TOWARDS PRECISION MEDICINE IN CONNECTIVE TISSUE DISEASES: GENOMIC AND TRANSCRIPTOMIC STUDIES

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Background: To date, 18 genotypes linked with enhanced interferon signalling and severe inflammatory multi-system disease, have been identified. Functional studies in these disorders has led to significant advances in the understanding of type I interferon signalling. Understanding the role of these same genes in the pathogenesis of Connective Tissue Diseases (CTDs) may help guide precision medicine in this field.

Objectives: To study the relationship between phenotypic, serological, genomic and transcriptomic characteristics in adults with Connective Tissue Diseases (CTDs).

Methods: Following clinical and serological phenotyping, targeted exome sequencing in adults with CTD identified potential mono-allelic variants in 18 genes associated with type I interferon signalling. An ISG signature was present in 35% of the cohort and showed significant correlation with phenotypic features associated with autoimmune diseases, particularly lupus. Type I interferon-associated genes, such as TREX1, C1q and PEPD.

Results: Targeted exome sequencing in adults with CTD identified potential mon-allelic variants in 5% of cases, with causative genes including known type I interferon-associated genes, such as TLR5 and HLA.

Conclusions: Drug development in CTDs is notoriously slow. However, recent drug developments in type I interferon modulation in terms of JAK-STAT inhibition and interferon receptor antibodies offer great promise for a subset of patients. Our work demonstrates that through deep phenotyping of patients with corollary omic studies, a CTD subset, that is not restricted to a single diagnostic grouping, can be identified in whom targeted anti-interferon therapy would likely be of great value.

REFERENCES:

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POLYMORPHISMS IN PHASE I-METABOLIZING ENZYME AND HORMONE RECEPTOR GENES INFLUENCE THE RESPONSE TO ANTI-TNF THERAPY


Background: Although the etiology of rheumatoid arthritis (RA) remains unclear, there are evidences suggesting a role of sex steroid hormones in determining the onset and progression of the disease.

Objectives: The aim of this study was to evaluate whether 47 single nucleotide polymorphisms (SNPs) in steroid hormone-related genes are associated with the risk of RA and anti-TNF drug response.

Methods: We conducted a case-control study in 3 European populations including 2936 RA patients and 2197 healthy controls. Of those a total of 1985 RA patients were treated with anti-TNF blockers. The association of potentially interesting markers with RA risk or drug response in the discovery population was validated through meta-analysis with data from DREAM and DANBIO registries.

Results: The value of steroid hormone-related variants for prediction of anti-TNF drug response was also assessed using stepwise logistic regression analyses. The area under the curve (AUC) of a receiver operating characteristic (ROC) curve analysis and a –2 log likelihood ratio (LR) test were used to assess whether the genetic model fitted significantly better the data compared to the reference model. A randomization test (50,000 iterations) was run to confirm the consistency of the results.

Results: Although none of the selected variants played a relevant role in modulating RA risk, the meta-analysis of the linear regression data with those from the DREAM and DANBIO registries showed a significant correlation of the CYP3A5*17, CYP2C9*3, and CYP17A1*13 variants with changes in DAS28 after the administration of anti-TNF drugs (p<0.00074, and p=0.006). An overall haplotype

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