adiponectin on RA in both European (OR 0.97; 95% CI 0.78 – 1.22; p=0.81) and East Asian (OR 0.97; 95% CI 0.72 – 1.31; p=0.85) populations after adding BMI as a confounder in the multivariable MR model (Figure 1).

Conclusion: This MR study does not support a causal effect of genetically determined adiponectin levels on the risk of developing RA in both European and East Asian populations. By using multivariable MR to account for possible shared genetic predictors between circulating adiponectin levels and BMI we have shown that circulating adiponectin is not causally linked to RA risk after adjustment for BMI.

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POS0038 GENOMICS OF JAK-STAT SIGNALING IN VENOUS THROMBOEMBOLISM
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Background: Janus kinase inhibitors (JAKi) have been associated with an increased risk of venous thromboembolism (VTE) [1]. VTE comprises deep vein thrombosis and pulmonary embolism and is associated with complications such as recurrent VTE, post thrombotic syndrome, pulmonary hypertension, and death. These concerns limit the use of JAKi-based therapy. To improve risk stratification and drug development, it is crucial to understand the possible implication of dysregulated JAK-signal transducers and activators of transcription (STAT) signaling in the pathogenesis of VTE.

Objectives: The objective of this study is to clarify the putative genomic vulnerability to dysregulated JAK-STAT signaling in VTE.

Methods: We are systematically mine and analyze large-scale genomic datasets generated from studies comparing VTE patients with healthy controls. Using VTE genome-wide associated (GWA) summary statistics we evaluate the representative genotypes encoding the JAK-STAT pathway (KEGG hsa04630) in associated loci and assess their association to VTE. Further, we examine the genetic VTE risk burden in the chromatin interactome of STAT family transcription factors (TFs). We extract available STAT family (STAT-1-3) TF binding site (TFBS) consensus DNA motifs (JASPAR database) and assess the association of genes containing STAT family TFBS within their promoter sequence (TSS ~2000bp) to VTE. Through mining of deposited OMICs data from VTE patients, we examine molecular characteristics related to JAK-STAT signaling, including potential enrichment of STAT family TFBS among query promoter sequences of differentially expressed genes (DEGs).

Results: We do not observe a significant overrepresentation of JAK-STAT genes (n_total=162) among genes annotated to VTE significant GWA loci (n_overlap=147, p<0.48). Similarly, the JAK-STAT gene set show no cumulative association to VTE (p=0.98). Applying the same gene set association approach to the STAT target gene sets (n_total=4570) does not reveal significant association between VTE and STAT1 (n_overlap=18, p=0.17) and STAT3 (n_overlap=23, p=0.20) target gene sets. At the functional molecular level, we do not see any significant overlap between molecules acting in the JAK-STAT pathway and DEGs (n_overlap=507, p=0.06) or differentially abundant proteins (DAPs; n_overlap=35, p=0.57). However, we observe a significant overlap between downregulated DEGs (n_overlap=362) and the STAT1:STAT2 heterodimer target gene set (n_overlap=2155, p_overlap=48, p<0.0001) including downregulation of IL-27RA and CCND3 (Figure 1). Supporting the biological relevance of this finding, we find a weak but statistically significant enrichment of STAT1 TFBS motifs in the promoter sequence of downregulated DEGs compared to non-DEGs (p=0.02).

Conclusion: Here, we provide a coherent approach to assess the genomic basis for the reported association between JAKi treatment and VTE. Our preliminary data suggest that genes under transcriptional control of STAT family TFs may be dysregulated in VTE patients. It is conceivable, that the genomic actions of JAKi is overlapping with the molecular risk profile of VTE. CCND3 is especially interesting because VTE occurs in up to 10% of patients treated with cyclopentadependent kinase inhibitors such as Palbociclib [2]. Obviously, genomic data mining alone cannot guide medical decision making concerning the use of JAKi. However, our results provide a basis for further investigation of adverse events seen with JAKi.

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POS0039 MONOCYTE TRANSCRIPTIMICS AND TARGETED PROTEINOMICS DEFINE HETEROGENDUS SUBGROUPS IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND SUBCLINICAL AHEROSCLEROSIS
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