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

Presentation PL2-04

A CCG expansion in TBC1D7 defines a novel neuromuscular disorder – lessons for the next wave of gene discovery

L. Van de Vondel (1,2), R. Curro (3), S. Facchini (3), I. Xu (1), J. De Winter (2,4), I. Quartesan (3), A. Monticelli (2), A. Alonso-Jimenez (4), W. De Ridder (4), S. Zuchner (1), J. Baets (2,4), A. Cortese (3)

(1) Dr. John T. Macdonald Foundation Department of Human Genetics and John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA
(2) Translational Neurosciences, Faculty of Medicine and Health Sciences, University of Antwerp, Belgium
(3) Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK
(4) Neuromuscular Reference Centre, Department of Neurology, Antwerp University Hospital, Belgium

75 tandem repeat (TR) loci are established to be disease-causing, of which several play a causal role in rare neuromuscular diseases. TR loci are complex and technically challenging to characterise, a hurdle that can be overcome by employing novel long-read (LR) sequencing and analysis techniques.

In this study, we identify a 5' UTR CCG expansion in TBC1D7 as a novel cause of oculopharyngodistal myopathy (OPDM), analogous to previously identified 5' UTR CCG expansions (OPDM1-6). Combining several LR technologies, including PacBio HiFi, Oxford Nanopore Technology and Optical Genome Mapping, we delineate the TR locus in patient tissues and large control datasets. We characterise the locus to be particularly variable in the control population, a recently identified hallmark of pathogenicity. We furthermore establish somatic length variability as well as epigenetic silencing of the repeat locus, leading to non-penetrance. We find increased transcript levels in patient-derived fibroblasts and observe intranuclear inclusions on muscle biopsy, rendering it likely that this particular CCG expansion results in repeat-associated non-AUG translation and polyalanine-mediated aggregation.

Our findings establish the 5' UTR of TBC1D7 as a novel disease locus, and add to the disease-specificity of 5' UTR CCG expansions causing OPDM. We currently identified three families, of which one through a family-based LR analysis and the other two through a cohort-based analysis of patients with similar phenotypes. As the two converging analyses were performed independently, both avenues are valid options when analysing datasets of patients with unsolved Charcot-Marie-Tooth disease or related neuropathies. As increasing evidence points to genotype-phenotype relations for TRs to be dependent on TR motif and location, and less so specific gene function, we will use the identification of TBC1D7 as a guideline for the identification of novel pathogenic motifs causative of neuropathies.