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Novel anoctamin-3 missense mutation responsible for early-onset myoclonic dystonia

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Myoclonus-dystonia (MD) is an autosomal dominant disorder characterized by bilateral, alcohol-sensitive, myoclonic jerks mainly involving the arms and axial muscles. In most MD families, disease is linked to a locus on chromosome 7q21 involving the ε-sarcoglycan gene (DYT11), a part of the dystrophin-associated protein complex in the brain [1]. However, DYT11 analysis may be negative in some patients experiencing MD. We report a case of early-onset myoclonic dystonia associated with a novel *de novo* missense mutation in the anoctamin-3 gene (ANO3).

The patient without noticeable family history progressively exhibited brief sudden movements of the trunk and upper limbs at the age 10 years. Two years later, he developed axial dystonia, hyperlordosis and hyperextension of the neck that disappeared when lying down. Electrophysiological investigations revealed no giant somatosensory evoked potential, nor clear organization of abnormal muscular activity. The diagnosis of MD was retained but DYT11 genetic testing was negative. At that time, a diagnosis of Tourette's syndrome was evoked because the patient reported partial voluntary control of his movements. However, aripiprazole and cognitive behavioral treatment were found ineffective. Thereafter, the phenotype progressively worsened. At the age of 19 years, it included generalized dystonia, mostly axial with severe myoclonic jerks involving the four limbs and triggered by specific positions such as sitting on a chair (video). No dopa-sensitivity was observed. Zonisamide was only partially effective. At that time, the patient's phenotype resembled myoclonic dystonia more than an ε-sarcoglycan-related myoclonus-dystonia phenocopy, as dystonia was predominant [2].

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.04.019.

Symptomatic dystonia was hypothesized but copper and ceruloplasmin levels were unremarkable. Brain MRI was normal. The patient had no psychiatric features. A genetic analysis of the panel of 127 genes linked to movement disorders [3] revealed a heterozygous missense mutation [c.1943A > G, p.Asn648Ser; genomic position: Chr11(GRCh37): 26655820A > G] in exon 19 of the anoctamine-3 (ANO3) gene (NM_031418.2(ANO3) that has not been reported in any of the public databases such as dbSNP, Exome Sequencing Project (ESP), Exome Aggregation Consortium (ExAC) and Genome Aggregation Database (GenomAD). Further analyses by Sanger sequencing confirmed the presence of the mutation in the patient and revealed its absence in his parents, therefore establishing its very likely *de novo* occurrence. This hypothesis was reinforced through confirmation of maternity and paternity based on segregation analysis of alleles corresponding to 15 STR markers [4]. No other relevant SNV or copy number variation was evidenced by sequencing of the panel of 127 genes that includes the SGCE gene. The relevance and imputability of this specific ANO3 *de novo* mutation was also supported by in silico analyses (including those based on MutationTaster, Polyphen-2 and SIFT) that showed a high conservation across species (including in C Elegans) of the amino acid Asp648 (concerned by the identified variant), and predicted the likely pathogenic effect of the Asn648Ser substitution. Moreover, this variant was predicted to figure among the 1% most deleterious substitutions in the human genome as its CADD PHRED score was evaluated to be 26.0 [5].

This ANO3-related case of early-onset myoclonic dystonia adds to the growing number of patients with childhood-onset dystonia with *de novo* mutations in the ANO3 gene and highlights its importance in this group of patients. ANO3 is highly expressed in the putamen [6]. Mutated fibroblasts experimentally release less ATP-induced calcium signal and exhibit reduced calcium stock in the endoplasmic reticulum [6]. So far, most reported cases of the ANO3 mutation had a predominantly cranio-cervical dystonia evolving to segmental but not generalized dystonia [6–13], sometimes associated with upper-limb tremor or laryngeal dystonia [6,11,12]. Jerks [8] and superimposed myoclonus [6,7] were only occasionally reported. A hyperkinetic syndrome with motor and vocal tics was found in a 53-year-old woman [14]. However, this description should be interpreted with caution as motor tics and myoclonus semiology might have overlapped, as in our observation. Interestingly, several cases of generalized dystonia have been reported recently, starting in infancy and associated with superimposed myoclonic jerks [8,15–17] or tremor [18]. All the previous ANO3 variants reported in the literature are summarized in Table 1.

Besides ANO3-related dystonia, several other genes were recently reported to be associated with early-onset hyperkinetic/myoclonic dystonia such as ADCY5 and KCTD17. Indeed, ADCY5-related dystonia is often associated with chorea and episodic worsening that might be related to sleep. However, the clinical spectrum is broad and ADCY5 mutations should be sought in hyperkinetic early-onset movement disorders [19,20]. KCTD17-related dystonia was recently described as early-onset myoclonic dystonia with predominant and worsening

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Table 1
ANO3-mutation-associated dystonia.

