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

Presentation PL1-06

Long-read sequencing reveals SORD/SORD2P inversions as a common cause of SORD-CMT missed by short-read sequencing

I. Quartesan (1), S. Facchini (1,2), A. Manini (3), R. Parolin Schnekenberg (1), C. Pisciotta (4), S. Magri (5), S. Negri (6), C. Gaetano (6), A. Rebelo (7), J. Schatzman Raposo (7), R. Mazanec (8), R. Curro (1), N. Dominik (1), S. Efthymiou (1), M. Laurà (1), T. Grider (9), S. M.E. Feely (10), V. Fridman (11), A. Bertini (1,4), G. M. Alves (1,12), L. Ferullo (1,13), A. Ghia (2), C. Caccia (5), F. Balistreri (5), P. Saveri (4), L. Crivellari (4), I. Moroni (14), F. R. Danti (14), T. Mongini (15), F. Taroni (5), M. Auer-Grumbach (16), E. Bugiardini (1), J. N. Sleigh (1,17), A. Tucci (18,19), H. Houlden (1), P. Laššuthová (20), P. Seeman (20), A. Basile (21), E. Giorgio (21,22), M. E. Shy (23), S. Zuchner (7), M. M. Reilly (1), D. Pareyson (4), A. Cortese (1)

(1) Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, WC1N 3BG, UK
(2) Department of Brain and Behavioural Sciences, University of Pavia, 27100 Pavia, Italy
(3) Department of Pathophysiology and Transplantation, "Dino Ferrari" Centre, Università degli Studi di Milano, Milan, Italy
(4) Unit of Rare Neurological Diseases, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, 20133, Italy
(5) Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
(6) Laboratorio di Epigenetica, Dipartimento Medicina Riabilitativa NeuroMotoria - MeRiNM, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, 27100, Italy
(7) Dr. John T. Macdonald Foundation, John P. Hussman Institute for Human Genomics, University of Miami, Miami, FL 33136, USA
(8) Neurological Department of the Motol University Hospital, Prague, Czech Republic
(9) Neurology, The University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, IA, USA
(10) Division of Pediatric Neurology, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA, USA.
(11) Department of Neurology, University of Colorado Denver School of Medicine, Aurora, CO 80045, USA
(12) Department of Neurosciences and Behaviour Sciences, Neuromuscular Disorders, University of São Paulo, Ribeirao Preto 14040-900, Brazil
(13) Department of Clinical and Experimental Sciences, University of Brescia, 25121 Brescia, Italy
(14) Department of Pediatric Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
(15) Department of Neurosciences Rita Levi Montalcini, University of Turin, Turin, Italy
(16) Department of Orthopaedics and Trauma Surgery, Medical University of Vienna, Vienna, Austria
(17) UK Dementia Research Institute, University College London, London, UK
(18) William Harvey Research Institute, Queen Mary University of London, London EC1M 6BQ, UK
(19) Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, UK.
(20) Department of Paediatric Neurology, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic
(21) Department of Molecular Medicine, Medical Genetics Unit, University of Pavia, 27100 Pavia, Italy
(22) IRCCS Mondino Foundation, Neurogenetics Research Centre, 27100 Pavia, Italy
(23) Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, IA 52242, USA.

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

Background

Pseudogenes are non-functional gene copies arising from duplication or retrotransposition. Although traditionally viewed as genomic relics, they can cause human disease via recombination with their parental genes. Despite the broad adoption of short-read whole-genome sequencing (srWGS), over half of Mendelian disease cases remain undiagnosed, highlighting intrinsic limitations of short-read approaches in detecting structural variants (SVs), especially within repetitive or homologous genomic regions.

Methods

We first performed a genome-wide analysis of 1,019 long-read sequencing (LRS) samples from the 1000 Genomes Project to identify recurrent gene–pseudogene inversions present in healthy individuals. To assess whether these inversions might contribute to genetic disorders, we next applied LRS and optical genome mapping (OGM) to a cohort of unsolved axonal neuropathy cases.

Results

We found that recurrent gene–pseudogene inversions occur in at least 3.6% of healthy individuals yet remain systematically undetected by srWGS and mostly absent from gnomAD SVs database. The SORD/SORD2P locus exhibited the highest inversion frequency. We therefore studied patients clinically suspected of having SORD-related Charcot–Marie–Tooth disease (SORD-CMT) but with only a single pathogenic SORD variant identified by srWGS. Combining LRS and OGM, we demonstrated that recurrent inversions between SORD and SORD2P represent the third most common pathogenic allele for SORD-CMT. Crucially, these inversions explained 75% of patients with only one previously identified SORD variant, enabling enrolment for an ongoing therapeutic trial of the aldose-reductase inhibitor govorestat (NCT05397665).

Conclusions

These findings suggest that gene–pseudogene inversions may represent largely overlooked pathogenic SVs in Mendelian disease. Their systematic detection through long-read technologies has the potential to improve diagnostic yield and inform future clinical decision-making.