Journal of the Neurological Sciences 396 (2019) 199–201

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

# A recurrent *de-novo ANO3* mutation causes early-onset generalized dystonia

ARTICLE INFO

*Keywords:*
ANO3
Early-onset generalized dystonia
Myoclonus

*Dear Editor,*

Anoctamin 3 (*ANO3*) mutations have first been reported in families with autosomal dominant cervical, laryngeal and/or upper-limb tremulous dystonia in 2012 [1]. Since then a number of studies have described rare *ANO3* variants in dystonia patients often with inconclusive segregation in available family members [2,3]. Notably, rare *ANO3* missense variants could also be detected in 0.3–0.5% of presumably healthy individuals [4]. Thus, the pathogeneity of *ANO3* variants in dystonia is still under debate [5]. Recently, pathogenicity was supported by the description of *de-novo* variants in patients with childhood-onset dystonia [6,7].

Here, we present a 3-year old German boy with progressive generalized dystonia combined with multifocal myoclonic jerks. After an unremarkable pregnancy, he was born as the second child of healthy parents at 41 + 3 weeks of gestation. Postpartal adaptation (APGAR 9/10/10), birth weight (3850 g/82th percentile), body length (56 cm/97th percentile), and head circumference (36 cm/84th percentile) were normal. Early development during the first year of life was also unremarkable (e. g. sitting at age of 6, crawling at 9, assisted walking at 10, speech at 12 months). At the age of 15 months, he started dragging his left leg behind when attempting to crawl. Assisted standing and walking was no longer possible because his legs began to tremble. Symptoms progressed within the next months. On examination at that time, he had brisk reflexes in the lower extremities accompanied by some degree of spasticity, pyramidal signs, and generalized dystonia including cervical and laryngeal dystonia, dysphagia, and also superimposed myoclonic jerks, which markedly impaired voluntary movements (Video 1). There were no cerebellar signs. Oculomotor examination and sensory testing were normal. Comprehensive neuropediatric consultation revealed initially elevated CK (298-405 U/l), LDH (332-396 U/l) and arylsulfatase (9.9 nmol/h/ml), which were normal at repeat investigations. Repeated measurements of lactate, amino acids in serum, urine and cerebrospinal fluid and other routine laboratory tests were normal. Also, enzyme analyses were not indicative of metabolic and storage diseases. EEG, nerve conduction studies, and both brain and spine MRI were all unremarkable. Symptomatic treatment with L-Dopa (up to 130 mg/day; 4 mg/kg TID) had no effect. Under medication with baclofen (2 mg TID) and trihexyphenidyl (4 mg TID), there was an amelioration of spasticity and dystonia, and hand motor skills slightly improved, e.g. he was able to grasp toys.

A gene panel analysis of 29 dystonia and other movement disorder genes (including *TOR1A, THAP1, GNAL, KMT2B, SGCE, GCH1*, and *ANO3*) identified a rare missense variant in *ANO3* that has recently been reported in a patient from Korea with a strikingly similar phenotype[6] (c.1952G > A, p.Ser651Asn, NM_031418; Table 1). The mutation was absent in the parents and thus arose de novo. In addition, trio exome sequencing revealed no additional plausible genetic cause of the disease (no additional de novo variant; no variant in any other gene that has previously been linked to dystonia). The *ANO3* variant is absent from public databases and 500 in-house controls. This variant is in-silico predicted to be disease-causing by Mutationtaster (http://mutationtaster.org/) and a CADD score of 28.4 and highly conserved [6].

*ANO3* encodes a $Ca^{2+}$-activated $Cl^-$ -channel leading to endoplasmatic reticulum-related calcium signaling abnormalities [8]. ANO3 was found to be expressed predominantly in the striatum [1,9] compatible with the assumption that basal ganglia dysfunction are the basis of dystonia. In addition to dystonia, our patient also shows some spasticity that has not previously been reported in any *ANO3* mutation carrier (www.mdsgene.org). If spasticity is related to the *ANO3* variant or co-occurs cannot be determined in this single patient. Known causes of spasticity were not detected in the patient by the exome sequence analysis.

In conclusion, we report a second patient with the c.1952G > A *de-novo* mutation in *ANO3* presenting with early-onset generalized combined dystonia. While many of the initially reported patients had an age of onset in the 4th decade of life, onset often in the neck with symptoms usually not generalizing (www.mdsgene.org), *de-novo* variants seem to lead to childhood-onset, generalized dystonia which in the three confirmed cases started in an extremity. Thus, there might be an as yet under-recognized manifestation of *ANO3* mutations in children.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2018.11.024.

