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A Second Case With the V374A *KCND3* Pathogenic Variant in an Italian Patient With Early-Onset Spinocerebellar Ataxia

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Abstract

Background and Objectives

To date, approximately 20 heterozygous mainly loss-of-function variants in *KCND3* have been associated with spinocerebellar ataxia (SCA) type 19 and 22, a clinically heterogeneous group of neurodegenerative disorders. We aimed at reporting the second patients with the V374A *KCND3* mutation from an independent family, confirming its pathogenic role.

Methods

We describe the clinical history of a patient with SCA and conducted genetic investigations including mitochondrial DNA analysis and exome sequencing.

Results

This male patient was reported to have unstable gait with tremors at the lower limbs and dysarthric speech since childhood. A neurologic examination also showed dysarthria, nystagmus, action tremor, dysmetria, and weak deep tendon reflexes. He had marked cerebellar atrophy at brain MRI, more evident at vermis. Molecular analysis, including exome sequencing and an in silico panel analysis of genes associated with SCA, revealed the c.1121T>C [p.V374A] mutation in *KCND3*.

Discussion

This report consolidates the pathogenicity of the V374A *KCND3* mutation and suggests that the ataxic paroxysmal exacerbations are not a key phenotypic feature of this mutation.

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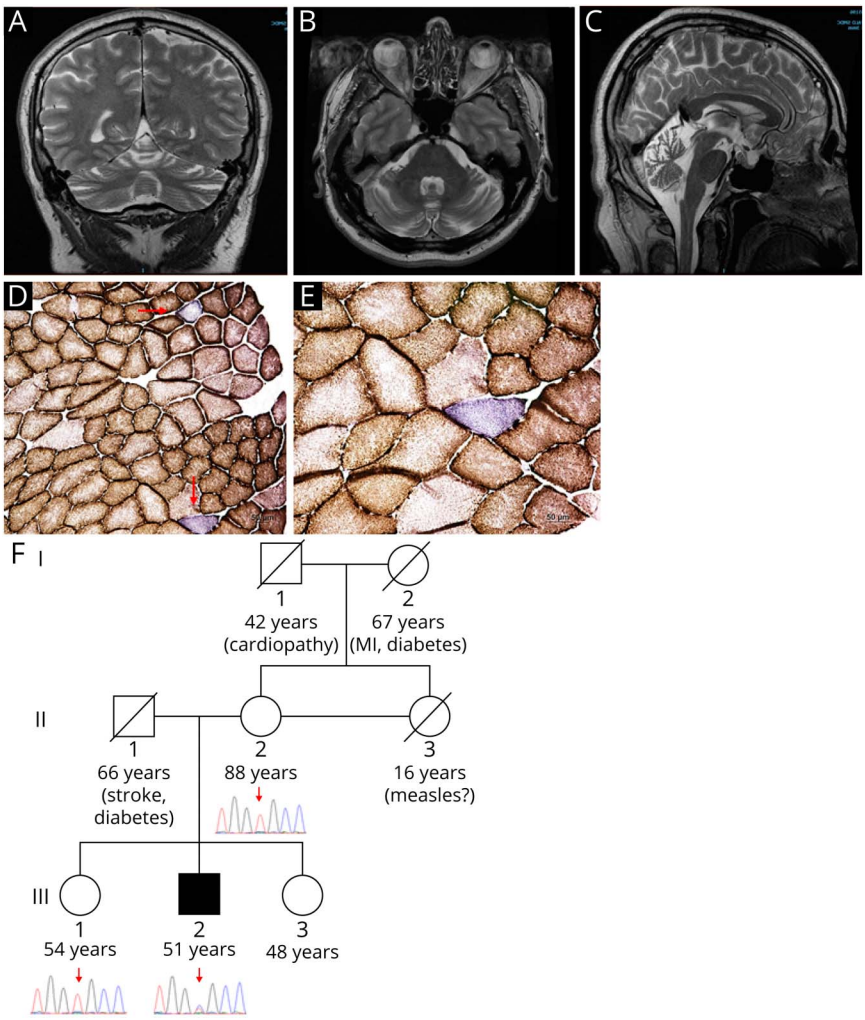
KCND3 gene encodes the voltage-dependent potassium channel Kv4.3, an alpha subunit of the Shal family of A-type K^+ channels, essential in membrane repolarization in excitable cells. Heterozygous loss-of-function mutations in *KCND3* have been associated with spinocerebellar ataxia type 19 and 22 (SCA19/22), a clinically heterogeneous group of neurodegenerative disorders characterized by variable degrees of cerebellar ataxia, parkinsonism, cognitive dysfunction, epilepsy, and extrapyramidal signs (MIM#607346).[1-3] Recently, it has been reported a case with paroxysmal ataxia exacerbations carrying the heterozygous pathogenic variant V374A in the *KCND3* gene.[4] In this study, we present a second case carrying the same pathogenic variant, confirming this genotype-phenotype association.

