Movement Disorders
CLINICAL PRACTICE

CASE SERIES

Another Twist in the Tale: Intrafamilial Phenotypic Heterogeneity in *ANO3*-Related Dystonia

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ABSTRACT: Background: Mutations in the anoctamin 3 (*ANO3*) gene cause autosomal dominant craniocervical dystonia (DYT24), presenting from childhood to mid-life. However, in the past years, the clinical spectrum of this disorder has widened. We present a family with heterogeneous presentation, exemplifying phenotypic diversity in DYT24.

Cases: The index case presented with myoclonic dystonia at age 10. His family history was remarkable for cervical dystonia with myoclonus in his grandfather, cervical and upper limb dystonia along with dopa-responsive parkinsonism in his father and lower-limb dystonia in his teenage sister. Magnetic resonance imaging and blood work-ups of all the affected family members were normal. The genetic panel for inherited forms of dystonia disclosed a point mutation c.1787C > A (p.Ser596Tyr) segregated in all affected family members.

Conclusions: *ANO3* mutations usually present with craniocervical dystonia and rarely generalized or leg dystonia. This family exemplifies the heterogeneous presentation of this disorder as well as a wide phenotypic variability within the same family.

DYT24 is an autosomal dominant disorder caused by anoctamin 3 (*ANO3*) variants (OMIM 610110). It typically presents as a craniocervical dystonia emerging from childhood to mid-life.[1] Younger patients presenting with generalized dystonia starting in the lower limb[2] and myoclonic dystonia were also described.[3] Recently, variants in *ANO3* have been described as the cause of levodopa-responsive parkinsonism with craniocervical dystonia, and these patients might even present with abnormal Dopamine transporter scan (DaTSCANs).[4] We describe the phenotypic heterogeneity within a family with 4 affected members harboring a novel *ANO3* variant (Fig. 1).

Case Series

Case 1

A 17-year-old boy was first referred to the neuropediatrics clinic at the age of 10 due to jerks of the right upper limb while writing and progressive difficulty on holding the pen (Fig. 2). Birth history and psychomotor development were unremarkable. On examination he presented small-amplitude proximal myoclonic jerks with stretched arms posture and high-amplitude myoclonic jerks on the right hand, which were more prominent when performing motor tasks, particularly writing. There was dystonic

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Keywords: movement disorders, dystonia, neurogenetics, ANO3, DYT24.
[a]These authors contributed equally to this work.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 13 January 2021; revised 9 March 2021; accepted 21 March 2021.
Published online 23 April 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13209

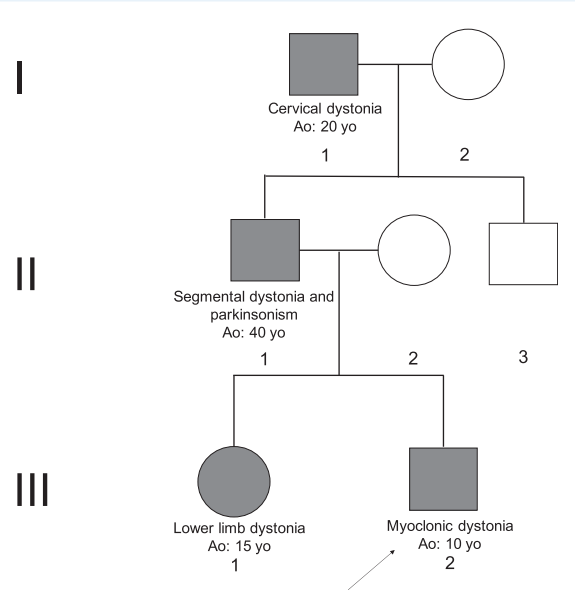


FIG. 1. Genealogic tree. Arrow indicates índex case. Ao, age of onset; yo, years old.

posturing of the right hand while writing and tremulous voice (Video 1, segment 1). Cognitive function and pyramidal, sensory, and cerebellar functions were normal. Parkinsonian features were absent. Electroencephalogram (EEG) and EEG/electromyography with back averaging were normal. Brain magnetic resonance imaging and a blood work-up were normal. Mutations in the *SCGE* and *DRD2* genes were excluded. Further genetic testing disclosed the point mutation c.1787C > A (p.Ser596Tyr) in the *ANO3* gene that was also present in his father. Over the years, disabling right limb dystonia evolved along with dystonic tremor. Also, laryngeal dystonia and mild blepharospasm became evident (Video 1, segment 2). Trials with clonazepam (3 mg/day), levetiracetam (500 mg/day), trihexyphenidyl (6 mg/day), and levodopa (300 mg/day) were carried out with no significant clinical benefit.

