# Same gene, different outcomes: Insights into the expanding landscape of RNA polymerase III disorders

**Luiza Pires Ramos* (1, 2), Jevin Parmar* (3), Robin Wijngaard* (4,5), Bianca Grosz* (6), Tamas Lazar (7), Ligia Mateiu (8), Steve Vucic (9), Kishore Kumar (10,11,12,13), Dennis Yeow (10,11,12), Laura Rudaks (10,11,12), Lonneke de Boer (14), Annemarie de Vreugd (14), David A. Koolen (4), Thatjana Gardeitchik (4), Anita Cairns (15), Krishnan Iyengar (16), Fernando Kok (17,18), Fernanda Barbosa Figueiredo (18), Alzira Alves de Siqueira Carvalho (19,20), Luiz Sergio Mageste Barbosa (21), Rodrigo Rezende Arantes (22), Ivaylo Tournev (23, 24), Tyler Rehbein (25), Jordan E. Bontrager (25), Elizabeth P. Wood (25), Janet E. Sowden (25), Ivy Cuijt (1, 2), Melina Ellis (6), Gonzalo Perez-Siles (6), Elyshia McNamara (3), Ronald van Beek (4), Celine Meijers (4), Stephan Zuchner (26, 27), Shoshana Wodak (7), Clara D.M. van Karnebeek (5, 28), Nigel Laing (3), David N. Herrmann (22), Velina Guergueltcheva (29, 30), Liana N Semcesen (31), David A Stroud (31), Marina Kennerson (6,10), Machteld M. Oud (4,5), Gianina Ravenscroft (3), Ayse Candayan# (1,2), Albena Jordanova# (1,2,32)**

1) Molecular Neurogenomics Group, VIB Center for Molecular Neurology, VIB, Antwerp, Belgium.
2) Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium.
3) Harry Perkins Institute of Medical Research, Centre for Medical Research, University of Western Australia, Nedlands, WA, Australia.
4) Department of Human Genetics, Radboud University Medical Centre, Nijmegen, The Netherlands.
5) United for Metabolic Diseases (UMD), The Netherlands.
6) Northcott Neuroscience Laboratory, ANZAC Research Institute SLHD & Faculty of Medicine and Health, University of Sydney, Sydney, Australia.
7) VIB Center for Structural Biology, VIB, Brussels, Belgium.
8) Department of Medical Genetics, University of Antwerp, Antwerp, Belgium.
9) Sydney Medical School, University of Sydney, Camperdown, Sydney Australia.
10) Molecular Medicine Laboratory and Neurology Department, Concord Repatriation General Hospital, Sydney, Australia.
11) Faculty of Medicine and Health, The University of Sydney, Camperdown, New South Wales, Australia.
12) Translational Neurogenomics Group, Genomic and Inherited Disease Program, The Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia.
13) St Vincent's Healthcare Campus, Faculty of Medicine, UNSW Sydney, Darlinghurst, New South Wales, Australia.
14) Department of Pediatrics, Amalia Children's Hospital, Radboud University Medical Centre, Nijmegen, The Netherlands.
15) Neurosciences Department, Queensland Children's Hospital, Brisbane, QLD, Australia.
16) Department of Anatomical Pathology, Royal Brisbane and Women's Hospital. Brisbane, QLD, Australia.
17) Department of Neurology, University of Sao Paulo School of Medicine, Sao Paulo, Sao Paulo, Brazil.
18) Mendelics Genomic Analysis, Sao Paulo, Sao Paulo Brazil.

19) Neuromuscular Reference Center, Department of Paediatrics, University and University Hospital of Liege, Liege, Belgium
20) Faculty of Medicine of ABC, Santo André, Sao Paulo, Brazil.
21) Neuromuscular Disease Centre, Department of Neurology, University Hospital of the Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.
22) Medical Genetics Service, University Hospital of the Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
23) Department of Neurology, Clinic of Nervous Diseases, Medical University of Sofia, UMBAL Aleksandrovska, 1431 Sofia, Bulgaria.
24) Department of Cognitive Science and Psychology, New Bulgarian University, 1618 Sofia, Bulgaria.
25) Department of Neurology, University of Rochester, Rochester, NY 14627, USA.
26) John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, Miami, Florida, USA.
27) John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, Florida, USA.
28) Department of Pediatrics and Human Genetics, Emma Center for Personalized Medicine, Amsterdam University Medical Center, Amsterdam, The Netherlands.
29) Department of Neurology, University Hospital Sofiamed, 1797 Sofia, Bulgaria.
30) Department of Neurology, Sofia University "St. Kliment Ohridski", 1504 Sofia, Bulgaria.
31) Department of Biochemistry and Pharmacology, Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville, VIC, Australia.
32) Department of Medical Biochemistry, Medical University-Sofia, Sofia, Bulgaria.

RNA polymerase III (Pol III) is a large enzymatic complex responsible for transcribing small noncoding RNAs. Pathogenic variants in multiple genes encoding Pol III subunits are known to cause neurological disorders such as hypomyelinating leukodystrophy (HLD), Wiedemann-Rautenstrauch syndrome (WRS), and spastic ataxia/paraplegia. These disorders, collectively known as POLR3-related disorders, primarily affect the central nervous system (CNS) and are caused by biallelic mutations to Pol III subunit genes.

Our group recently identified a patient with a de novo variant in the POLR3A gene encoding the largest Pol III subunit. The proband presented with early-onset, severe demyelinating Charcot-Marie-Tooth (CMT) disease which is a disorder of the peripheral nervous system (PNS). Through international collaboration, we identified ten additional patients from seven distinct families worldwide, all carrying monoallelic POLR3A variants linked to similar CMT-like clinical features. Notably, these patients do not show the cardinal CNS features typical for patients with biallelic POLR3-related disorders. Our functional genomics studies suggest that these newly identified POLR3A variants disrupt the Pol III complex assembly and cause downregulation of crucial RNA molecules transcribed by Pol III. Interestingly, the CMT-causing variants occur in close proximity to those causing biallelic POLR3-related disorders, yet they result in a distinct phenotype affecting the PNS rather than the CNS.

This discovery expands the clinical landscape of POLR3-related disorders beyond classical CNS phenotypes and underscores the importance of considering monoallelic POLR3A variants in the genetic evaluation of peripheral neuropathies, thus improving the diagnostic yield.