDRITIC CELLS

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Background: A single nucleotide polymorphism within the phosphatase *PTPN22*