Case 2

His 40-year-old father was referred to our neurology department by the index case neuropediatrician due to difficulty walking attributed to rigidity in his left leg. He denied any other complaints. His wife also noticed behavioral changes, with flat affect, and decreased verbal and motor initiative. His past medical history was unremarkable. Upon neurological examination he was slow and hypomimic. His cognition was preserved. He had a normal oculomotor examination. He had retrocollis and dystonic posturing in his right upper limb. Strength was normal, but the reflexes were brisk, with lower limb clonus bilaterally. His plantar responses were flexor. Sensory and cerebellar examinations were unremarkable. There was left upper limb bradykinesia and axial and limb rigidity, which was worse on the left. His gait was slightly slowed with normal tandem. Brain computed tomography and MRI were unremarkable. Formal neuropsychological assessment showed slightly impaired performance in divided attention tasks, verbal speed processing, and verbal abstract reasoning. Diagnostic work-up including ceruloplasmin (although no urinary and serum copper were performed) and thyroid function tests were normal. Cervical MRI showed spondylotic myelopathy, which could account for the pyramidal signs. He underwent surgical treatment with no improvement. He was first tested for parkin variants. Considering the hyperkinetic disorder in the father, Huntington's disease was also considered in the differential diagnosis, and therefore *HTT* expansions were excluded. Further genetic testing ruled out genetic variants in *TOR1A, ATN1*, *THAP1*, *SCGE*, and *GCH1* and disclosed a mutation in the *ANO3* gene. He was started on levodopa up to 400 mg/day and referred for physical rehabilitation with improvements in his mood, motor skills, and cognition.

Case 3

An otherwise healthy 27-year-old woman first presented with symptoms emerging at the age of 15 years. She fell at school and had an ankle sprain with swift recovery. A few months later she noticed that her foot deviated inwards involuntarily when she walked. She denied any pain, weakness, or spasms. On examination her cognition was normal as well as the cranial nerves. There were no pyramidal, sensory, or cerebellar deficits and reflexes were normal and symmetric. Dystonic posturing with inversion of her left foot was noted when she walked with normal posture at rest or when walking backward (Video 2). She was started on levodopa 150 mg daily without improvement, but she could not tolerate higher doses. At age 22, slight dystonic posturing was noticed in her left hand. At age 25, she developed slight laterocollis without head tremor. Trihexyphenidyl (2 mg × 3) was started with slight improvement. Brain MRI was normal as well as a blood work-up, including blood smear, blood and urine copper measurements, ceruloplasmin, and iron kinetics. Genetic testing disclosed the familial genetic variant in the *ANO3* gene.

Case 4

A 75-year-old man presented at the age of 30 to the movement disorders outpatient clinic due to action myoclonus in his upper limbs and neck. While aged in his 20s and working as a fisherman, he fell into the sea and nearly drowned. Shortly after that, he developed involuntary jerking of his right hand and started using his left hand to eat or write. At the time, his neurological examination was remarkable for upper right limb tremor, neck dystonia, and myoclonus in his mouth, tongue, and limbs. A brain CT was performed, which was normal, and later an MRI and an EEG, which were also normal. Despite this, the symptoms were attributed to post–anoxic encephalopathy in the absence of any family history. After the diagnosis of his family, he was again referred to the neurology clinic. At the age of 75, his neurological examination presented jaw tremor, which

