Movement Disorders
CLINICAL PRACTICE
LETTERS: NEW OBSERVATION

Reply to: Partially Levodopa-Responsive Parkinsonism in a Carrier of a Novel Pathogenic *CLTC* Variant

Francesca Nardecchia, MD, PhD,[1,*] Simone Martinelli, PhD,[2] Luca Pollini, MD, PhD,[1,3] and Vincenzo Leuzzi, MD[1]

We read with interest the article by Usnich and colleagues, reporting on a patient harboring a new pathogenic variant in the *CLTC* gene, who presented with a mild neurodevelopmental disorder in early life, which developed into parkinsonism in young adulthood. This clinical observation is reminiscent of the patient we reported some years ago.[1] Together, these two individuals are among the oldest carriers of a pathogenic variant in *CLTC* described in the literature, supporting the importance of a protracted clinical follow-up for a complete comprehension of the phenotypic spectrum associated with this condition.

The genotype of the two reported subjects was different. We described a 30-year-old woman harboring the recurrent c.2669C>T (p.Pro890Leu) missense mutation, whereas Usnich et al[2] reported a 23-year-old woman carrying a small out-of-frame deletion (c.4686_4687del; p.Glu1564Valfs*48), which is expected to lead to *CLTC* haploinsufficiency, although persistence of the truncated form of the protein was not ruled out. Based on the relatively mild phenotype of this patient, however, a dominant negative behavior of the mutated form of clathrin is unlikely.

The presence of brain malformations, such as frontal pachygyria, although enhancing the list of neurodevelopmental alterations so far associated with this gene,[3,4] suggests a possible intriguing connection with lateralized parkinsonism, which was contralateral to the brain malformation, supporting the importance of the cortex integrity for the determinism of this movement disorder. This second adult patient confirms that *CLTC* is a novel gene associated with movement disorder and suggests the need to start including this gene in multi-gene panels for parkinsonism.

Interestingly, Usnich et al reported a significant improvement of parkinsonian features under dopamine therapy. The efficacy of this treatment, however, was transient and lasted 8 months. Increased levodopa dosage led to dyskinesia. Levodopa administration proved to be ineffective in our patient,[1] although a relevant/moderate effect on achalasia/bradykinesia was observed under treatment with selegiline, an irreversible inhibitor of monoamine oxidase B (MAO-B). Of note, this molecule was shown to improve bradykinesia and cognitive function in a more severely affected 5-year-old girl harboring the c.2023A>T (p.Ile675Phe) variant.[5]

Clathrin is a self-assembling vesicle coat protein involved in fundamental biological processes, including cell division, endocytosis, intracellular trafficking, and synaptic vesicle recycling/neogeneration. Among these, neurotransmitters' release/recycling and aberrant trafficking have been proposed as the pathogenic mechanism(s) underlying *CLTC*-related movement disorder. In line with that, patient's-derived fibroblasts carrying the p.Pro890Leu substitution showed defective clathrin-mediated endocytosis, and a genetically modified *C. elegans* strain carrying the same variant displayed defective release of neurotransmitters, which accumulate at the presynaptic terminus, synaptic vesicle depletion at the neuromuscular junction, and altered synaptic plasticity.[6]

In conclusion, the imbalance of neurotransmitter homeostasis because of *CLTC* mutations might explain the improvement of parkinsonism observed under MAO-B inhibitor or dopamine precursor administration, although additional observations and a deeper comprehension of the pathogenic mechanisms of the disease are needed. The reported case may help in this direction.

[1]*Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy;* [2]*Department of Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy;* [3]*Laboratory of Neurophysiology and Plasticity, IRCCS Fondazione Santa Lucia, Rome, Italy*

***Correspondence to:** Dr. Francesca Nardecchia, Unit of Child Neurology and Psychiatry, Department of Human Neuroscience, Sapienza University of Rome, Via dei Sabelli 108, 00185, Rome, Italy; E-mail: francesca.nardecchia@uniroma1.it
Keywords: parkinsonism, CLTC, clathrin, neurodevelopmental disorders, movement disorders.
Relevant disclosures and conflict of interest are listed at the end of this article.
Potential conflict of interest: The authors declare that there are no conflicts of interest relevant to this work.
Received 27 February 2024; accepted 19 March 2024.
Published online 14 April 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.14039

Author Roles

(1) Research Project: A. Study Concept and Design; (2) Manuscript Preparation: A. Writing of the First Draft, B. Review and Revision.

F.N.: 1A, 2A
S.M.: 1A, 2A
L.P.: 1A, 2B
V.L.: 1A, 2B

Disclosures

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.

Funding Sources and Conflicts of Interest: No specific funding was received for this work. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the Previous 12 Months: L.P. received a speaker honorarium from PTC Therapeutics. The other authors have nothing to declare. ■

References

1. Manti F, Nardecchia F, Barresi S, et al. Neurotransmitter trafficking defect in a patient with clathrin (CLTC) variation presenting with intellectual disability and early-onset parkinsonism. *Parkinsonism Relat Disord* 2019;61:207–210. https://doi.org/10.1016/j.parkreldis.2018.10.012.
2. Usnich T, Becker LF, Nagel I, et al. Partially Levodopa-Responsive parkinsonism in a carrier of a novel pathogenic CLTC variant. *Mov Disord Clin Pract* 2024. https://doi.org/10.1002/mdc3.14037.
3. Nabais Sá MJ, Venselaar H, Wiel L, et al. De novo CLTC variants are associated with a variable phenotype from mild to severe intellectual disability, microcephaly, hypoplasia of the corpus callosum, and epilepsy. *Genet Med* 2020;22(4):797–802. https://doi.org/10.1038/s41436-019-0703-y.
4. Martín Fernández-Mayoralas D, Muñoz Jareño N, Alba Menéndez A, Fernández-Jaén A. Periventricular heterotopias: broadening of the clinical spectrum of the clathrin 1 gene (CLTC) pathogenic variants. *Neurologia (Engl Ed)* 2021;36(4):327–329. https://doi.org/10.1016/j.nrl.2020.06.008.
5. Nardecchia F, Bove R, Pollini L, et al. Improvement of movement disorder and neurodevelopment under selegiline in a CLTC-deficient patient. *Mov Disord Clin Pract* 2023;10(9):1430–1432. https://doi.org/10.1002/mdc3.13834.
6. Pannone L, Muto V, Nardecchia F, et al. The recurrent pathogenic Pro890Leu substitution in CLTC causes a generalized defect in synaptic transmission in Caenorhabditis elegans. *Front Mol Neurosci* 2023;16:1170061. https://doi.org/10.3389/fnmol.2023.1170061.