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LETTER TO THE EDITOR

Spinocerebellar Ataxia 13 Presenting with Pure Cerebellar Syndrome in a Korean Family

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Dear Editor,

Spinocerebellar ataxia 13 (SCA13) is a rare cause of autosomal-dominant cerebellar ataxia, which is caused by a heterozygous mutation in the *KCNC3* gene, which results in voltage-gated potassium channel (Kv3.3) dysfunction.[1] A French pedigree with childhood-onset ataxia and cognitive decline and a Filipino pedigree with adult-onset ataxia were separately reported and later found to share a mutated gene, *KCNC*.[1] Additional SCA13 cases were subsequently reported; they were characterized by childhood- to adult-onset progressive ataxia with occasional cognitive decline and/or seizures. In this study, we describe a mother-daughter pair with SCA13 (Figure 1C) who demonstrated adolescent-onset pure cerebellar ataxia. This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital, Korea (05-2020-075).

A 42-year-old woman visited our clinic with progressive unsteadiness starting during her mid-teens. Developmental delays or seizures were ruled out. She denied any similar symptoms in her parents or siblings. Neurological examination revealed cerebellar-type dysarthria, spontaneous and gaze-evoked nystagmus, slow saccades, limb ataxia, and ataxic gait. The Scale for the Assessment and Rating of Ataxia (SARA) score was 8. Other neurological abnormalities, such as pyramidal or extrapyramidal signs or sensory loss, were not observed. Deep tendon reflexes were normal. Cognition was grossly intact; the Mini-Mental State Examination and Montreal Cognitive Assessment scores were 29 and 28, respectively. She could walk independently and perform most of the activities in daily life. Brain magnetic resonance imaging (MRI) demonstrated diffuse cerebellar atrophy; the brainstem and middle cerebellar peduncles were relatively unaffected (Figure 1A).

Her 13-year-old daughter also exhibited pure cerebellar ataxia with the SARA score of 5. The perinatal history was unremarkable. Cognitive and motor developmental milestones were normal, and her school performance was similar to the class average. No history of seizure was reported. The results of electroencephalography, nerve conduction studies, and ophthalmoscopic examination were normal. Diffuse cerebellar cortical atrophy was noted on the brain MRI (Figure 1B).

Genetic tests for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA17, and dentatorubral-pallidoluysian atrophy were normal. Next-generation sequencing using an ataxia panel identified a pathogenic variant, c.1268G>A (p.R423H) in the *KCNC3* gene in the daughter. This result was verified with Sanger sequencing in the mother (Figure 1D).

Thus far, SCA13 has been identified in approximately 50 patients; genotype-phenotype correlations are not yet applicable due to the limited number of cases. In addition, patients demonstrated variable ages of onset and heterogeneous clinical features, which are illustrated in the supplementary material.

p.R423H resides in the transmembrane domain (S4), and a previous functional study revealed that the mutation produced a nonfunctional protein with a strong dominant-negative effect when coexpressed with wild-type KCNC3.[2] Five patients were

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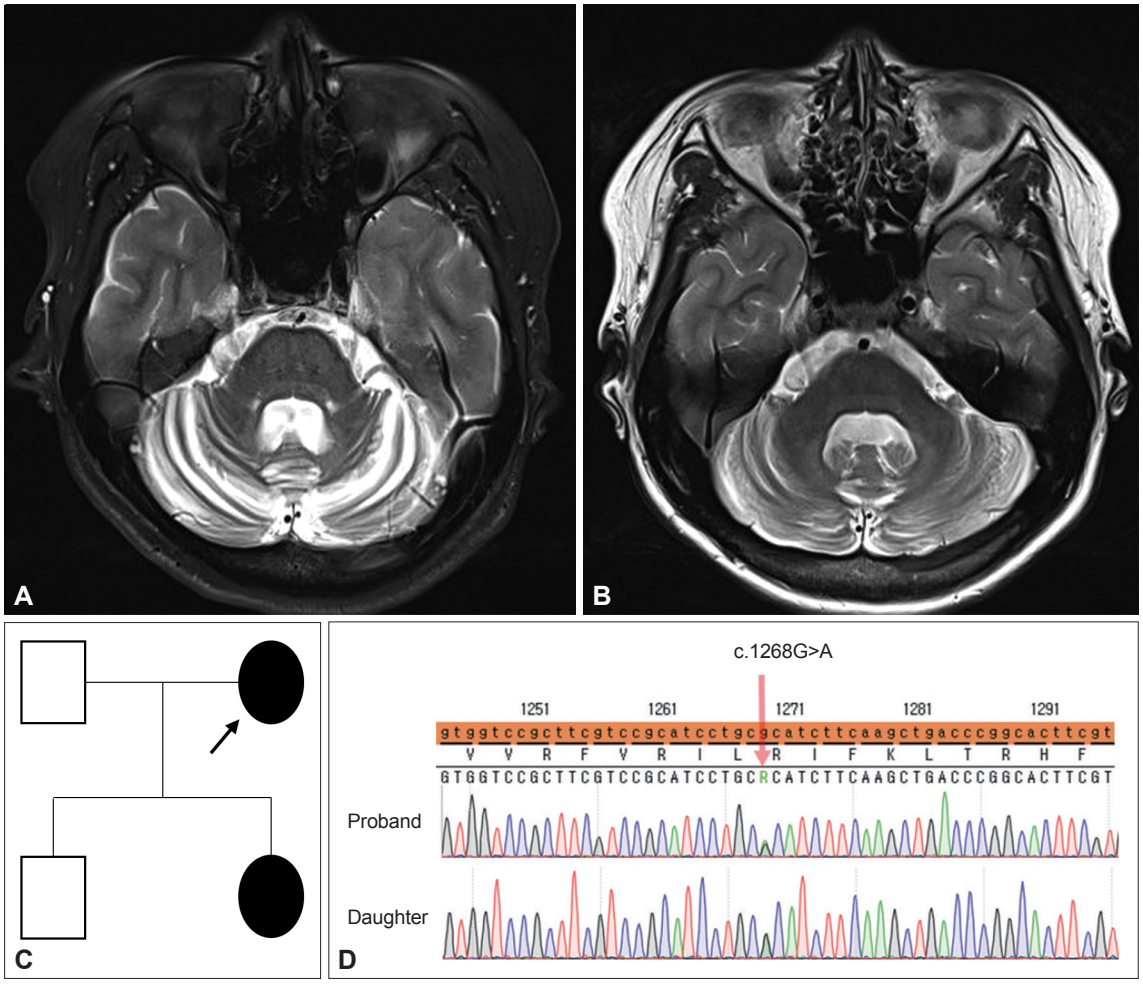

