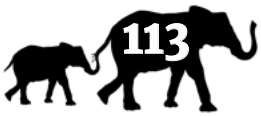

113: Early-onset parkinson's disease with 22q11.2 microdeletion and pathogenic *GBA1* variant

Nikolai Gil D. Reyes,[1,2,3,4], Daniel G. Di Luca[2,5], Ivan Martinez-Valbuena[2,10,11], Erik Boot[3,6,7], Maria Corral[2], Ryan K.C. Yuen[8,9], Connie Marras[2], Anthony E. Lang[2,10], and Anne S. Bassett[1,3,4,12]

[1]Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Edmond J. Safra Program in Parkinson's Disease, the Rossy Progressive Supranuclear Palsy Centre, and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, Toronto, Ontario, Canada; [3]Dalglish Family 22q Clinic, Toronto General Hospital, Toronto, Ontario, Canada; [4]Clinical Genetics Research Program, Centre for Addiction & Mental Health, Toronto, Ontario, Canada; [5]Department of Neurology, Washington University in St. Louis, St. Louis, MO, USA; [6]Advisium, 's Heeren Loo Zorggroep, Amersfoort, The Netherlands; [7]Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Institute (MHeN)s, Maastricht University, Maastricht, The Netherlands; [8]Genetics and Genome Biology, The Hospital for Sick Children; Toronto, Ontario, Canada; [9]Department of Molecular Genetics, University of Toronto; Toronto, Ontario, Canada; [10]Krembil Research Institute, Toronto Western Hospital, Toronto, Ontario, Canada; [11]Tanz Centre for Research in Neurodegenerative Diseases. University of Toronto, Toronto, Ontario, Canada; [12]Department of Psychiatry, University of Toronto, Toronto General Hospital Research Institute, and Campbell Family Mental Health Research Institute, Toronto, ON, Canada.

Background: It is well recognized that early-onset Parkinson's disease (EOPD) is strongly influenced by genetic factors. Oligogenic cases—where co-occurring variants jointly influence risk and expression—may exhibit phenotypic differences compared to typical sporadic and monogenic PD. However, reports describing combined effects of distinct high-risk variants remain limited. **Methods:** We present a case of oligogenic EOPD associated with 22q11.2 microdeletion and a severe pathogenic *GBA1* variant, and discuss potential implications. **Results:** A 27-year-old male with a *de novo* 2.5 Mb LCR22A-LCR22D 22q11.2 microdeletion developed new-onset parkinsonian motor features. Other neuropsychiatric features common in 22q11.2 deletion syndrome were present, including mild intellectual disability and anxiety/mood disorders treated with standard SSRI therapy. Short-term low-dose risperidone had been discontinued long before motor symptom onset. Neurologic examination demonstrated asymmetric parkinsonism. Brain MRI and laboratory investigations were unremarkable. Skin-based α-synuclein seed amplification assay was negative and serum neurofilament light chain was low (8.8 pg/mL). Levodopa/carbidopa therapy resulted in significant symptomatic improvement (MDS-UPDRS III: 26→17). Given the EOPD, and family history of PD and consanguinity, we pursued targeted genetic testing, which identified a severe, pathogenic heterozygous *GBA1* c.1448T>C (p.Leu483Pro) variant. **Conclusion:** This case highlights the potential additive, or possibly synergistic, effects of co-occurring high-risk genetic variants on PD penetrance and expression. The very early age at presentation relative to expectations for either 22q11.2 microdeletion or the *GBA1* variant alone supports an oligogenic model of disease expression in EOPD. For clinicians, these findings underscore the crucial role of comprehensive genetic evaluation—including both single-nucleotide and copy number variations—for individuals with EOPD and/or multisystem presentations. Further studies are needed to clarify how overall rare, high-risk variant burden modifies PD risk, clinical trajectory, and underlying mechanisms.