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A Novel *KCND3* Variant in a Korean Family With SCA19

Hongmin Ha[a]
Minkyeong Kim[a]
Bora Chung[a]
Chan Hyun Lee[a]
Seung Hwan Oh[b]
Heeyoung Kang[a,c,d]
Oh-Young Kwon[a,c,d]

[a]Department of Neurology, Gyeongsang National University Hospital, Jinju, Korea
[b]Department of Laboratory Medicine, Pusan National University Yangsan Hospital, Yangsan, Korea
[c]Department of Neurology, Gyeongsang National University College of Medicine, Jinju, Korea
[d]Institute of Health Science, Gyeongsang National University College of Medicine, Jinju, Korea

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Correspondence
Oh-Young Kwon, MD, PhD
Department of Neurology, Gyeongsang National University College of Medicine, 15 Jinju-daero 816beon-gil, Jinju 52727, Korea
Tel +82-55-750-8288
Fax +82-55-750-1709
E-mail oykwon@gnu.ac.kr

Minkyeong Kim, MD, PhD
Department of Neurology, Gyeongsang National University Hospital, 79 Gangnam-ro, Jinju 52727, Korea
Tel +82-55-750-9582
Fax +82-55-750-1709
E-mail doctorminmd@gmail.com

Dear Editor,

Spinocerebellar ataxias (SCAs) are autosomal dominant (AD) hereditary diseases with 48 subtypes identified to date.[1] Genetically, SCAs are divided into trinucleotide repeat (TNR) expansions and nonrepeat mutations. Polyglutamine repeat mutations are a major cause of SCAs, and missense mutations, deletions, and duplications also lead to SCAs.[1,2] Since SCAs present with heterogeneous clinical features that overlap different subtypes,[2] genetic tests are useful for a definitive diagnosis.

SCA19 (MIM 607346) is an adult-onset cerebellar ataxia due to a missense mutation in *KCND3*. We identified a Korean family with SCA19 harboring the novel c.1054A>G (p.T352A) variant in *KCND3* (*NM_004980.5*).

A 44-year-old male complained of progressive gait disturbance that began in his early twenties. He had never suffered from any perinatal events, developmental delays, or seizures. He presented with saccadic pursuit, hypermetric saccades, cerebellar dysarthria, limb ataxia, and hyperreflexia (Supplementary Video 1 in the online-only Data Supplement). His score on the International Cooperative Ataxia Rating Scale was 43, with the following subscores: static, 17; limb coordination, 19; dysarthria, 4; and oculomotor, 3. His modified Barthel Index score was 81, indicating that he required assistance to ensure safe walking (Supplementary Table 1 in the online-only Data Supplement). Brain magnetic resonance imaging showed diffuse cerebellar atrophy (Fig. 1A).

The proband's family history suggested an AD trait, since his mother, two older sisters, grandfather, and two uncles on his mother's side were also affected (Fig. 1B). Dysarthria, unsteadiness, or hand incoordination appeared in the third or early in the fourth decade of life, and the symptoms progressed slowly without affecting daily activities (Supplementary Table 1 in the online-only Data Supplement).

The patient's mother had previously tested negative in an SCA panel test that included SCA1, SCA2, SCA3, SCA6, SCA7, and SCA8. We therefore conducted next-generation sequencing on the proband, which identified the c.1054A>G (p.T352A) variant in *KCND3* (Fig. 1C). This variant had not been reported in the following databases: the Genome Aggregation Database (https://gnomad.broadinstitute.org), the Korean Reference Genome Database (https://coda.nih.go.kr/coda/frt/index.do), PubMed (https://pubmed.ncbi.nlm.nih.gov), or the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php).

The variant was predicted to be deleterious by in silico analysis tools: SIFT (https://sift.bii.a-star.edu.sg), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), and MutationTaster (https://www.mutationtaster.org). Sanger sequencing confirmed that this variant was present in the mother and the symptomatic sisters (Fig. 1C), but absent in the asymptomatic sister. According to the American College of Medical Genetics guideline, the variant was classified as likely pathogenic based on the following criteria: PM1, PM2, PM5, PP2, and PP3.