Sequence mutation	AA change	Phenotype	Age of onset	Ref
c.-190C > T		Cervical dystonia and upper-limb tremor, myoclonic jerk	Late teens	Charlesworth, 2012
c.161C > T	p.Thr54Ile	Familial essential tremor	?	Charlesworth, 2012
c.433-2A > G	Splice site change	Writer's cramp	25 years	Olschewski, 2019
c.674A > G	p.Asn225Ser	Facial and cervical dystonia	44 years	Zech, 2017
c.702C > G	p.Cys234Trp	Hyperkinetic syndrome/chorea, motor and vocal tics, craniocervical dystonia	52 years	Blackburn, 2016
c.835T > A	p.Tyr279Asn	Facial and cervical dystonia	65 years	Zech, 2017
c.860G > A	p.Arg287Gln	Cervical and upper-limb dystonia	54 years	Yoo HS, 2018
c.982C > T	p.Arg328Cys	Focal dystonia (upper-limb or cervical and shoulder) ± dystonic tremor, partial response to levodopa	28–36 years	Olschewski, 2019
c.1199G > T	p.Gly400Val	Cranio-cervical and upper-limb dystonia	7 years	Zech, 2017
c.1387G > A	p.Val463Met	Focal upper-face dystonia	50 years	Zech, 2017
c.1470G > C	p.Trp490Cys	Cervical dystonia, laryngeal dystonia, ± oromandibular dystonia, blepharospasm. Upper-limb dystonia and tremor ± head tremor, cervical jerks.	3–30 years	Charlesworth, 2012, Stamelou, 2014
c.1480A > T	p.Arg494Trp	Cervical dystonia, laryngeal dystonia, ± blepharospasm, oromandibular dystonia. Head and upper-limb postural tremor.	19–40 years	Charlesworth, 2012, Stamelou, 2014
*c.1528G > A**	*p.Glu510Lys*	*Writer's cramp evolving into craniocervical, bulbar, laryngeal, truncal and lower limb dystonia. Upper-limb postural tremor. Myoclonic jerks.*	*9 years*	*Zech, 2017*
*c.1682T > A**	*p.Val561Glu*	*Generalized dystonia*	*3 years*	*Olschewski, 2019*
*c.1819A > T**	*p.Ile607Phe*	*Generalized dystonia, myoclonus, parkinsonism, bradykinesia, developmental regression*	32 months	*Nelin, 2018*
*c.1952G > A**	*p.Ser651Asn*	*Lower-limb dystonia evolving to generalized dystonia including laryngeal dystonia. Multifocal myoclonic jerks.*	*1-3 years*	*Yoo D, 2018, Tunc, 2019*
c.1943A > G*	***p.Asn648Ser***	***Trunk and upper-limb jerks evolving into generalized dystonia with superimposed myoclonic jerks.***	***10 years***	***Current study***
c.1964_ 1966dupATA	p.Tyr655_ Ile656insAsn (in frame insertion)	Facial and cervical dystonia	51 years	Zech, 2017
c.1969G > A	p.Ala657Thr	Cervical dystonia ± blepharospasm, eye-lid opening apraxia, oromandibular dystonia. Jerky foot movement evolving into generalized dystonia. Lower-limb and trunc jerks.	40–53 years 12 years	Miltgen, 2016, Zech, 2017
c.2053A > G	p.Ser685Gly	Autosomal dominant cervical, laryngeal and upper-limb dystonia. Upper-limb action ± postural tremor. ± proximal upper-limb jerks. One case of laryngeal dystonia in late twenties. Cervical and upper-limb dystonia ± myoclonus, mild parkinsonism and levodopa-responsiveness	First decade 5–15 years	Charlesworth, 2012, Stamelou, 2014, Kuo, 2019
c.2497A > G	p.Ile833Val	Cervical dystonia and dystonic head tremor	40 years	Zech, 2014
c.2540A > G	p.Tyr847Cys	Cervical dystonia, head tremor. ± blepharospasm, oromandibular dystonia, dysphonia, upperlimb tremor and dystonia	39–56 years	Ma, 2015
c.2586G > T	p.Lys862Asn	Cervical and oromandibular dystonia	?	Charlesworth, 2012
c.2894T > G	p.Leu965Trp	Mandibular and hand dystonia	46 years	Olschewski, 2019
c.2906G > A	p.Arg969Gln	Functional dystonia (writer's cramp and mouth musician's dystonia)	15–45 years	Olschewski, 2019
c.2917G > C	p.Gly973Arg	Blepharospasm and oromandibular dystonia	69 years	Zech, 2014

* *de novo mutations.*

dystonia, mild myoclonus and no alcohol sensitivity [21–23]. TOR1A mutation-related dystonia could also be associated with myoclonus [24].

Together with those reported in the literature, this case suggests that the ANO3 missense mutation should be sought in cases of non-DYT11 early-onset generalized myoclonic dystonia. It also shows that the differential diagnosis between the latter and tics is not always easy in children at disease onset.

Author's role

AD, PB and DG were involved in the care of the patient. JC, ND, CT and MA were involved in genetic analysis and interpretation. AD and PB wrote and reviewed the manuscript, JC, DG and MA reviewed the manuscript. All authors approved the final version of the manuscript.

Ethical statement

Informed consent was obtained from the patient for publication of his data and video, including online publication and dissemination.

Conflicts of interest

None of the authors has a conflict of interest in relation to the present article.

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