2nd European CMT Specialists Conference
Antwerp, 23-25 October 2025

Presentation PL2-02

Advancing genetic diagnostics in Charcot-Marie-Tooth disease: Lessons learned from long-read sequencing

A. Candayan (1,2), L. L. P. Ramos (1,2), E. De Vriendt (1,2), T. De Pooter (3,4), P. De Rijk (3,4), M. Strazisar (3,4), A. Jordanova (1,2,5)

(1) Molecular Neurogenomics Research Group, Center for Molecular Neurology, VIB, University of Antwerp, Antwerpen, Belgium
(2) Molecular Neurogenomics Research Group, Department of Biomedical Sciences, University of Antwerp, Antwerpen, Belgium
(3) Neuromics Support Facility, Center for Molecular Neurology, VIB, University of Antwerp, Antwerpen, Belgium
(4) Neuromics Support Facility, Department of Biomedical Sciences, University of Antwerp, Antwerpen, Belgium
(5) Molecular Medicine Center, Department of Medical Chemistry and Biochemistry, Faculty of Medicine, Medical University-Sofia, Sofia, Bulgaria

Charcot-Marie-Tooth (CMT) disease is marked by striking clinical and genetic heterogeneity, leaving over 35% of patients without a definitive genetic diagnosis despite extensive testing. The causal gene discovery rate has significantly decelerated over the past years, partly due to technical limitations of short-read sequencing. In contrast, long-read sequencing (LRS) is emerging as a powerful tool to uncover elusive variants and previously unrecognized mutational mechanisms that contribute to the heritability gap in CMT disease.

In this study, we applied nanopore whole-genome sequencing using the PromethION platform to 35 individuals from 14 families presenting with CMT, all of whom had remained genetically undiagnosed after in-depth analyses with short-read technologies. This cohort provided a unique opportunity to explore the diagnostic potential of LRS. We achieved a 28% diagnostic uplift through a combination of targeted and gene-agnostic approaches, providing long-awaited answers for families who had previously reached a diagnostic dead end.

While LRS for rare disease research revealed substantial promise, it also uncovered significant practical challenges. Key issues included variable data quality from archived samples, limited availability of large, ancestry-matched structural variant databases, demanding bioinformatic workflows, and difficulty in orthogonal validation of candidate structural variants.

Our findings highlight the ability of LRS in improving diagnostic yield and demonstrate that this technology holds great promise as a first-line diagnostic tool. Moreover, our experience offers practical insights for other researchers navigating this rapidly evolving field. As long-read technologies continue to shape the next paradigm shift in human genetics, openly sharing experiences and knowledge among early adopters of the technology will be essential to accelerate progress, ultimately benefiting both patients and the research community.