Journal of the Neurological Sciences 415 (2020) 116909

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Letter to the Editor

Novel *CACNA1A* variant may cause cervical dystonia and cerebellar ataxia syndrome

ARTICLE INFO

Keywords:
Dystonia
Ataxia
CACNA1A
SCA

Dear Editor,

Pure spinocerebellar ataxias (SCA) are rare in isolation; they commonly appear in association with other neurological disorders. Very rarely, cerebellar ataxia (typically slowly progressive) is associated with isolated cervical dystonia. This combination of disorders gives rise to great diagnostic uncertainty. The literature includes reports of several recent cases of this association, which rule out the mutations causing common SCAs and do not identify a definite cause. It has been suggested that this combination of disorders may be a distinct clinical entity. We present the case of a patient with a syndrome of cervical dystonia and cerebellar ataxia similar to those reported in the literature, in which we detected an as yet undescribed pathogenic mutation that may be the cause of the syndrome, at least in our patient.

The patient is a 62-year-old man who had more than 40 years' history of gait instability, and in the past 5 years had required unilateral support; the forced deviation of the head had appeared more recently, approximately 15 years before he consulted our department. The general physical examination revealed no abnormalities; the neurological examination showed a clear rightward deviation of the head, shoulder flexion, and dysmetria of both lower limbs and the right arm. The patient displayed ataxic gait with increased base of support, inability to walk in tandem, and mild positive Romberg sign. No neuropathic, pyramidal, or parkinsonian signs were detected (Supplementary Video S1). A blood analysis yielded normal results. A peripheral blood smear tested negative for acanthocytes. A brain MRI displayed cerebellar atrophy predominantly involving the vermis. A genetic study for SCA, dentatorubral-pallidoluysian atrophy, Friedreich ataxia, and Huntington disease returned normal results. Massively parallel sequencing was performed for 62 genes involved in ataxia syndromes, identifying a heterozygous mutation in the autosomal dominant gene *CACNA1A* on chromosome 19p13. The variant detected was the one-nucleotide insertion c.4056_4057insG (p.Pro1353Alafs*3), which causes a reading frame shift resulting in a premature stop codon 3 amino acids after the insertion (Fig. 1). This variant is not described in the clinical or population databases consulted.

Few genetically confirmed cases of cervical dystonia and cerebellar ataxia have been reported. The literature documents the uncertainties surrounding the syndrome, which may in fact represent a distinct clinical entity associated with undescribed novel mutations. A study group from the National Hospital for Neurology and Neurosurgery in London reported 11 cases of slowly progressive cerebellar ataxia and cervical dystonia, which clinically appears to be condition not explained by the known mutations causing ataxia [1,2]. The phenomenology and clinical course suggest a heterogeneous background that may include unidentified genetic disorders, although causation by a single gene mutation with variable expression and penetrance cannot be ruled out [1]. The CACNA1A gene, in which we detected a novel mutation, encodes the transmembrane pore-forming subunit (alpha 1A) of the P/Q type or CaV2.1 voltage-gated calcium channel [3]. These channels not only mediate the passage of calcium into excitable cells, but also play a role in a range of other calcium-dependent processes, including muscle contraction, the release of hormones, neurotransmitters, and gene expression [4]. Furthermore, a fragment of the gene is involved in the production of the CACNA1A c-terminal polypeptide (alpha-1ACT), a transcription factor involved in cerebellar development [5]. Point mutations, deletions, duplications, and CAG repeat mutations in CACNA1A cause at least 4 diseases: episodic ataxia type 2 (OMIM 108200), familial hemiplegic migraine type 1 (OMIM 141500), SCA6 (OMIM 283086) [6], and the rare early infantile epileptic encephalopathy 42 (OMIM 617106) [7]. We report a novel CACNA1A variant, which is predicted to result in a truncated, incomplete, and non-functional protein product that may be responsible for our patient's syndrome of cervical dystonia and cerebellar ataxia.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.116909.

Financial Disclosures of all authors

None.

Informed consent

Informed consent was obtained from all individual participants included in the study.

https://doi.org/10.1016/j.jns.2020.116909
Received 27 February 2020; Received in revised form 7 May 2020; Accepted 12 May 2020
Available online 17 May 2020

