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 genes and interferon alpha was directly assayed by single-molecule array (Simoa) digital ELISA technology 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-related 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 correlative 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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Acknowledgments: This research was funded by the NIHR Manchester Biomedical Research Centre. The views expressed are those of the author (S) and not necessarily those of the NHS, the NIHR or the Department of Health. YJC acknowledges support from the European Research Council (fellowship GA 309449), and a state subsidy managed by the Agence Nationale de la Recherche (ANR; France) under the “Investments for the Future” program bearing the reference ANR-10-IAHU-01, YJC and DD acknowledge support from the ANR (CE1700102) and Immunoqure for provision of SIMOA mAbs.