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Proteomics Based Discovery of Biomarkers for Disease Activity in CIDP

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Introduction

Objective disease activity biomarkers are lacking in chronic inflammatory demyelinating polyneuropathy (CIDP), impacting treatment decisions in clinical care and outcomes in clinical trials. Using proteomic profiling, we aimed to identify candidate serum protein biomarkers for disease activity.

Methods

A total of 106 CIDP patients were studied and divided into three cohorts:

1) IT cohort (patients starting induction treatment);
2) MT cohort (stable patients on maintenance treatment starting treatment withdrawal);
3) Patients in long-term remission

Serum samples and clinical data were obtained at baseline and at six months, or earlier in case of relapse. Disease activity was defined based on improvement or deterioration by the minimally clinically important difference (MCID) on both the inflammatory Rasch-built overall disability scale (I-RODS) and grip strength or the Medical Research Council (MRC) sum score.

Using proximity extension assay (Olink), 1463 serum proteins were assessed. Candidate proteins were selected based on fold change >0.5 or <-0.5 and p <0.05 between active and inactive disease. Clustering and gene ontology (GO) enrichment analyses were performed and longitudinal changes of candidate proteins between baseline and follow-up were analyzed.

Results

A) We identified 66 candidate proteins with a fold change of >0.5 or <-0.5, p<0.05, shown here in a volcano plot.

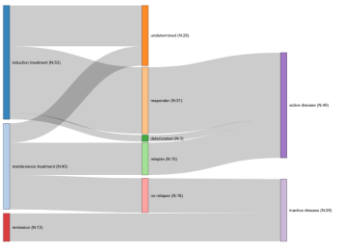
B) Five of these proteins (SUGT1, IRAK4, DCTN1, NT5C3A, GLRX) showed significant and *opposing* longitudinal changes consistent with disease activity changes (black outline indicates significance).

C) Proteins showing the largest contribution to the first principal component in a principal component analysis of fold-change values (active vs. inactive disease) included SUGT, IRAK4, DCTN1, and GLRX.

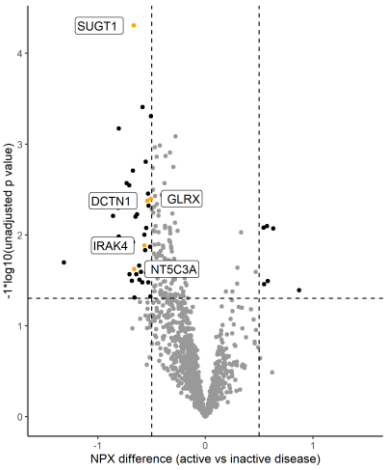
D) DCTN1 showed the highest count in the 39 GO enriched processes. (Pink represents candidate proteins selected by a FC of >0.05 or <-0.5 and p<0.05; blue represents proteins that did not meet selection criteria)

Active disease: baseline samples IT cohort showing response or deterioration + follow-up samples MT cohort showing relapse (n:49)

Inactive disease: follow-up samples M cohort without relapse and samples remission cohort (n:29)



A



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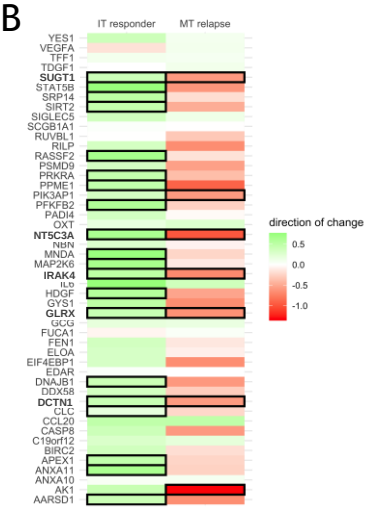

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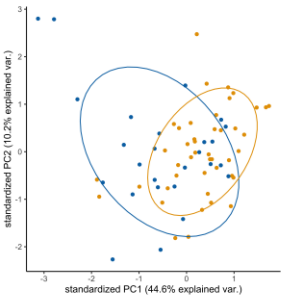

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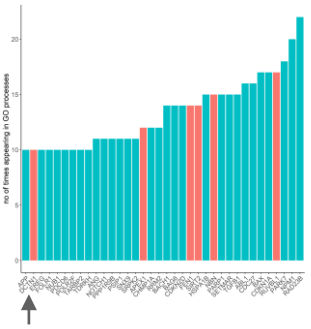

Conclusion and discussion

We identified unique pathways implicating inflammasome functioning (IRAK 4 and SUGT1), ubiquitination (SUGT1) and axonal degradation (DCTN1), justifying further validation studies to determine the value of these proteins as biomarker of disease activity and potential new therapeutic targets.

Amsterdam Neuroscience is a collaboration between: Amsterdam UMC University Medical Centers | VU Vrije Universiteit Amsterdam | University of Amsterdam