markers initiative cohort using α-synuclein seed amplification: a cross-sectional study. Lancet Neurol 2023;22(5):407–417. https://doi.org/10.1016/S1474-4422(23)00109-6

2. Garrido A, Fairfoul G, Tolosa E, Marti MJ, Ezquerra M, Green AJE. Brain and cerebrospinal fluid α-synuclein real-time quaking-induced conversion identifies Lewy body pathology in LRRK2-PD. Mov Disord 2022;38(2):333–338. https://doi.org/10.1002/mds.29284

3. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol 2012;123(1):1–11. https://doi.org/10.1007/s00401-011-0910-3

4. Kovacs GG, Wagner U, Dumont B, et al. An antibody with high reactivity for disease-associated α-synuclein reveals extensive brain pathology. Acta Neuropathol 2012;124(1):37–50. https://doi.org/10.1007/s00401-012-0964-x

5. Kim A, Martinez-Valbuena I, Li J, Lang AE, Kovacs GG. Disease-specific α-synuclein seeding in Lewy body disease and multiple system atrophy are preserved in formaldehyde-fixed paraffin-embedded human brain. Biomolecules 2023;13(6):936. https://doi.org/10.3390/biom13060936

6. Martinez-Valbuena I, Swinkin E, Santamaria E, et al. α-Synuclein molecular behavior and nigral proteomic profiling distinguish subtypes of Lewy body disorders. Acta Neuropathol 2022;144(2):167–185. https://doi.org/10.1007/s00401-022-02453-0

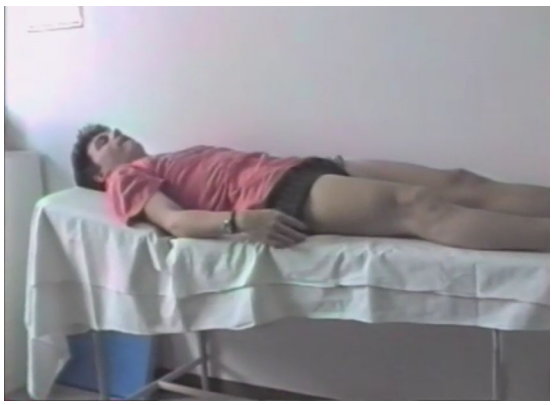
ANO3 as a Cause of Early-Onset Chorea Combined with Dystonia: Illustration of Phenotypic Evolution

Here, we signpost a case of a childhood-onset chorea-dominant phenotype later evolved into a dystonia-dominant phenotype during adulthood, in a subject carrying a missense pathogenic variant (c.1528 G > A; p.Glu510Lys)[1] in the anoctamin 3 protein-coding gene (*ANO3*, DYT24, OMIM 610110).[2]

This white, Caucasian, right-handed male presented with lower limb chorea-dystonia at the age of 8, initially involving the right leg and rapidly spreading to left leg and upper limbs. By the age of 16, a generalized choreo-dystonic syndrome was reported, with dystonic dysarthria and upper limbs tics (Video 1, segments 1–2). Neither pyramidal nor cerebellar signs were present. Over time, the chorea-dominant phenotype evolved to a dystonia-dominant one, which has remained stable since the age of 22 (Video 1, segments 3–6). The patient manifested severe psychiatric symptoms (depression, insomnia, and irritability) since the late adolescence. Brain magnetic resonance imaging was unremarkable for basal ganglia or cerebellar-brainstem alterations.

A widespread workup for chorea and dystonia (acanthocytes, liver function, ceruloplasmin, cupruria, cupremia, thyroid function, paraneoplastic screening, sedimentation rate, connective tissue disorders screening, anti-thyroid peroxidase antibodies, and tissue transglutaminase antibodies), genetic testing for Huntington's disease, *DYT1* and *DYT6* proved negative. A next-generation sequencing gene panel for dystonia revealed a heterozygous variant in *ANO3*, c.1528 G > A (p.Glu510Lys) in exon 15: this variant is not present in GnomAD, is predicted to be pathogenic by in silico analysis (Combined Annotation Dependent Depletion score 32), and reported in ClinVar as likely pathogenic. This variant has been previously described by Zech et al[1] in a male patient with childhood-onset generalized combined dystonia. Patient's father and sister had normal neurological examination and tested negative for this variant. Patient's mother died at the age of 66 and her DNA was not available for segregation analysis; she was reported to be not affected by involuntary movements or psychiatric disturbances (Fig. 1).

He has tried a variety of drugs including haloperidol (up to 45 mg daily, since age 10—with initial benefit on lower limbs dyskinesias—discontinued at age 16 because of akathisia and hand tremor), Gabapentin (since age 38, stable at 500 mg daily), baclofen (up to 75 mg daily), levodopa (250 mg daily, age 17), and trihexyphenidyl (since age 17, stable at 28 mg daily, with benefit on dystonic gait). Given the severe psychiatric comorbidity, the patient was not considered eligible for



Video. 1. Time-evolution of the clinical features presented by the patient. Three time periods are shown, referring to 1990, age 17 (segments 1 and 2) (under trihexyphenidyl 28 mg daily), to 2016, age 43 (segments 3 and 4, under trihexyphenidyl 28 mg + Gabapentin 300 mg, daily), and to 2022, age 48, at the last available follow-up (segments 5 and 6, under trihexyphenidyl 28 mg + Gabapentin 500 mg, daily). Captions are embedded into the video. [Color figure can be viewed at wileyonlinelibrary.com]
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.29672

Key Words: dystonia, chorea, *ANO3*, DYT24, DYT23, anoctamin, putamen, basal ganglia

***Correspondence to:** Dr. Luigi M. Romito, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via G. Celoria, 11, 20133 Milano, Italy; E-mail: luigi.romito@istituto-besta.it

Relevant conflicts of interest/financial disclosures: Authors state no conflict of interest.
Luigi M. Romito and Valentina Leta contributed equally as first authors. Miryam Carecchio and Roberto Eleopra contributed equally as last authors.