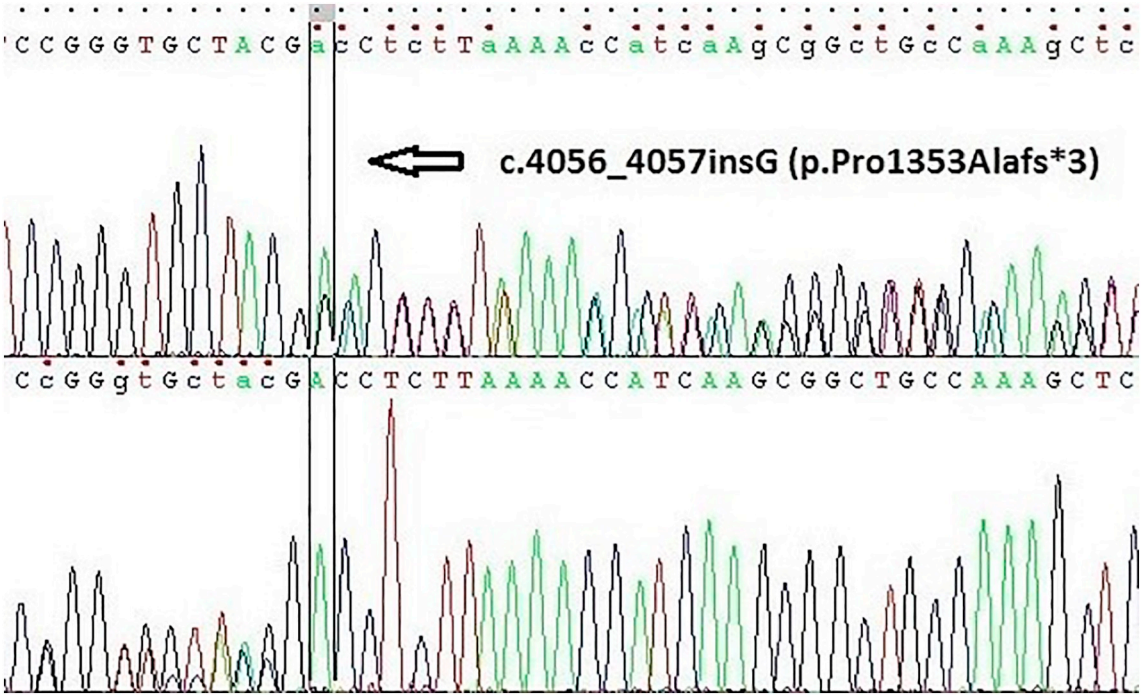

Fig. 1. Sanger sequencing of CACNA1A. The arrow indicates the insertion of a G nucleotide between positions 4056 and 4057. This insertion is a frameshift mutation that makes the reference sequence unusable. We can see the two peaks on the right of the insertion for the forward sequence (6585710_25F). Both peaks can also be seen on the left of the reverse sequence (6585710_25R).

Declaration of Competing Interest

The authors declare no conflicts of interest.

References

[1] B.P. Van de Warrenburg, P. Giunti, S.A. Schneider, et al., The syndrome of (predominantly cervical) dystonia and cerebellar ataxia: new cases indicate a distinct but heterogeneous entity, J. Neurol. Neurosurg. Psychiatry 78 (2007) 774–775.

[2] M. Kuoppamäki, P. Giunti, N. Quinn, et al., Slowly progressive cerebellar Ataxia and cervical dystonia: clinical presentation of a new form of Spinocerebellar Ataxia? Mov. Disord. 18 (2003) 200–206.

[3] H.B. Kordasiewicz, R.M. Thompson, H.B. Clark, et al., C-termini of P/Q-type Ca2+ channel alpha1A subunits translocate to nuclei and promote polyglutamine-mediated toxicity, Hum. Mol. Genet. 15 (2006) 1587–1599.

[4] S. Diriong, P. Lory, M.E. Williams, et al., Chromosomal localization of the human genes for alpha 1A, alpha 1B, and alpha 1E voltage-dependent Ca2+ channel subunits, Genomics 30 (1995) 605–609.

[5] X. Du, J. Wang, H. Zhu, et al., Second cistron in CACNA1A gene encodes a transcription factor mediating cerebellar development and SCA6, Cell 154 (2013) 118–133.

[6] G.S. Grieco, S. Gagliardi, I. Ricca, et al., New CACNA1A deletions are associated to migraine phenotypes, J Headache Pain 19 (2018) 75.

[7] Epi4K Consortium, De novo mutations in SLC1A2 and CACNA1A are important causes of epileptic encephalopathies, Am. J. Hum. Genet. 99 (2016) 287–298.

A. Fuerte-Hortigón[a,*], R. Pérez-Noguera[a], J. Dotor García-Soto[a], I. Royo Boronat[b], S. Álvarez de Andrés[c], J.M. García-Moreno[a]

[a] *Department of Neurology, Virgen Macarena Hospital, Sevilla, Spain*

[b] *Reference Laboratory SA, Hospitalet de Llobregat, Barcelona, Spain*

[c] *Spanish National Cancer Research Centre (CNIO), Madrid, Spain*

E-mail address: alejandro.fuerte.sspa@juntadeandalucia.es (A. Fuerte-Hortigón).

* Corresponding author at: 0000-0003-3634-7076. C/José Laguillo 29, 3rd portal. 4°A, 41008, Spain.