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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.

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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.

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Figure.

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OP0019 **DEFINING SYSTEMIC LUPUS ERYTHEMATOSUS MOLECULAR TAXONOMY THROUGH DATA-DRIVEN RESTRATIFICATION AND IDENTIFICATION OF CLUSTER-TAILORED DRUGS FOR A PERSONALIZED MEDICINE APPROACH**

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Background: Systemic Lupus Erythematosus (SLE) is characterized by lack of treatment diversity, largely empirical treatment decisions, and paucity of novel compound development.

Objectives: We sought to stratify SLE patients based on their molecular phenotype and predict personalized therapeutic compounds, tailored to the molecular fingerprint of each subgroup.

Methods: We performed a co-expression analysis using our publicly available whole blood RNA-seq data of 120 SLE patients. Modules of commonly regulated genes were established and used to re-stratify patients through hierarchical clustering, in a data-driven, clinically independent, manner. Next, we established an in silico, subgroup signature-based, drug prediction pipeline. Investigated drugs included both those currently in practice and those who have been tested in

SLE clinical trials and are listed in the iLINCS prediction databases. Finally, drug repurposing analysis was performed, to identify novel perturbagens that counteract group-specific SLE signatures.

Results: Molecular taxonomy identified five distinct lupus molecular endotypes, each characterized by a unique gene module enrichment pattern. A group defined by strong neutrophilic signature encompassed almost exclusively patients with active nephritis, while a B-cell expression group included patients with severe lupus phenotype. Metabolic processes enrichment defined a group of patients with disease of moderate severity and serologic activity. Finally, patients with mild lupus features were distributed in two groups, which demonstrated enhanced basic cellular functions, myelopoiesis, and autophagy. The ability of different compounds to reverse the transcriptomic aberrancies observed in each patient group was examined. Bortezomib efficiently reversed disturbances in the "neutrophilic" cluster. Azathioprine and ixazomib might be a reasonable option for patients of the "B-cell" cluster, whereas fostamatinib appeared efficacious for the "Metabolism" patient subgroup.

Conclusion: The clinical spectrum of SLE encompasses distinct molecular endotypes, each defined by unique pathophysiologic aberrancies, which can be utilized to guide personalized care and direct novel compound development.

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OP0020 **HOMEBOX D TRANSCRIPTION FACTORS SHAPE DIFFERENTIAL JOINT ENVIRONMENT BETWEEN ANTERIOR FINGER JOINTS AND THUMB**

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Background: The expression of embryonic Homeobox (HOX) genes is tightly regulated based on anatomic location in human adult dermal and synovial fibroblasts. Previously, we showed that HOX-D10, -D11 and -D13 are higher expressed in synovial fibroblasts from small distal joints from the hands and feet, in particular in digits II-V and wrists compared to thumb and that this expression pattern is epigenetically imprinted¹. The consequences of the tightly restricted expression of these transcription factors are largely unknown.

Objectives: To elucidate the function of HOXD10, -D11 and -D13 in synovial fibroblasts.

Methods: Synovial tissues were isolated from paws of naïve C57BL/6 mice (n=8), from patients with rheumatoid arthritis (RA), osteoarthritis (OA) and from healthy controls. Synovial fibroblasts were cultured and transfected with GapmeR to silence HOXD10, -D11, and -D13, respectively or with control GapmeR. RNA sequencing was performed on the NovaSeq platform and pathway analysis was done using R packages and web-based tools (GSEA, EnrichR, Cytoscape). HOXD target gene expression was measured by qPCR (n=3-6).

Results: To confirm and further analyze the distinctive expression pattern of HOXD genes, we measured their expression in healthy synovial tissues of different joints of human feet and mouse paws. Similar to what we had found in hands, HOXD10, -D11 and -D13 were less abundant in the joints of the first digit of human feet compared to digits II-V (n=3-4 in each joint). Measurements in joints of mouse paws showed lower expression of HoxD10, -D11 and -D13 in distal interphalangeal joints compared to proximal interphalangeal joints and metacarpophalangeal (MCP) joints, respectively. Silencing of HOXD10, -D11 and -D13, affected the expression of 5333, 2217 and 7347 genes, respectively, in cultured RA synovial fibroblasts from human wrists (n=3).

There were more transcripts equally regulated by HOXD10 and -D13 (40% of all HOXD10 and 31% of all HOXD13 regulated transcripts), than by HOXD11 and either -D10 or -D13 (18% of all HOXD10 regulated genes and 16% of all HOXD13 regulated genes), suggesting most redundancy between HOXD10 and -D13 (Figure 1). Among genes differentially expressed in SF isolated from MCP II-V versus thumb joints, 19%, 4% and 33% were regulated by HOXD10, -D11 or -D13, respectively, supporting a role for HOXD13 in particular in shaping the joint specific environment. All three HOXD transcription factors regulated genes involved in cell cycle progression, demonstrating dependence of synovial fibroblasts on these HOX genes for cell division. Other enriched pathways were Toll-like receptor and integrin signaling pathways, regulation of unsaturated fatty acid synthesis and autophagy and extra-cellular matrix protein organization. We could