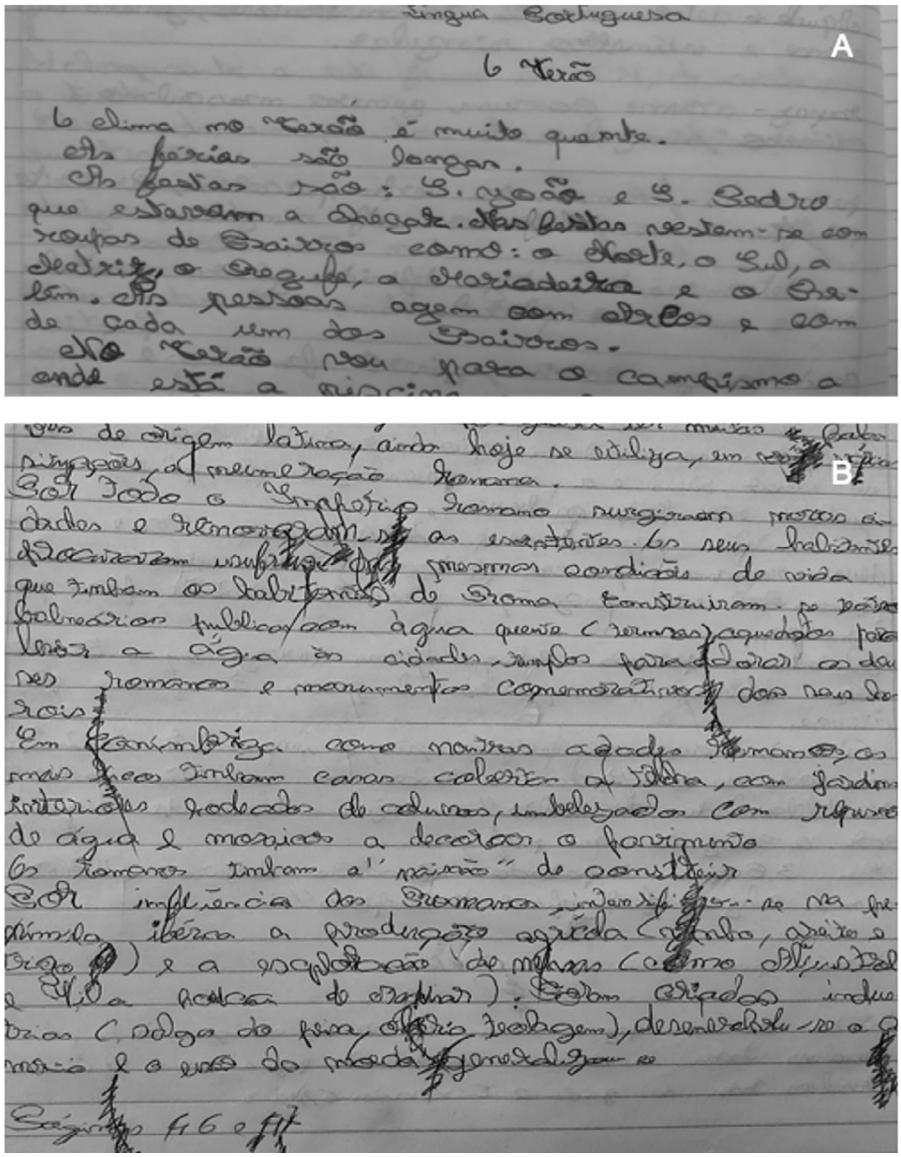
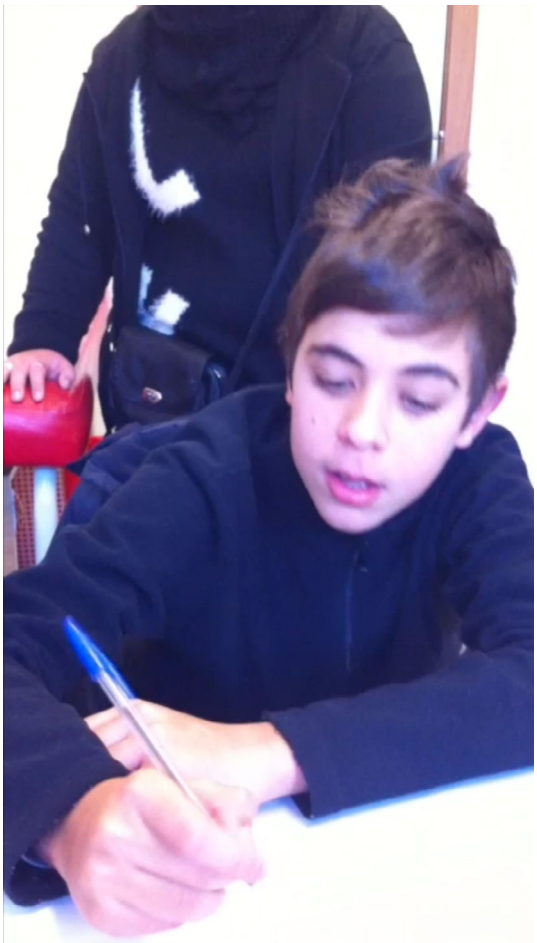


FIG. 2. (**A**) Writing of patient 1 at the age of 8; (**B**) writing of the same patient at the age of 10. Myoclonic jerks are shown by the erratic lining within the words.