## Acknowledgments

We thank the patient and his family for contributing to this research and Dr. Anca Mannhardt for helpful discussions on this patient. This work was supported by the German Ministry of Education and Research (BMBF, DYSTRACT consortium, 01GM1514B, to K.L. and A.M.) and the Possehl-Stiftung (Lübeck, A.M.).

https://doi.org/10.1016/j.jns.2018.11.024
Received 12 October 2018; Received in revised form 14 November 2018; Accepted 20 November 2018
Available online 22 November 2018
0022-510X/ 

**Table 1**
Comparison of the phenotypes in patients with confirmed *de-novo* mutations.

| Patient | Our index | Yoo et al. [ 6] | Zech et al. [ 7] Patient 7 |
|---|---|---|---|
| Mutation (NM_031418) | c.1952G > A, p.Ser651Asn | c.1952G > A, p.Ser651Asn | c.1528G > A, p.Glu510Lys |
| Consequence | missense | missense | missense |
| Sex | male | male | male |
| Age at onset | 15 months | 3 years | 9 years |
| Age at time of publication | 3.5 years | 17 years | 44 years |
| Dystonia onset site | left leg | left leg | writer's cramp |
| Progression to generalized dystonia | Rapid progression within 15 months | Continuous slow progression over 14 years | Continuous slow progression |
| Additional features | Multifocal myoclonic jerks, generalized dystonia including laryngeal dystonia, intelligence within normal range | Multifocal myoclonic jerks, generalized dystonia including laryngeal and speech dystonia, intelligence within normal range | craniocervical, bulbar, laryngeal, truncal, and lower limb dystonia, upper limb postural tremor, superimposed myoclonic-like jerks, exaggerating with action and during speech |
| Treatment | Poor response to L-Dopa; alleviation of dystonic posture and jerky movements under trihexyphenidyl and baclofen | Poor response to L-Dopa; alleviation of dystonic posture and jerky movements under trihexyphenidyl | Deep brain stimulation of Globus pallidus internus at age of 31 years led to substantial improvement of dystonia and tremor, but not myoclonus. |

## Study funding

This work was supported by the German Ministry of Education and Research (BMBF, DYSTRACT consortium, 01GM1514B, to K.L. and A.M.) and the Possehl-Stiftung (Lübeck, A.M.).

## Author disclosures

Dr. Sinem Tunc is supported by Deutsche Forschungsgemeinschaft (DFG; SFB 936/project C5 and the Margot and Jürgen Wessel Stiftung in Lübeck. She received travel grants from the Movement Disorders Society, Merz and Actelion Pharmaceuticals.

Dr. Jonas Denecke has no disclosures relevant to the manuscript.

Luisa Olschewski has no disclosures relevant to the manuscript.

Dr. Davor Lessel has no disclosures relevant to the manuscript.

Prof. Tobias Bäumer is supported by the Possehl-Stiftung, Lübeck, the Bundesministerium für Bildung und Forschung (BMBF): DysTract consortium, and the Innovationsausschuss of the Gemeinsamer Bundesausschuss: Translate NAMSE (structural support for the Lübeck Center for Rare Diseases). He received honaria from Merz Pharmaceuticals, Ipsen Pharma, and Allergan. He served on the scientific advisory board for Merz Pharmaceuticals.

Prof. Alexander Münchau is the Speaker of the Lübeck Centre for Rare Diseases. He is a member of the advisory board of the Tourette Gesellschaft Deutschland (German Tourette syndrome association). He received commercial research support with grants by Pharm Allergan, Ipsen, Merz Pharmaceuticals, Actelion, and honoraria for lectures from Pharm Allergan, Ipsen, Merz Pharmaceuticals, Actelion, GlaxoSmithKline, Desitin and Teva. He was supported from non-profit foundations or societies: Possehl-Stiftung, Lübeck; Dystonia Coalition (USA); Tourette Syndrome Association (Germany); European Huntington Disease Network; N.E.MO. Charity supporting the research of paediatric movement disorders; Ärztekammer Schleswig-Holstein; Fortbildungsakademie der Deutschen Gesellschaft für Neurologie; Förderstiftung des Universitätsklinikums Schleswig-Holstein (UKSH), the Foundation of the University Medical Center Schleswig Holstein "Gutes Tun!". Prof. Münchau received academic research support from the European Union: Multicentre Tics in Children Studies (EMTICS) as part of the FP 7 programme (HEALTH.2011.2.2.1–3: Addictive and/or compulsive behaviour in children and adolescents: translating pre-clinical results into therapies), German Research Foundation (DFG): project „Intentional inhibition and self-control in Gilles de la Tourette syndrome "(MU 1692/3-1); DFG: project "Connectivity and plasticity in cortical motor networks in Parkin gene associated parkinsonism and dopa responsive dystonia" (SFB 936); DFG: project „Psychophysische Methoden im Kontext pharmakologischer und verhaltens-therapeutischer Ansätze zur Behandlung des Gilles de la Tourette Syndroms "(MU 1692/4–1); Bundesministerium für Bildung und Forschung (BMBF): DysTract consortium. He receives royalties from the publication of the book *Neurogenetics* (Oxford University Press).

Prof. Katja Lohmann is supported by the German Research Foundation (DFG), German Ministry of Education and Research (BMBF, DYSTRACT consortium, 01GM1514B), and the International Parkinson's disease and Movement Disorder Society (MDS).

## Appendices

| Authors name | Location | Role | Contribution |
|---|---|---|---|
| Sinem Tunc | University of Lübeck, Germany. | Author | Design and conceptualized study; interpretation of data; drafted the manuscript. |
| Jonas Denecke | University Medical Center Hamburg-Eppendorf, Hamburg, Germany. | Author | Acquisition and interpretation of data, critical revision of manuscript for intellectual content. |
| Luisa Olschewski | University of Lübeck, Germany. | Author | Interpretation of data, critical revision of manuscript for intellectual content. |
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