

Novel heterozygous mutation in ANO3 responsible for craniocervical dystonia

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Novel Heterozygous Mutation in *ANO3* Responsible for Craniocervical Dystonia



To determine the genetic basis of dystonia, we performed exome sequencing in 4 patients from a multigenerational family from Flemish origin, with no *TOR1A* or *THAP1* mutations (Fig. 1). In the proband (III-1), the age of onset for movement disorders was 53 years. She complained mainly of involuntary eyelid movements. Neurological examination showed severe blepharospasm accompanied by apraxia of eyelid opening, a mild oromandibular and cervical dystonia (right, painful torticollis). Blepharospasm improved with a high dose of botulinum toxin A (OnabotulinumtoxinA, 30 units to each side every 3 months). The proband's mother (II-1) presented movement disorders from the age of 40. Neurological examination showed a blepharospasm and a cervical dystonia. According to the proband, her grandmother (I-2) and her grandmother's

two brothers (I-6 and I-8) had displayed jerky, involuntary movements of the head. This could not be confirmed by a clinical examination because all were deceased at the time of the study. One of the proband's brothers (III-4) is being treated for cervical dystonia, which began at 40 years old, without additional dystonic symptoms. In another brother (III-6), clinical examination at 68 years of age showed a postural tremor of the upper limbs, without additional neurological symptoms. Onset age is unknown because III-6 had not noticed his tremor before the examination. An isolated, postural tremor of upper limbs was also found in two sons of the proband (IV-1 and IV-4) beginning in childhood and adolescence, respectively. The tremor did not fit with the specific pattern of dystonic tremor in any of the 3 patients (III-6, IV-1, and IV-4). Based on neurological observations, this familial tremor is concordant with physiological tremor or essential tremor, although drug-induced tremor cannot be ruled out for IV-1, given that he has received dopamine antagonist treatment from childhood for behavioral disorders associated with mental retardation. Therefore, we concluded that tremor and dystonia are two distinct entities in this family. Finally, neurological findings were normal for IV-10 (35 years old).

Exome sequencing identified the c.1969G>A (p.Ala657Thr) variant in *ANO3*, a gene associated with dystonia (see Supplementary Data).¹ The variant in exon 19 is carried by all 3 affected patients (II-1, III-1, and III-4) presenting neither tremor nor myoclonus, one asymptomatic family member (IV-10), but also by IV-1, who presented with postural tremor that may have been drug induced. This variant is not reported in the Exome Aggregation Consortium (ExAC). It involves a highly conserved residue and is predicted as disease causing by UMD-Predictor² and MutationTaster.³ Twelve *ANO3* variants have previously been described in dystonia cases.^{1,4,5} The c.1969G>A mutation is the first variant to be located in a transmembrane domain (domain-5) of the anoctamin 3 protein encoded by *ANO3* and is predicted to switch hydrophobicity of this segment.⁶ No pathogenic variant was identified in other dystonia genes.

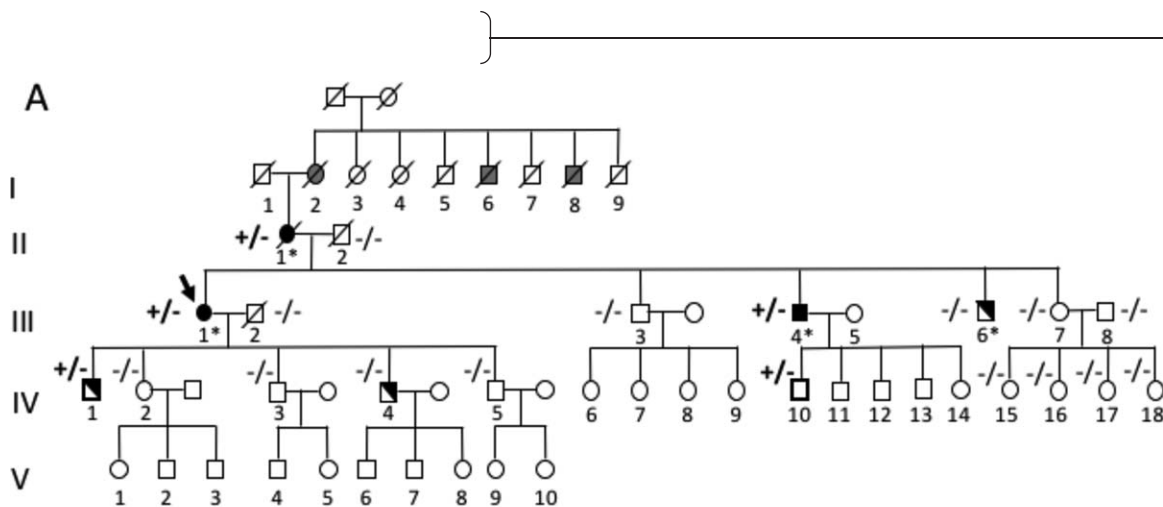
To conclude, we report a novel c.1969G>A mutation in the *ANO3* gene in a family presenting with a typical dystonia phenotype consistent with previous reports^{4,5,7}; onset mainly after the fourth decade, begins as cervical dystonia, but evolves to segmental dystonia, without leg involvement or any generalized dystonia. ■

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| Patient | Sex | Age | Age of onset | Site of onset | Age at last examination | Clinical description |
|---------|-----|-----|--------------|---------------|-------------------------|--|
| II-1* | F | 90 | 40 | UK | 87 | Cervical dystonia, blepharospasm |
| III-1* | F | 73 | 53 | Eyelids | 72 | Blepharospasm, cervical dystonia, oromandibular dystonia |
| III-4* | M | 64 | 40 | Neck | 51 | Cervical dystonia |
| III-6* | M | 71 | UK | Upper limbs | 68 | Postural tremor |
| IV-1 | M | 51 | Childhood | Upper limbs | 50 | Postural tremor |
| IV-4 | M | 47 | Adolescence | Upper limbs | 45 | Postural tremor |
| IV-10 | M | 35 | - | - | 35 | Asymptomatic |

FIG. 1. Pedigree with the c.1969G>A (p.Ala657Thr) mutation in the ANO3 gene. (A) Pedigree structure of the studied family. Symbols filled in black represent patients presenting with dystonia; Symbols half-filled in black represent patients presenting with isolated tremor; Symbols filled in grey represent patients reported with cervical dystonia (not examined). +/- ANO3 heterozygous mutation carrier. -/- Homozygous wild-type allele carrier. Arrow indicates proband. (B) Detailed clinical description. UK: Unknown. Individuals on whom WES was performed are indicated with a star. Exome sequencing analysis of the proband's brother (III-6) presenting with isolated tremor does not identify any pathogenic variation in the known tremor-causing genes (DRD3, FUS, SNC4A and TENM4).

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.