Myotonic Dystrophy-1 and Parkinson's Disease: Clarify the Role of CTG-repeat Size and Variants in *VPS13C*, *SYNJ1*, and *DNAJC6*

We read with interest the article by Misra *et al*. on a 45-year-old female with myotonic dystrophy type-1 (MD1) due to a cytosine-thymine-guanine (CTG)-repeat expansion >50 repeats in the dystrophia myotonica-protein kinase (*DMPK)* gene who also had Parkinson's disease.[1] In addition to the classical stigmata of Parkinson's disease, the patient presented with proximal, spastic quadruparesis.[1] Despite a documented CTG-repeat expansion, the patient also underwent whole exome sequencing (WES), which revealed variants in vacuolar protein sorting 13 homolog C (*VPS13C*), synaptojanin 1 (*SYNJ1*), and dual heat shock protein family member C6 (*DNAJC6*), that were predicted to be disease-causing by in-silico testing.[1] L-3,4-dihydroxyphenylalanin (L-DOPA) was hardly effective.[1] The study is excellent but has limitations that should be discussed.

The first limitation of the study is that the exact CTG-repeat size in *DMPK* was not specified.[1] Unfortunately, although genetic testing of CTG-repeat expansion indicated an expanded allele, the repeat size could not be determined.[1] Knowing the exact repeat size is critical to assessing the

extent to which the phenotype is actually due to the expansion. CTG-repeats between 51 and 100 may only manifest slightly with ptosis and cataracts. In such a case, the rest of the phenotype must be explained by other causes. Knowing the exact repeat-size is also crucial for assessing the progression and outcome of the condition. A strong argument against large expansion is that several of the classic phenotypic traits of adult MD1, such as frontal baldness, myopathic face, cognitive impairment, cerebral atrophy, white matter lesions, ptosis, cataract, hypoacusis, creatine-kinase elevation, distal weakness, and atrioventricular block-I were absent in the index patient.[1]

A second limitation of the study is that the pathogenicity of the newly discovered variants in *VPS13C*, *SYNJ1*, and *DNAJC6* was assessed only by in-silico methods and not by functional or biochemical studies. Since in-silico testing predicted pathogenicity,[1] it is imperative to confirm with more in-depth methods which of the three had the strongest impact on the phenotype. *VPS13C* variants are known to cause childhood onset movement disorders.[2] In addition, *VPS13C* is considered as a risk gene for Parkinson's disease.[3] Variants in *SYNJ1* have been reported to cause early-onset neurodegenerative disease manifesting as pervasive developmental delay, failure to thrive, acquired microcephaly, intractable seizures, and hypotonia.[4] Biallelic variants in *SYNJ1* have been reported in association with early-onset Parkinson's disease.[5] Mutations in *DNAJC6* have been reported in association with Parkinson's disease[6] but not in association with neuromuscular diseases.

A third limitation of the study is that no family history was reported.[1] Since the disorder described is apparently genetic, it is critical to know which other first-degree family members were also clinically affected, with what degree of severity, and which family members carried the variant thought to be pathogenic in the index patient. We should also know if the index patient's parents were consanguineous. Segregation analysis can be useful in assessing the pathogenicity of the reported variants, assessing genetic and phenotypic heterogeneity, assessing disease progression and outcome, and providing genetic counseling to mutation carriers.

Overall, the interesting study has limitations that challenge the results and their interpretation. Addressing these limitations could further strengthen and reinforce the statement of the study. In patients suspected of having MD1, the exact CTG-repeat size needs to be determined, and if WES detects variants in genes thought to be causative of the disease, their impact on the phenotypic spectrum needs to be thoroughly evaluated. Since Parkinson's disease is not a classical phenotypic trait of MD1, it is more likely that one of the variants found by WES is causative for this trait.

Ethical compliance statement

The authors confirm that the approval of an institutional review board or patient consent was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Misra AK, Nanda S, Mukherjee J, Kumar S, Agasti N. Myotonic dystrophy type 1-An atypical presentation having symmetric Parkinsonism and early proximal muscle involvement. Ann Indian Acad Neurol 2023;26:201-3.
2. Gauthier J, Meijer IA, Lessel D, Mencacci NE, Krainc D, Hempel M, *et al.* Recessive mutations in VPS13D cause childhood onset movement disorders. Ann Neurol 2018;83:1089-95.
3. Olsen AL, Feany MB. Parkinson's disease risk genes act in glia to control neuronal α-synuclein toxicity. Neurobiol Dis 2021;159:105482.
4. Al Zaabi N, Al Menhali N, Al-Jasmi F. SYNJ1 gene associated with neonatal onset of neurodegenerative disorder and intractable seizure. Mol Genet Genomic Med 2018;6:109-13.
5. Lesage S, Mangone G, Tesson C, Bertrand H, Benmahdjoub M, Kesraoui S, *et al.* Clinical variability of *SYNJ1*-associated early-onset Parkinsonism. Front Neurol 2021;12:648457.
6. Jacquemyn J, Kuenen S, Swerts J, Pavie B, Vijayan V, Kilic A, *et al.* Parkinsonism mutations in DNAJC6 cause lipid defects and neurodegeneration that are rescued by Synj1. NPJ Parkinsons Dis 2023;9:19.

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