KCND3 mutations may result in both loss and gain of function, as seen in cases of SCA19

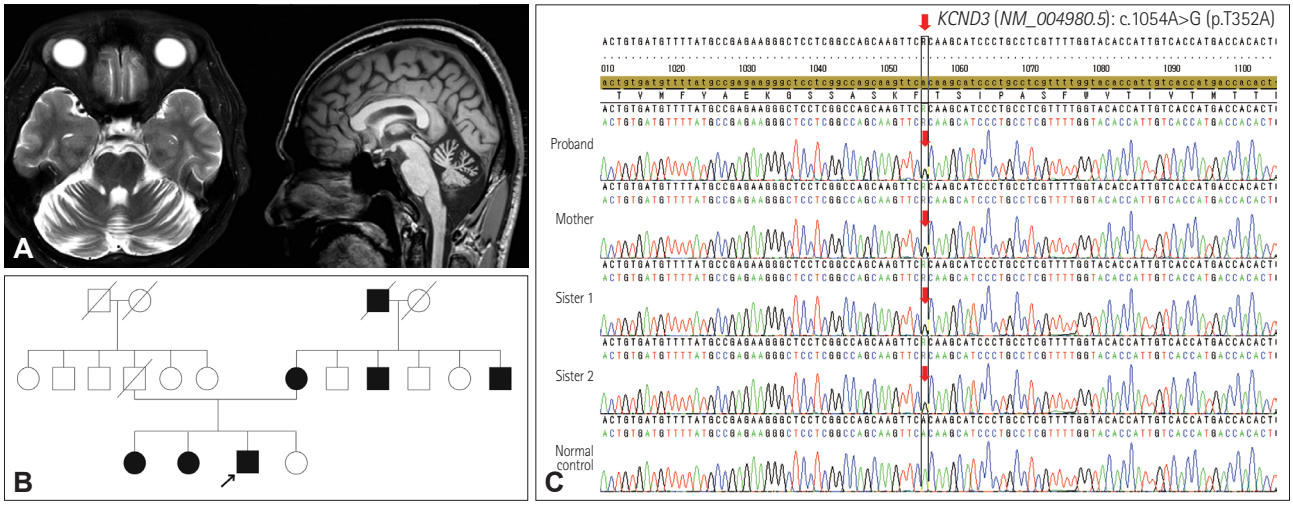

Fig. 1. Brain magnetic resonance imaging (MRI) and the family pedigree of the proband, and electropherograms of the proband and family members. A: Brain MRI of the proband revealed diffuse cerebellar atrophy. B: The family pedigree of the 44-year-old male (arrow) showed an autosomal dominant inheritance pattern. C: Electropherograms illustrating the c.1054A>G (p.T352A) missense mutation in *KCND3* that was detected as a heterozygous peak (arrow) in the proband, his mother, and his symptomatic sisters.

and Brugada syndrome 9, respectively.[3] *KCND3* encodes Kv4.3, an alpha subunit of the Shal family of the A-type voltage-gated potassium channel.[3] Approximately 70 cases of *KCND3*-related neurological disorders have been reported, with diverse onset ages and additional phenotypes including parkinsonism, cognitive decline, and epilepsy (Supplementary Table 2 in the online-only Data Supplement).[4] The clinical heterogeneity may be associated with pathological evidence variously involving the cerebellar Purkinje cell layer, substantia nigra pars compacta, nucleus raphe interpositus, and cerebral cortex.[5]

As described in Supplementary Table 2 (in the online-only Data Supplement), we were unable to find links between specific nucleotide or amino acid alterations and clinical features. Patients with the p.T352P variant, which is a missense mutation in the same extracellular loop of *KCND3* as that of our family case, present with complex phenotypes,[6] and those with the p.T377M variant demonstrate diverse clinical characteristics.[7] Even within our family case, a genotype–phenotype association could not be determined; the proband had additional pyramidal tract involvement while the other affected family members showed pure cerebellar ataxia.

In summary, we report a novel variant in *KCND3* in a Korean family with SCA19. When a patient exhibits cerebellar ataxia with apparent AD inheritance, both TNR and non-TNR SCAs should be considered in the differential diagnosis.

Supplementary Video Legend

Video 1. Findings of a neurological examination of the proband. The patient had gaze-evoked nystagmus, saccade pursuit, hypermetric saccades, and limb ataxia. His gaze-evoked nystagmus was transient. With his feet together, he was very unstable and fell when he closed his eyes. He exhibited a wide-base gait, and he could not perform a tandem gait. The patellar reflex increased bilaterally, but Babinski and Chaddock signs were absent.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.1.90.