improved with action, and cervical left laterocollis, torticollis, and torticaput with dystonic tremor. He also presented with rest tremor on his left hand, bilateral postural and kinetic jerky tremor, and high-amplitude myoclonic jerks on the upper limbs (Video 3, segments 1 and 2). Slight bradykinesia was evident on the left hand without rigidity. He had a stooped posture, but no postural instability. His gait was fast, with decreased stride length and step height, with decomposed turns, but there was no freezing or decreased arm swing (Video 3, segment 3). Genetic testing showed the same variant in the *ANO3* gene present in his son and both grandchildren. For the myoclonus, several drugs were tried, namely, high-dose piracetam, clonazepam, trihexyphenidyl, and levodopa, without any improvement. Cervical dystonia improved partially under botulinum toxin injections, but he refused further treatment.

Discussion

We present in detail 4 patients with the same *ANO3* variant displaying dystonia with diverse topographical involvement and range of severity; 1 of the patients also displayed parkinsonism and 2 of them myoclonus. The point mutation c.1787C > A



Video 1. Segment 1 (patient is 10 years old): dystonic posturing of the right hand with intermittent myoclonic jerks while writing was present. Segment 2 (patient is 17 years old): laryngeal dystonia and mild blepharospasm become evident; disabling right hand dystonia and dystonic tremor are visible.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13209

Video 2. Segment 1: dystonic posturing of the left lower limb when walking forward and slight dystonic posturing of both hands. Segment 2: remission of the lower limb dystonia when walking backward.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13209

(p.Ser596Tyr) was documented, located in a highly preserved residue, considered likely pathogenic in bioinformatic analysis, and segregated in all 4 patients. This mutation has not been previously reported.

This new variant can express phenotypically as a wide spectrum of dystonia, myoclonus, and parkinsonism phenotypes, which is not surprising as *ANO3* encodes anoctamin-3, a calcium-activated chloride channel protein that is highly expressed in the striatum.[5] Patient 1 presented in childhood with *SCGE*-negative myoclonic dystonia.[6] On the other hand, patient 2 developed dystonia and parkinsonism in his 40s resembling parkin-associated Parkinson's disease[6]; patient 3 presented in her teen years with lower limb dystonia, a phenotype classically associated with *TOR1A*-related dystonia[7]; and patient 4 displayed craniocervical dystonia and limb myoclonus.[1] Although all of the phenotypes in our family have been previously reported in *ANO3* patients,[2–4] such phenotypic variability in the same family has not been described so far to the best of our knowledge. Laurencin et al[3] also described a kindred with phenotype heterogeneity, with tremor in the grandfather, hemidystonia and blepharospasm in the father, and progressive lower leg dystonia and tremor in the proband and in her child. However, none of the patients presented myoclonic dystonia nor levodopa-responsive parkinsonism. The causes of such variability remain unknown. Of note, the clinical benefit derived from levodopa was different across the different patients.

This family highlights the heterogeneous presentation of this disorder as well as a wide phenotypic variability within the same family. *ANO3* variants should be considered whenever there is family history or direct observation of either craniocervical dystonia, myoclonic dystonia, lower limb dystonia, head or arm tremor, or early-onset parkinsonism and dystonia. This condition should also be

Video 3. Segment 1: rest jaw tremor and left laterocollis, torticollis and torticaput with dystonic tremor, and rest tremor on the left hand. Segment 2: bilateral postural jerky tremor and myoclonic jerks. Segment 3: stooped posture with slow turns. Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13209

considered in patients with a family history of autosomal dominant dystonia despite marked intrafamilial clinical variability.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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J. Massano: 1A, 3B
T.T.: 1A, 3B

Disclosures

Ethical Compliance Statement: Written consent was obtained from the patients before manuscript writing. The authors confirm that the approval of an institutional review board 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: This work received no funding. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the Previous 12 Months: The authors declare that there are no financial disclosures to report from the previous 12 months. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Figure S1. Patient 2's magnetic resonance imaging. (**A**) Sagittal T1-weighted imaging. (**B**) Axial T2–fluid inversion recovery weighted imaging. (**C**) Coronal plane T2-weighted imaging. (**D**) Axial T2*-weighted imaging.

Figure S2. Patient 3's magnetic resonance imaging. (**A**) Sagittal T1-weighted imaging. (**B**) Axial T2–fluid inversion recovery weighted imaging. (**C**) Coronal plane T2-weighted imaging. (**D**) Axial T2*-weighted imaging.