Clarification on "Myotonic Dystrophy Type 1 – An Atypical Presentation"

Dear Editor,

We read with interest the letters to the editor[1,2] written to highlight the limitations of our article about a 45-year-old female with myotonic dystrophy type-1 due to a CTG-repeat expansion with >50 repeats in the *DMPK* gene, who also had Parkinson's disease.[3] We would like to give answers for the limitations mentioned in the review.

The review mentioned the first limitation as not specifying the exact CTG-repeat size of the *DMPK* gene in our article.[3] Figure 1 of our article clearly shows that one CTG allele in the normal range (five repeats), another expanded allele (>50 repeats), and triplet repeat primed PCR confirm the presence of a pathogenically expanded allele. It was not mentioned in the text to reduce the size of the manuscript.

To discuss the second limitation, we would like to describe the matter in detail. Thanks for the concern regarding the pathogenic nature of the novel variants identified in *VPS13C*, *SYNJ1*, and *DNAJC6* genes. Our article identified three frameshift variants (one in each gene) that led to premature termination codon mutations. These frameshift mutations lead to a truncated protein, which means protein function loss. The other missense variants were predicted to be disease causing using bioinformatic analysis. Numerous publications are available in the literature where the authors conducted whole exome sequencing analysis, and the pathogenic nature can be predicted using bioinformatic analysis only. From a clinician's perspective, validating our genetic data with cell culture/animal model study is beyond our scope. The age range of *VPS13C* mutant individuals varies from 25 to 45 years. In our cases, the index case had an age at the onset of 45 years, concordant with public literature.[4]

The third limitation mentioned was not reporting any family history. We agree with the reviewer's observation. We want to add that there was no history of similar clinical phenotype or any history of parkinsonism or myotonia in any known family member of the patient in three generations. The parents were not consanguineous. However, examining the genetic data on V*PS13C,* S*YNJ1,* and D*NAJC6* reported in this article revealed that all these variants were heterozygous. If the index patient's parents were consanguineous, there would be more chance of getting homozygous mutations rather than heterozygous mutations.

The review also mentioned not performing segregation analysis. All the Parkinson's disease-related genes reported in this article are inherited in an autosomal recessive manner. Therefore, segregation analysis cannot predict the pathogenic nature of these variants.

To aid in the diagnosis, whole exome sequencing and repeat primer PCR approach were considered, so that a comprehensive differential diagnosis could be obtained. The patient has a mutation in the *DMPK* gene and PD-related genes (*VPS13C, SYNJ1, DNAJC6*). Therefore, these two different clinical presentations may be due to the involvement of multiple genes. Although the review mentioned the limitations of our article nicely, our clarifications will help the reader understand the matter more clearly.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Finsterer J, Scorza FA. Myotonic dystrophy-1 and Parkinson's disease: Clarify the role of CTG-repeat size and variants in VPS13C, SYNJ1, and DNAJC6. Ann Indian Acad Neurol 2023;26:847–8.
2. Finsterer J. Double trouble myotonic dystrophy type-1 and Parkinson syndrome associated with variants in SYNJI, VPS13C, and DNAJC6. Ann Indian Acad Neurol 2023;26:784–5.

3. 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.
4. Guadagnolo D, Piane M, Torrisi MR, Pizzuti A, Petrucci S. Genotype-phenotype correlations in monogenic Parkinson disease: A review on clinical and molecular findings. Front Neurol 2021;12:648588.

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