Case Report

This male patient, now aged 50 years, with a negative family history, had unstable gait with tremors at the lower limbs and dysarthric speech since childhood. Our first evaluation was at age 40 years. A neurologic examination showed dysarthria, nystagmus in all directions of gaze, action tremor, dysmetria, weak deep tendon reflexes, truncal ataxia, ataxic gait, and instability in upright position with a positive Romberg sign. He also had bilateral pes cavus. He had marked cerebellar atrophy at brain MRI, more evident at vermis (Figure, A–C). Somatosensory-evoked potential displayed slightly increased time in cortical responses. At the last cognitive evaluation in 2017, the Mini-Mental Status Exam score and the score at the Brief Test of Cognition (IQ at the lower range of the normal values) were normal. At the Brief Neuropsychological Examination test, the patient presented a mild intellectual disability with abnormalities in attentive/executive functions, unchanged compared with the cognitive evaluation in 2010. The abnormalities in executive/praxic functions are likely due to a deficit in planning strategies. EMG, EEG, and ECG findings and audiometry and ophthalmologic examination findings were normal. Polysomnography revealed the presence of moderate sleep apnea syndrome. The patient is overweight (weight: 125

Figure Clinical, Histologic, and Genetic Findings of the Patient



(A–C) Brain MRI shows severe cerebellar atrophy more evident at vermis. (D and E) Muscle biopsy (cytochrome c oxidase/succinic dehydrogenase staining) of the patient performed at the age of 39 years showed scattered cox-negative fibers (red arrows). (F) Chromatogram showing *KCND3* c.1121T>C segregation within the family in available members. Ages represent age at death (for those marked as deceased) or current age. Moreover, major clinical features are also indicated. MI = myocardial infarction.

Table 1 Clinical Features of Patients With *KCND3* V374A Mutation

V374A patients	Present case	II:1[4]	I:1[4]
Ataxia	+	+	+
Dysarthria	+	+	+
Onset/current age (years)/sex	6/50/M	25/35/M	46/62/F
Deep tendon reflexes	Weak	Normal	Normal
Cognitive impairment	Mild (verbal logic and constructive apraxia)	+	+
Nystagmus	+	+	+
Other features	Moderate obstructive sleep apnea syndrome, action tremor, dysmetria, bilateral pes cavus	Paroxysmal ataxia exacerbation; lower limb hypertonus	Mild hand posturing
EEG	Normal	Slow activity in temporoparietal regions	Moderate diffuse slow activity
EMG	Normal		
ECG	Normal	Normal	Normal
Brain MRI	Severe cerebellar atrophy (vermis)	Severe cerebellar atrophy (vermis and superior part of the cerebellar hemispheres)	Mild atrophy in the cerebellum (vermis and superior cerebellar peduncles)

kg). Initially investigated for mitochondrial disease, lactic acid was normal, whereas 3 cytochrome c oxidase (COX)-negative fibers were noted at muscle biopsy (Figure, D and E). A complete sequencing of mitochondrial DNA (mtDNA) extracted from skeletal muscle did not show any pathogenic variant (haplogroup U2e2a1c) and pathologic accumulation of macrodeletions. Finally, the mtDNA copy number assessment was normal. The only noticeable result was a relative increase of 7S DNA. Assessment of coenzyme Q in muscle biopsy was also normal.

Genetic investigation was then expanded to exome sequencing, and an in silico panel analysis of genes associated with spinocerebellar ataxia (SCA) revealed the presence of a heterozygous missense variant, c.1121T>C [p.V374A], in *KCND3* (NM_004980.5). This variant has not been reported in the gnomAD database and was predicted to be damaging with a 24.4 CADD-PHRED score. According to the American College of Medical Genetics classification, the c.1121T>C was classified as likely pathogenic with the PM1, PM2, PP2, and PP3 criteria. Segregation analysis was consistent with a possible de novo origin of the V374A variant in the patient because available relatives tested were negative and neurologic disturbances were never reported in the parents and siblings (Figure, F).

Data Availability

Anonymized data not published here will be made available by request from any qualified investigator.

Discussion

We reported an independent case of SCA associated with the V374A variant in *KCND3* gene. The cases originally described were a mother and a son (index case) diagnosed with adult-onset slowly progressive cerebellar ataxia, bradyphrenia, and normal general intellectual ability despite low results in cognitive tests.[4] Both presented cerebellar atrophy, more severe in the index case, with moderate-to-severe cerebellar hypometabolism (Table 1). Notably, the index case experienced paroxysmal ataxia exacerbations responsive to acetazolamide when exposed to accelerations/decelerations. The V374A pathogenicity was confirmed in vitro: electrophysiology studies showed that the V374A variant was nonfunctional and caused a conductance reduction predicted to generate an increased Purkinje neuron firing frequency.[4] This family presented an additional A671V variant in the *KCNC3* gene (SCA13), for which a potential synergistic effect was excluded in vitro.

Our patient, differently from those described by Paucar et al., was affected by early-onset cerebellar ataxia, which progressively worsened, apparently without paroxysmal exacerbations. Notably, mild abnormalities in cognitive testing were also observed. The finding of rare COX-negative fibers and increased 7S DNA may be envisaged as secondary reflection on mitochondrial metabolism due to dysfunctional energy-consuming ion channeling. To date, approximately 20 mutations SCA19/22 have been described in patients with heterogeneous clinical presentations, mainly including cerebellar ataxia, cognitive dysfunction, and movement disorders such as parkinsonism (Table 2).

