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A Novel *KCNA1* Mutation in an Episodic Ataxia Type 1 Patient with Asterixis and Falls

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Dear Editor,

Episodic ataxia type 1(EA1) is a rare autosomal dominant ion channelopathy with incomplete penetrance that is typically characterized by brief attacks of ataxia and constant myokymia in early childhood.[1] Mutations of the *KCNA1* gene that encodes the Kv1.1 subunit of a potassium channel result in EA1.[2] However, a recent study found that approximately 20% of EA1 patients developed persistent cerebellar dysfunction, and various different clinical features have been reported.[1] Here we report one EA1 patient presenting with unique and atypical symptoms caused by a novel *KCNA1* mutation.

A 51-year-old female presented with progressive gait instability and intermittent falls that first appeared 8 years prior to admission. She had subsequently also developed intermittent involuntary jerking, and occasionally experienced sudden gait unsteadiness followed by falls, leading to multiple bruises. A neurologic examination revealed ataxic dysarthria, unsteady gait, and clumsiness of both hands. She showed episodes of generalized myoclonic seizure, sudden arm-dropping while eating, and falling on the floor without loss of consciousness. These episodes lasted a few seconds and occurred several times daily, and were provoked by exertion or emotional stress. An examination revealed a negative myoclonic movement when she was asked to outstretch her arms with dorsiflexion of the wrists. No vertigo, blurred vision, nausea, headache, limb weakness, parkinsonism, spasticity, myokymia, or neuromyotonia were found. Neurocognitive profiles revealed mild cognitive impairment with independence in functional activities of daily living. No family members were affected (Fig. 1A). Nerve conduction studies and EMG produced unremarkable findings. The EEG revealed generalized polyspike discharges at 3−5 Hz (Fig. 1B). Brain MRI revealed cerebellar atrophy (Fig. 1C).

Genetic testing was performed in the patient using a gene panel containing 30 genes known to be related to hereditary ataxia (*ANO10*, *APTX*, *ATM*, *C10orf2*, *CACNA1A*, *CACNB4*, *COQ8A*, *CYP27A1*, *FGF14*, *ITPR1*, *KCNA1*, *KCNC3*, *KCND3*, *PEX7*, *PNKP*, *PNPLA6*, *POLG*, *PRKCG*, *SACS*, *SETX*, *SIL1*, *SLC52A2*, *SNX14*, *SPG7*, *SPTBN2*, *SYNE1*, *TMEM240*, *TTBK2*, *TTPA*, and *WFS1*). The patient was found to have a novel heterozygous mutation of *KCNA1*: a frameshift mutation of c.791del (p.Pro264LeufsTer 10) (NM_000217.2). The detected variant was classified as pathogenic along with PVS1 (null variant), PM2 (absent from controls), and PP3(computational predictions) according to American College of Medical Genetics and Genomics guidelines.[3] Mutation prediction analysis using the PolyPhen-2 tool showed the novel variant to be probably damaging (Fig. 1D). *KCNA1* analysis in her unaffected younger brother was negative.

EA1 is mainly caused by missense genetic mutations,[4] whereas the present patient had a novel frameshift mutation of *KCNA1*. Although EA1 is the most common diagnosis resulting from a *KCNA1* mutation, patients can also exhibit various clinical features.[5] Besides recurrent ataxic attacks, our patient displayed several peculiar symptoms. She experienced generalized