Ethics Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of the Gyeongsang National University Hospital (No. 2021-05-005) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A waiver of informed consent was granted by the Institutional Review Board of the Gyeongsang National University Hospital, Korea.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

ORCID iDs

Hongmin Ha https://orcid.org/0000-0002-7348-7863
Minkyeong Kim https://orcid.org/0000-0001-8376-867X
Bora Chung https://orcid.org/0000-0001-7139-2919
Chan Hyun Lee https://orcid.org/0000-0003-0330-175X
Seung Hwan Oh https://orcid.org/0000-0002-1946-9939
Heeyoung Kang https://orcid.org/0000-0001-5404-1674
Oh-Young Kwon https://orcid.org/0000-0001-9576-1926

Author Contributions

Conceptualization: Minkyeong Kim, Oh-Young Kwon. Data curation: all authors. Formal analysis: Minkyeong Kim, Seung Hwan Oh. Investigation: all authors. Methodology: Hongmin Ha, Minkyeong Kim, Seung Hwan Oh, Oh-Young Kwon. Project administration: Minkyeong Kim, Oh-Young Kwon. Supervision: Minkyeong Kim, Oh-Young Kwon. Validation: Minkyeong

Kim, Seung Hwan Oh, Oh-Young Kwon. Visualization: Minkyeong Kim, Oh-Young Kwon. Writing—original draft: Hongmin Ha, Minkyeong Kim, Seung Hwan Oh, Oh-Young Kwon. Writing—review & editing: Hongmin Ha, Minkyeong Kim, Seung Hwan Oh, Oh-Young Kwon.

Conflicts of Interest

Oh-Young Kwon, an assoicate editor of the *Journal of Clinical Neurology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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Supplementary Table 1. Clinical characteristics of the proband with spinocerebellar ataxia 19 and affected family members

Characteristics	Proband	Mother	Sister 1	Sister 2
Onset age (yr)	20	20	25	35
Sex	Male	Female	Female	Female
Initial symptom	Imbalance	Dysarthria	Gait disturbance	Hand clumsiness
Age at enrollment (yr)	44	69	50	47
Disease duration at enrollment (yr)	24	49	25	12
Education duration (yr)	12	6	7	10
Ataxia	Yes	Yes	Yes	Yes
ICARS score (static/limb coordination/ dysarthria/oculomotor)	43 (17/19/4/3)	23 (7/12/4/0)	23 (6/13/2/0)	35 (8/19/4/4)
Spontaneous nystagmus	No	No	No	No
Gaze-evoked nystagmus	Yes, transient	No	No	Yes
Saccadic pursuit	Yes	No	No	Yes
Saccadic dysmetria	Yes	No	No	Yes
Parkinsonism	No	No	No	No
Dystonia	No	No	No	No
Myoclonus	No	No	No	No
Chorea	No	No	No	No
Pyramidal signs	Yes	No	No	No
Hyporeflexia	No	No	No	No
Urinary incontinence	Yes	Yes	No	No
Constipation	No	No	No	No
Glabellar sign/snout reflex/applause sign	No	No	No	No
K-MMSE score	30	24	28	29
K-MoCA score	28	15	26	28

ICARS, International Cooperative Ataxia Rating Scale; K-MMSE, Korean version of the Mini Mental State Examination; K-MoCA, Korean version of the Montreal Cognitive Assessment.

Supplementary Table 2. Review of studies on *KCND3*-related neurological disorders and the present case

