



HAL
open science

Novel heterozygous mutation in ANO3 responsible for craniocervical dystonia

Morgane Miltgen, Arnaud Blanchard, H el ene Mathieu, Alexandre Kreisler, Jean-Pierre Desvignes, David Salgado, Agathe Roubertie, Laura Barre, Ghadi Rai, Veronique Blanck, et al.

► To cite this version:

Morgane Miltgen, Arnaud Blanchard, H el ene Mathieu, Alexandre Kreisler, Jean-Pierre Desvignes, et al.. Novel heterozygous mutation in ANO3 responsible for craniocervical dystonia. *Movement Disorders*, 2016, 31 (8), pp.1251-1252. 10.1002/mds.26717 . hal-01670172

HAL Id: hal-01670172

<https://hal.science/hal-01670172v1>

Submitted on 21 Dec 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destin ee au d ep ot et  a la diffusion de documents scientifiques de niveau recherche, publi es ou non,  emanant des  tablissements d'enseignement et de recherche fran ais ou  trangers, des laboratoires publics ou priv es.

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.

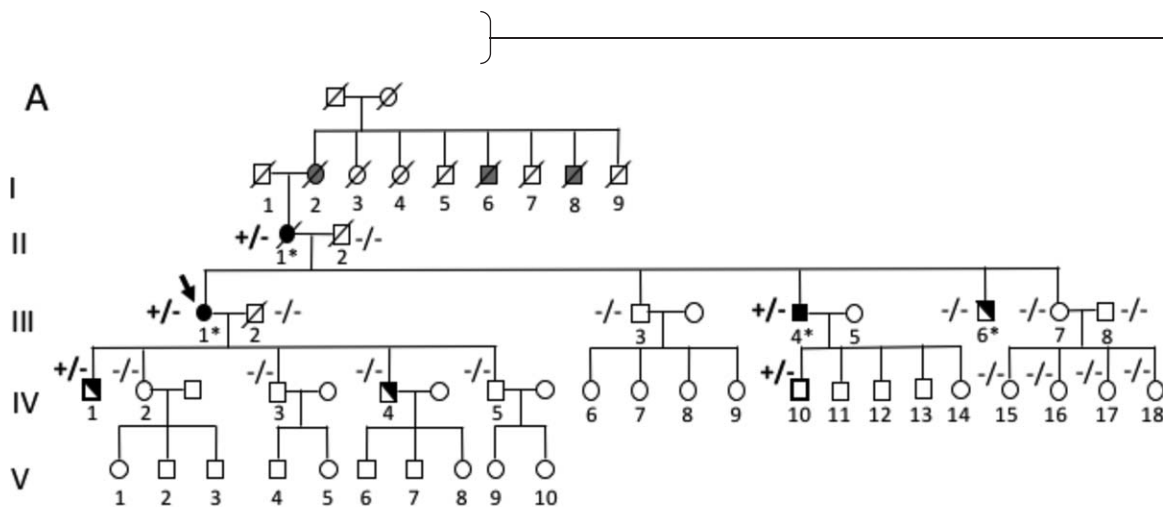
To conclude, we report a novel c.1969G>A mutation in the *ANO3* gene in a family presenting with a typical dystonia phenotype consistent with previous reports^{4,5,7}; onset mainly after the fourth decade, begins as cervical dystonia, but evolves to segmental dystonia, without leg involvement or any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

Morgane Miltgen, MS,¹ Arnaud Blanchard, PhD,¹
Hélène Mathieu, MS,¹ Alexandre Kreisler, MD, PhD,^{2,3}
Jean-Pierre-Desvignes, MS,¹ David Salgado, PhD,¹
Agathe Roubertie, MD, PhD,⁴ Laura Barre, MS,¹
Ghadi Rai, MS,¹ Veronique Blanck, MS,⁵
Melissa Frederic, PhD,¹ Xavier Douay, MD,²
Ronald Mazzoleni, MD,² Pierre Charpentier, MD,⁶
Victoria Gonzalez, MD, PhD,⁷ Alain Destee, MD, PhD,^{2,3}
Christophe Beroud, PharmD, PhD,^{1,5} and
Gwenaëlle Collod-Beroud, PhD¹

¹Aix Marseille Univ, INSERM, GMGF, Marseille, France; ²Université de Lille, CHRU de Lille, Service de Neurologie et Pathologie du Mouvement, Lille, France; ³INSERM UMR-S1172, Lille, France; ⁴CHRU Montpellier, Service de Neuro-pédiatrie, Hôpital Gui de Chauliac, Montpellier, France; Institut des Neurosciences de Montpellier, INSERM U1051, Université de Montpellier, BP 74103, Montpellier,

*Correspondence to: Dr. Gwenaëlle Collod-Bérout, INSERM UMR_S910, Medical Genetics and Functional Genomics, Faculté de Médecine la Timone, 27 Bd Jean Moulin, 13385 Marseille Cedex 05, France; E-mail: gwenaëlle.collod-beroud@inserm.fr

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.



B

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).

France; ⁵Hôpital La Timone, Département de Génétique Médicale, Marseille, France; ⁶CH Bèthune, Service de Neurologie, France; ⁷CHU Montpellier, Hôpital Gui de Chauliac, Service de Neurochirurgie, Montpellier, France

References

- Charlesworth G, Plagnol V, Holmstrom KM, et al. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. *Am J Hum Genet* 2012;91:1041-1050.
- Salgado D, Desvignes JP, Rai G, et al. UMD-Predictor: a high throughput sequencing compliant system for pathogenicity prediction of any human cDNA substitution. *Hum Mutat* 2016;37:439-446.
- Schwarz JM, Cooper DN, Schuelke M, et al. MutationTaster2: mutation prediction for the deep-sequencing age. *Nat Methods* 2014;11:361-362.
- Ma LY, Wang L, Yang YM, et al. Mutations in ANO3 and GNAL gene in thirty-three isolated dystonia families. *Mov Disord* 2015;30:743-744.
- Zech M, Gross N, Jochim A, et al. Rare sequence variants in ANO3 and GNAL in a primary torsion dystonia series and controls. *Mov Disord* 2014;29:143-147.
- Paulet D, Claustres M, Bérout C. Hydrophobic pulses predict transmembrane helix irregularities and channel transmembrane units. *BMC Bioinformatics* 2011;12:135.
- Stamelou M, Charlesworth G, Cordivari C, et al. The phenotypic spectrum of DYT24 due to ANO3 mutations. *Mov Disord* 2014; 29:928-934.

Supporting Data

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