In conclusion, our case consolidates the pathogenicity of this mutation, with a substantially overlapping phenotype except for the paroxysmal exacerbations, for which a synergistic effect of the A671V in *KCNC3* gene cannot be completely excluded, and the onset of the disease.

Table 2 Clinical Features and Inheritance of Patients With *KCND3* Mutations

KCND3 variant	Clinical feature	Inheritance
p.K214R	Episodic gait disorder, vertigo, paraesthesia, pyramidal signs, abnormal ocular movement	AD with incomplete penetrance
p.F227 deletion	Slowly progressive cerebellar ataxia, onset from teenage to middle age; oculomotor abnormalities, pyramidal signs parkinsonism, epilepsy, or cognitive impairment have been reported in some cases	AD, recurrent mutation
p.R293_F295 duplication	Early-onset cerebellar ataxia, intellectual disability, oral apraxia, and epilepsy	De novo mutation
p.S301P	Early onset forms with neurodevelopmental disorder, epilepsy, parkinsonism-dystonia, and ataxia in adulthood	Apparently de novo mutation
p.C317Y	Cerebellar ataxia onset at teenage, developmental delay, intellectual disability, myoclonus, and dystonia	De novo mutation
p.V338E	Adult-onset cerebellar ataxia; cognitive dysfunction	AD
p.G345V	Adult-onset cerebellar ataxia; variable pyramidal signs and oculomotor abnormalities	AD with incomplete penetrance
p.S347W	Adult-onset slowly progressive cerebellar ataxia	Undetermined
p.T352P	Mild cerebellar ataxia, cognitive impairment; variable degree of oculomotor disturbance, neuropathy, tremor, and myoclonus	AD
p.I362M	Cerebellar ataxia	AD
p.M365T	Cerebellar ataxia	AD
p.M373L	Adult-onset pure cerebellar ataxia	AD
p.V374A	Progressive cerebellar ataxia and bradyphrenia, cognitive impairment, paroxysmal ataxia exacerbations Cerebellar ataxia, dysarthria, and mild cognitive impairment	AD Apparently de novo mutation
p.P375S	Teenage-onset or adult-onset cerebellar ataxia; cognitive dysfunction, dystonia, and bradykinesia	AD
p.T377M	Adolescent-onset or adult-onset cerebellar ataxia; cognitive impairment in some patients	Recurrent mutation
p.G384S	Cerebellar ataxia, intellectual disability, dystonia, and myoclonus	De novo mutation
p.S390N	Teenage-onset or adult-onset cerebellar ataxia; cognitive dysfunction in some patients	Recurrent mutation
p.V392I	Cerebellar ataxia, intellectual disability, epilepsy, early repolarization syndrome, and paroxysmal atrial fibrillation	Undetermined
p.R419H	Slowly progressive cerebellar ataxia, parkinsonism, and cognitive dysfunction	Sporadic case
p.R431C	Episodic ataxia	Sporadic case
p.L450F	Late-onset cerebellar ataxia and pyramidal signs	AD
p.P633S	Late-onset cerebellar ataxia, decreased reflexes, and vibration sense	Sporadic case

Abbreviation: AD, autosomal dominant.
Adapted from Hsiao et al.[3]

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Disclosure

F. Palombo reports no disclosures. C. La Morgia reports Consultancies for Chiesi Farmaceutici, Regulatory Pharma Net, and Thenewway srl; speaker honoraria from Santhera Pharmaceuticals, Chiesi Farmaceutici, Regulatory Pharma Net, Thenewway srl, First Class srl, and Biologix; and PI/SI for clinical trials sponsored by GenSight Biologics and Santhera. C. Fiorini, L. Caporali, M.L. Valentino, and V. Donadio report no disclosures. R. Liguori acts as a scientific consultant in boards of Argenx BV, Alexion Pharma Italy s.r.l., and UCB Pharma S.p.A. and received speaker honoraria from Amicus Therapeutics s.r.l. and Editree s.r.l. V. Carelli acts as a scientific consultant in boards of GenSight Biologics, Stealth BioTherapeutics, Santhera Pharmaceuticals, and Chiesi and received speaker honoraria from Chiesi and an unrestricted research grant from Stealth BioTherapeutics. Go to Neurology.org/NG for full disclosure.

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Leonardo Caporali, PhD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Programma di Neurogenetica, Italy	Performed mitochondrial studies
Maria Lucia Valentino, MD	IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica, Italy Department of Biomedical and NeuroMotor Sciences (DIBINEM), University of Bologna, Italy	Performed and analyzed muscle biopsy and critical revision of the article
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Valerio Carelli, MD, PhD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Programma di Neurogenetica, Italy Department of Biomedical and NeuroMotor Sciences (DIBINEM), University of Bologna, Italy	Study design, supervised the study, and critical revision of the article

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