No.	Nucleotide change	Amino acid change	ACMG	dbSNP	No. of cases	Ethnicity	Life stage at onset	Sex (M:F)	Clinical features	References
1	Not identified	Not identified			10	Chinese	Adulthood	4:6	Cerebellar ataxia, dysarthria, hyporeflexia	1, 2
2	c.641A>G	p.K214R	VUS	rs142744204	1	European	Adulthood	1:0	Episodic cerebellar ataxia, oculomotor abn, pyramidal sg, sensory abn	3
3	c.680_682delTCT	p.F227del	LP	rs397515475	14	Chinese	Adolescence, adulthood	NA	Cerebellar ataxia, oculomotor abn, dysarthria, dysphagia	4
					10	French	Adulthood	NA	Cerebellar ataxia, oculomotor abn, dysarthria, pyramidal sg, sensory abn, tremor, parkinsonism, autonomic dysfunction	4
					16	French	Childhood to adulthood	7:9	Cerebellar ataxia, oculomotor abn, dysarthria, pyramidal sg, parkinsonism, cognitive decline, seizure	5
4	c.877_885dupCGCGTCTTC	p.V294_R296dup	LP	-	1	Belgian	Childhood	1:0	Cerebellar ataxia, oculomotor abn, dysarthria, dysphagia, myoclonus, cognitive decline, seizure	6
5	c.901T>C	p.S301P	LP	rs79821338	1	Italy	Childhood	1:0	Cerebellar ataxia, oculomotor abn, dystonia, tremor, parkinsonism, cognitive decline, seizure	7
6	c.950G>A	p.C317Y	LP	rs1571939905	1	Taiwanese	Infancy	0:1	Cerebellar ataxia, dystonia, myoclonus, cognitive decline, developmental delay	8
7	c.1013T>C	p.V338E	LP	rs1571939827	3	Japanese	Adulthood	NA	Cerebellar ataxia, dysarthria,	4
8	c.1034G>T	p.G345V	LP	rs797045634	3	Japanese	Adulthood	NA	Cerebellar ataxia	4
					1	Ashkenazi Jewish American	Adulthood		Cerebellar ataxia, oculomotor abn, dysarthria, pyramidal sg	
9	c.1054A>C	p.T352P	LP	rs397515476	13	Dutch	Adulthood	10:3	Cerebellar ataxia, oculomotor abn, pyramidal sg, sensory abn, myoclonus, tremor, cognitive decline	2, 9-11
10	c.1086T>G	p.I362M	LP	-	1	NA	NA	NA	NA	12
11	c.1094T>C	p.M365T	LP	-	1	NA	NA	NA	NA	12
12	c.1119G>A	p.M373I	LP	rs397515477	3	Dutch	Adulthood	2:1	Cerebellar ataxia, dysarthria	11
13	c.1121T>C	V374A	LP	-	2	Swedish	Adulthood	1:1	Cerebellar ataxia, oculomotor abn, dysarthria, cognitive decline	13
14	c.1123C>T	p.P375S	LP	rs1571636508	2	Taiwanese	Adolescence, adulthood	1:1	Cerebellar ataxia, oculomotor abn, dysarthria, blepharospasm, dystonia, cognitive decline	8
15	c.1130C>T	p.T377M	P	rs1571636501	4	Japanese	Adulthood	NA	Cerebellar ataxia, oculomotor abn, dysarthria, pyramidal sg	4
					1	Norwegian	Adolescence	0:1	Cerebellar ataxia, oculomotor abn	
					4	Swedish	Childhood, adolescence	2:2	Cerebellar ataxia, oculomotor abn, dysarthria, dysphagia, pyramidal sg, sensory abn	
16	c.1150G>A	p.G384S	LP	-	1	Japanese	Infancy	1:0	Cerebellar ataxia, oculomotor abn, dysarthria, pyramidal sg, dystonia, myoclonus, cognitive decline, developmental delay	14
17	c.1169G>A	p.S390N	LP	rs397515478	3	Dutch	Adulthood	2:1	Cerebellar ataxia, oculomotor abn, dysarthria, pyramidal sg, cognitive decline	11
18	c.1291C>T	p.R431C	VUS	rs777183510	1	Korean	Adolescence	0:1	Episodic cerebellar ataxia, oculomotor abn, dysarthria	15
19	c.1348C>T	p.L450F	VUS	rs780988439	1	French	Adulthood	1:0	Cerebellar ataxia, pyramidal sg	16
					1	NA	NA	NA	NA	12
20	c.1897C>T	p.P633S	VUS	rs397515478	1	NA	NA	NA	NA	12
21	c.1054A>G	p.T352A	LP	-	4	Korean	Adulthood	1:3	Cerebellar ataxia, oculomotor abn, dysarthria, pyramidal sg	Current case

abn, abnormalities; ACMG, American College of Medical Genetics and Genomics; dbSNP, Single-Nucleotide Polymorphisms Database; F, female; LP, likely pathogenic; M, male; NA, not available; P, pathogenic; sg, sign; VUS, variants of uncertain significance.

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