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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

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

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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 al¹ 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>

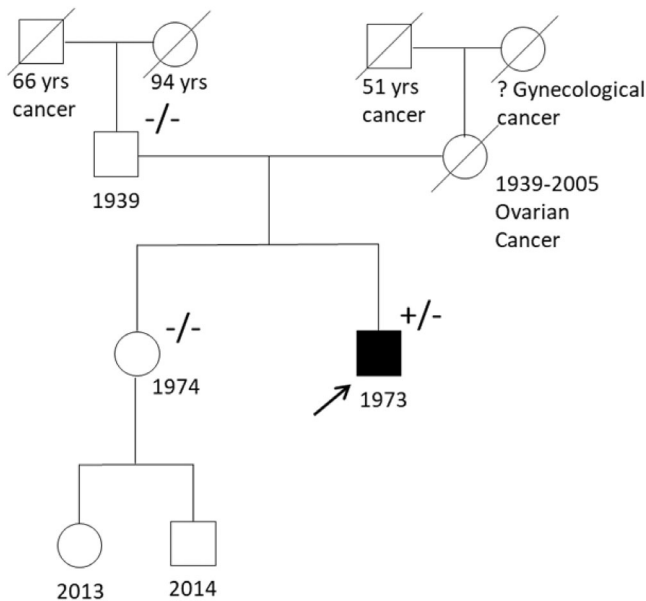


FIG. 1. Pedigree showing the structure of the patient's family and the date of born of the members. Definitely affected family members are represented by black filled symbols, and definitely unaffected family members are represented by empty symbols. Index patient is indicated by black arrow.

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. ■

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Data Availability Statement

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

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