THU0009

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 was performed in 100 adults with CTDs. The CTDs include: systemic lupus erythematosus, Sjogren's syndrome, mixed and undifferentiated CTD, limited and diffuse cutaneous systemic sclerosis and dermatomyositis. The targeted 200-gene panel was designed based on data from human or animal studies associating gene function with autoimmune diseases, particularly lupus. Type I interferon stimulated gene (ISG) signature score was calculated from quantitative PCR assessment of six interferon stimulated genes¹ and interferon alpha was directly assayed by single-molecule array (Simoa) digital ELISA technology² in all cases.

Results: Targeted exome sequencing in adults with CTD identified potential monogenic causes in 5% of cases, with causative genes including known type I interferon-associated genes, such as TREX1, C1q and PEPD.

An ISG signature was present in 35% of the cohort and showed significant correlation with the Simoa interferon alpha assay ($r=0.854$) (figure 1).

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.

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THU0010

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

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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 were corrected for multiple testing (Meff method; $p=0.0011$).

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 CYP3A4_{rs11773597} and CYP2C9_{rs1799853} variants with changes in DAS28 after the administration of anti-TNF drugs ($p=0.00074$, and $p=0.006$). An overall haplotype