

Letter to the Editor

A novel heterozygous ANO3 mutation responsible for myoclonic dystonia



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Dear Editor,

Mutations of Anoctamine 3 gene (ANO3) are a rare cause of dystonia, which have first been described in families with tremulous craniocervical dystonia [1]. Since then, the phenotypic spectrum has been extended [2]. Notably, isolated tremor at the beginning of the disease has been observed, and could be misdiagnosed as essential tremor. More recently, childhood onset generalized dystonia has been reported [3]. Here, we present a family carrying ANO3 mutation and exhibiting a myoclonic dystonia and tremor phenotype.

1. Case report

Our family is composed of 4 affected members as described in the family tree (Fig. 1).

The grandfather (II.1) presented a tremor. His son (Patient III.1) developed walking difficulties when 12 years-old because of a left leg dystonia with myoclonus. He also exhibited a mild dystonia of the left arm and a slight facial dystonia with blepharospasm (Video S1). Trihexyphenidyl was partially effective. The evolution was slow and he could still walk, albeit with help, when 60 years-old. He died at 65 years old from unknown cause. Patient III.3 developed bilateral postural arm and head tremor at the age of 16. She was diagnosed with essential tremor. Then, 20 years later, she progressively developed walking difficulties with axial and lower limbs dystonia (Video S2). She had a daughter (patient IV.5) who developed a left leg dystonia when 12 years-old. Then, the dystonia became generalized in the following 10 years with an axial presentation. She also developed generalized myoclonus and action tremor (Video S3). Multiple treatments were tried but only zonisamide was partially effective on myoclonus. Finally, she underwent pallidal deep brain stimulation (Gpi-DBS) at 33 years of age with a significant improvement.

None of the patients were exposed to neuroleptics, responsive to levodopa or had a neonatal anoxia history. Alcohol did not produce any improvement. Genetic testing for DYT-TOR1A, DYT-THAP1 and DYT-SGCE mutations were negative. Brain MRI and [123 I]-FP- β -CIT SPECT imaging were normal.

Genetic analysis was then performed from a panel of 127 genes responsible for movement disorders including 69 genes responsible for dystonia [4]. This targeted high-coverage sequencing was applied to

DNA samples taken from patients III.3 and IV.5 (Fig. 1) revealed a heterozygous missense mutation [c.1820T > C, p. Ile607Thr; genomic position: chr11:26621245T > C] in exon 17 of anoctamine-3 (ANO3) gene (NM_031418). Further analyses by Sanger sequencing confirmed the presence of the mutation in the patients and showed its absence in the asymptomatic brother of patient IV.5, subject IV.4, which supports the pathogenicity of this mutation which has not been reported in large public databases such as Exome Aggregation Consortium (ExAC), Genome aggregation database (GenomAD) and 1000 genomes project. Relevance of this specific mutation was also supported by in silico analyses (including those based on MutationTaster, Polyphen-2 and SIFT) that showed a high conservation across species of the amino acid, Ile607 (concerned by our variant) and predicted the likely pathogenic effect of the Ile607Thr 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 25.2 [5].

2. Discussion

We report a new ANO3 mutation responsible initially of young onset lower limb dystonia or tremor. Then, the clinical presentation slowly worsens and leads to generalized dystonia combined with tremor and/or myoclonus. Interestingly there is, within this family a significant phenotypic variability. This phenotype expands the clinical spectrum of ANO3 mutation. Furthermore, Gpi-DBS was partially effective in one patient. Only one other case of Gpi-DBS for a dystonic patient with an ANO3 mutation have been described, with a good result on dystonia and tremor [6]. This case series illustrates that autosomal dominant cases of young-onset generalized dystonia should be screened for ANO3 mutations. Gpi-DBS can be considered in patients with hyperkinetic movements disorders due to ANO3 mutations.

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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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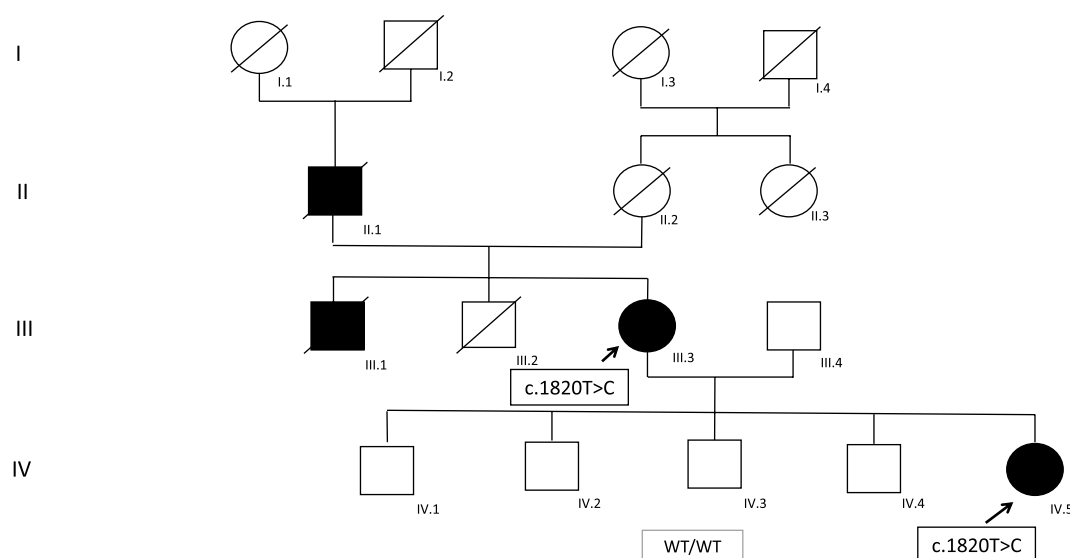


Fig. 1. Family tree. WT = wild type. Pedigree showing affected members by filled symbols and asymptomatic members by empty symbols. Patient II.1 developed isolated tremor (never been examined by a neurologist). Patient III.1. developed generalized dystonia with myoclonus. Patient III.3. developed isolated tremor and then generalized dystonia with tremor. Patient IV.4. not carrying the mutation and asymptomatic. Patient IV.5 developed segmental and then generalized dystonia with tremor and myoclonus.

C.L.: 1A, 1B, 1C, 3A

E.B.: 1A, 3B

T.D.: 1A, 3B

M.A.: 1A, 1B, 3B

J.C.: 1C, 3B

S.T.: 1A, 3B

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