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Poster P27

Circulating transcriptional biomarkers serve as surrogates of disease progression in Charcot-Marie-Tooth 1A disease

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Charcot-Marie-Tooth disease type 1A (CMT1A), the most common inherited peripheral neuropathy, results from PMP22 gene duplication and presents with progressive motor and sensory deficits. Despite well-defined genetics, therapeutic development is hindered by the lack of sensitive clinical outcome assessments (CAO) given slow disease progression and variable severity. This study aimed to identify robust transcriptomic biomarkers from blood which may serve as surrogate outcome measures for monitoring disease progression.

A cohort of 139 genetically confirmed CMT1A patients was longitudinally assessed over 2 years using standardized clinical tests and blood RNA sequencing at 3 expert sites across Germany. Parallel analyses were conducted in a Pmp22-overexpressing rat model over 12 weeks. Differential expression analysis, cross-species comparisons, and integration with functional data were employed to identify candidate biomarkers associated with disease severity and progression.

Over the two-year follow-up, we confirm deterioration of the Charcot-Marie-Tooth Neuropathy Score (CMTNSv2) (0.32 (95%-CI [0.05; 0.59]) per year (p = 0.019)). Out of a pool of consistently upregulated disease markers in CMT1A patients and CMT rats (vs.controls) based on RNA Seq data sets at baseline, 9 regulated genes were validated via Real-Time Quantitative PCR (RT-PCR). Transcriptional expression of Actb, E2F2, MFAP, SAMD14, SEMA5A and SPI1 show a significant increase over time, whereas UQCRB declined over time. These 7 genes show properties fitting to diagnostic, prognostic and predictive biomarkers.

Transcriptomic profiling revealed several blood-derived mRNA candidates in CMT1A patients correlate with longitudinal changes in CAOs and overlap with findings from the CMT rat model. These markers may offer a minimally invasive, scalable tool for disease monitoring in future clinical trials.