Figure 1. Family pedigree, imaging, and genetic results. A: Brain magnetic resonance imaging (MRI) of the mother demonstrated prominent cerebellar atrophy, while the brainstem and middle cerebellar peduncles were relatively preserved (T2-weighted axial image). B: Brain MRI of the daughter showed diffuse cerebellar cortical atrophy (T2-weighted axial image). C: The patients' family pedigree shows that only the proband and her daughter were affected. D: An electropherogram illustrated a missense mutation (c.1268G>A, p.R423H) of the *KCNC3* gene in the mother, which verified the ataxia panel sequencing result of the daughter (heterozygous peaks, arrow).

reported to have the variant p.R423H, which was characterized by infantile or early childhood onset and slowly progressive ataxia.[2-5] However, the other clinical characteristics were diverse. Patients with European ancestry demonstrated hyperreflexia in one case and motor developmental delay in three cases; brain MRI was performed in only one patient at the age of 3, which yielded normal results.[2] In an American family, pyramidal signs, delayed motor milestones, and cerebellar atrophy in brain MRIs were found both in a mother and a son, while seizure and cognitive decline were exclusively observed in the son.[3] Another patient from Germany showed hyperreflexia, mild cognitive decline, and slow motor development; their family history was negative.[4] Myoclonus has been frequently observed in SCA13 patients in France; thus, the authors suggested that SCA13 could be categorized as mild-progressive myoclonus ataxia that differed from typical progressive myoclonus epilepsy.[5] In contrast, our patients only manifested cerebellar ataxia starting in childhood.

KCNC3 encodes Kv3.3, which is expressed in granule cells, Purkinje cells, and deep cerebellar nuclei of the cerebellum.[6] Kv3.3 assists with rapid repolarization without a refractory period, which is important for the rapid firing of cerebellar neurons. Its deficiency causes incoordination or myoclonus.[6] The action of Kv3.3 is regulated by, or associated with, other proteins such as protein kinase C or Kv3.1.[2,7] Therefore, individual or ethnic differences in these factors may contribute to heterogeneous clinical manifestations, even in the same family. Furthermore, the Purkinje cell-specific restoration of Kv3.3 improved coordination, but twitching persisted in mice.[7] The different distribution of mutant Kv3.3 may explain why myoclonus was only observed in some patients.[5]

To our knowledge, this is the first report of SCA13 patients in Korea who had p.R423H variants and presented with adolescent-onset pure cerebellar syndrome. Additional patients will likely

be identified with various phenotypes, and SCA13 should be considered a genetic etiology of cerebellar ataxia.

Conflicts of Interest

The authors have no financial conflicts of interest.

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None.

Author Contributions

Conceptualization: Minkyeong Kim, Jae-Hyeok Lee. Data curation: Minkyeong Kim, Seun Hwan Oh, Jae Wook Cho. Investigation: Minkyeong Kim, Seun Hwan Oh, Jae Wook Cho, Jae-Hyeok Lee. Methodology: Seun Hwan Oh, Jae-Hyeok Lee. Project administration: Jae-Hyeok Lee. Resources: Jae-Hyeok Lee. Supervision: Jae Wook Cho, Jae-Hyeok Lee. Validation: Seun Hwan Oh. Visualization: Minkyeong Kim, Seun Hwan Oh. Writing—original draft: Minkyeong Kim, Jae-Hyeok Lee. Writing—review & editing: Minkyeong Kim, Seun Hwan Oh, Jae Wook Cho, Jae-Hyeok Lee.

Ethical Standards

All procedures in this study involving human participants were performed in accordance with the ethical standards of the Institutional Review Board of Pusan National University Yangsan Hospital, Korea and with the 1975 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all the patients included in the study.

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