Received: 21 October 2023; **Revised:** 4 November 2023; **Accepted:** 7 November 2023

Published online 10 December 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29672

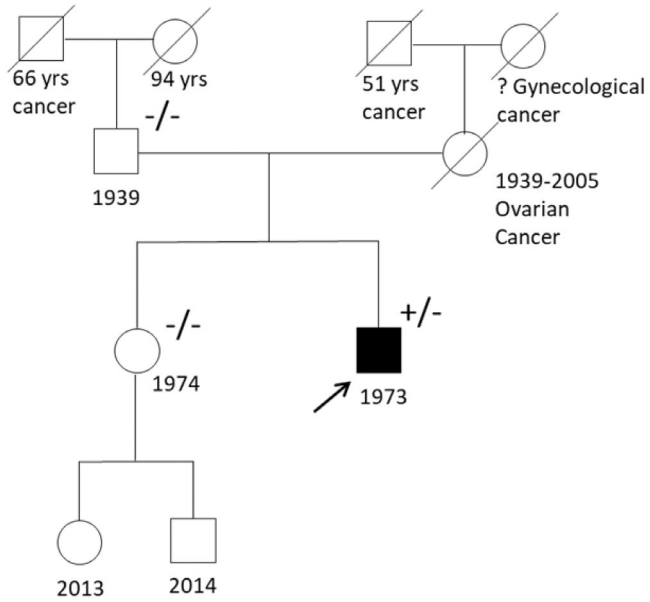


FIG. 1. Pedigree showing the structure of the patient's family and the date of born of the members. Definitely affected family members are represented by black filled symbols, and definitely unaffected family members are represented by empty symbols. Index patient is indicated by black arrow.

pallidal deep brain stimulation for dystonia treatment in adulthood.

We believe this clinical case highlights two major points of discussion: (1) the evolution of the motor phenomenology from a chorea-dominant to a dystonia-dominant motor phenotype might reflect the natural history of this rare disease driven by changes in brain neuroplasticity occurring with aging.[3,4] (2) In line with previous reports,[5-7] chorea is a possible relevant phenotype of specific *ANO3* variants, potentially justified by the finding that *ANO3* mRNA expression is significantly higher in the putamen.[2] Therefore, we propose to consider testing for variants in the *ANO3* in patients displaying early-onset choreo-dystonic syndromes dominated by chorea, even with a negative familial history.

This case expands the genetic, neurological, and psychiatric spectrum of *ANO3*-related disease, prompting movement disorder specialists to suspect variants of this gene not only in patients with isolated dystonia, but also in patients with chorea combined with dystonia.

Acknowledgment: We thank our patient and his family. We thank Dr. Danilo Romito MGeol for the professional handling of the media. Open access funding provided by BIBLIOSAN.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Luigi M. Romito, PhD,[1,2*] Valentina Leta, MD,[1,3] Barbara Garavaglia, PhD,[4] Celeste Panteghini, MS,[4] Giovanna Zorzi, MD,[5] Antonio E. Elia, PhD,[1] Fabiana Colucci, PhD,[1,6] Miryam Carecchio, PhD,[7] and Roberto Eleopra, MD[1]

[1]*Parkinson and Movement Disorders Unit, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy,* [2]*Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy,* [3]*Parkinson's Centre of Excellence at King's College Hospital and King's College London, London, United Kingdom,* [4]*Medical Genetics and Neurogenetics Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy,* [5]*Department of Pediatric Neuroscience, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy,* [6]*Department of Neuroscience and Rehabilitation, University of Ferrara, Ferrara, Italy, and* [7]*Department of Neuroscience, University of Padua, Padua, Italy*

References

1. Zech M, Boesch S, Jochim A, et al. Clinical exome sequencing in early-onset generalized dystonia and large-scale resequencing follow-up. Mov Disord 2017;32(4):549–559. https://doi.org/10.1002/mds.26808
2. Charlesworth G, Plagnol V, Holmstrom KM, et al. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. Am J Hum Genet 2012;91(6):1041–1050. https://doi.org/10.1016/j.ajhg.2012.10.024
3. Marchand WR, Lee JN, Suchy Y, et al. Age-related changes of the functional architecture of the cortico-basal ganglia circuitry during motor task execution. Neuroimage 2011;55(1):194–203. https://doi.org/10.1016/j.neuroimage.2010.12.030
4. Rodriguez-Sabate C, Morales I, Rodriguez M. The influence of aging on the functional connectivity of the human basal ganglia. Front Aging Neurosci 2021;13:785666. https://doi.org/10.3389/fnagi.2021.785666
5. Blackburn PR, Zimmermann MT, Gass JM, et al. A novel ANO3 variant identified in a 53-year-old woman presenting with hyperkinetic dysarthria, blepharospasm, hyperkinesias, and complex motor tics. BMC Med Genet 2016;17(1):93. https://doi.org/10.1186/s12881-016-0354-7
6. Koya KS, Mulroy E, Magrinelli F, Di LG, Latorre A, Bhatia KP. Huntington disease-like phenotype in a patient with ANO3 mutation. Parkinsonism Relat Disord 2021;90:120–122. https://doi.org/10.1016/j.parkreldis.2021.02.022
7. Danek A. Huntington disease-like phenotype in a patient with ANO3 mutation. Expert Comment Parkinson Relat Disord 2021;90:123–124. https://doi.org/10.1016/j.parkreldis.2021.07.009