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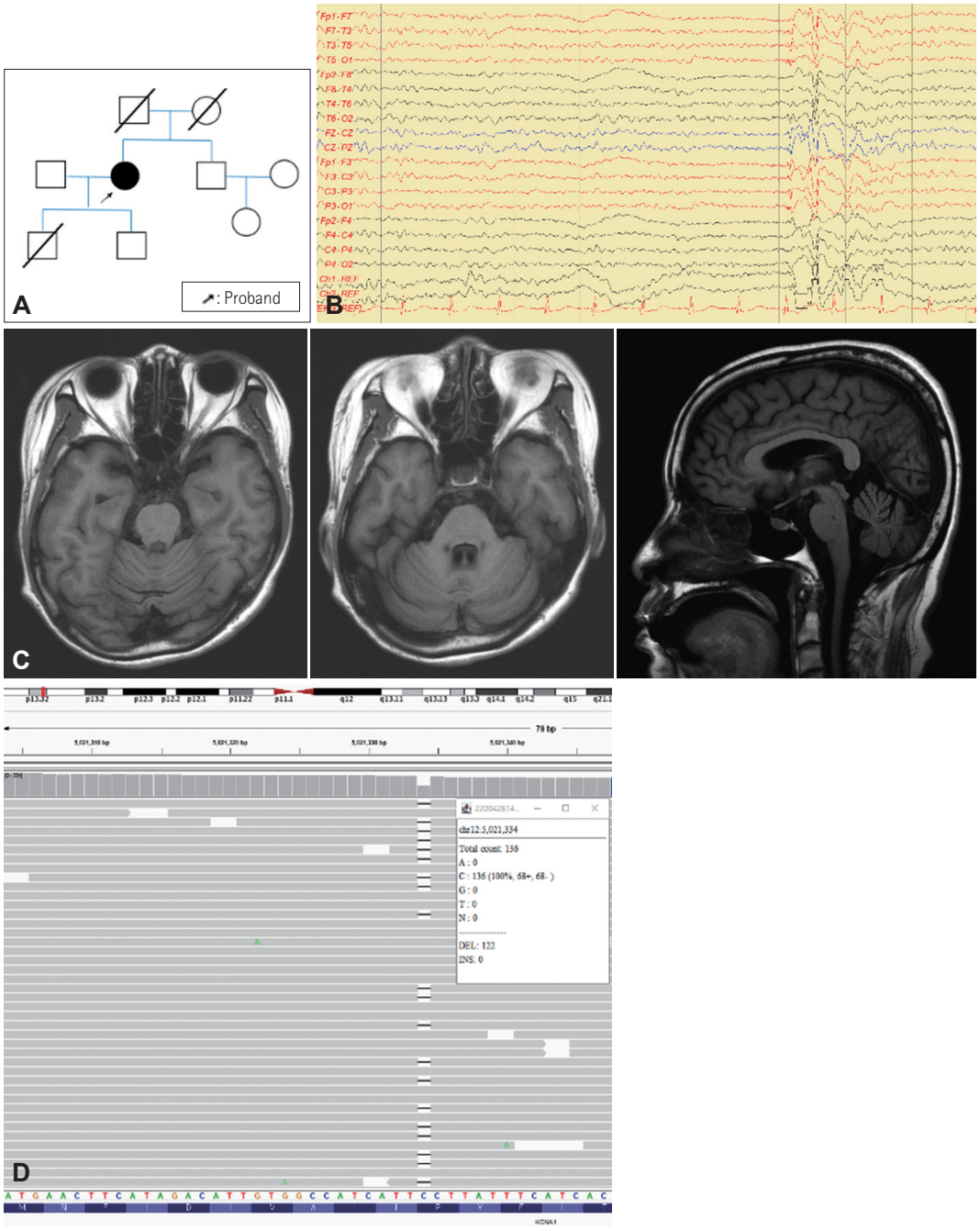

Fig. 1. Pedigree, EEG, brain MRI, and next-generation sequencing of the *KCNA1* mutation. A: There was no family history on the pedigree of the proband. B: EEG signals associated with myoclonic jerks reveal polyspike discharges at 3–5 Hz. C: Brain MRI showed cerebellar atrophy. D: Next-generation sequencing confirmed the heterozygous status for the c.791del (p.Pro264LeufsTer 10) mutation of *KCNA1*.

myoclonic movement,[4] which was considered to be myoclonic epilepsy based on the EEG findings. She also showed asterixis presenting as sudden wrist- or arm-dropping and falls, which had reportedly never occurred previously. Furthermore, myokymia and neuromyotonia were not observed, which are commonly reported in EA1.[1] Persistent cerebellar dysfunction supported by prominent cerebellar atrophy in brain MRI was found, which is unusual in EA1.[1] The frequency of ataxic attacks and myoclonic epilepsy decreased dramatically with levetiracetam administration, but not with acetazolamide. Our proband presented mild cognitive dysfunction related to epileptic encephalopathy, which is also a rare symptom of EA1.[6] To validate the complex phenotype of the causative *KCNA1* mutation, we applied genetic and nongenetic tests to exclude other mutations and the possibilities that the complex phenotype was due to additional disorders. We performed other

genetic tests including those of spinocerebellar ataxia 1, 2, 3, 6, 7, 8, and 17 genes, *DRPLA*, and *RRNP* related to progressive cerebellar ataxia, which were all negative (Supplementary Table 1 in the online-only Data Supplement). Several genes responsible for progressive myoclonic epilepsy with cerebellar ataxia were also negative (Supplementary Table 1 in the online-only Data Supplement). The results of toxicity, metabolism, and neoplasia tests such as for tumor markers, thyroid hormones/antibodies, and vitamins were normal. Furthermore, the patient was negative for serum autoimmune/paraneoplastic antibodies (anti-Hu, anti-Ri, anti-Yo, anti-amphiphysin, anti-CV2, anti-PNMA1, anti-recoverin, anti-SOX1, and anti-titin) and cerebrospinal fluid malignancy. Nongenetic tests were not contributory.

Here we have expanded the genetic and clinical spectrum of EA with asterixis and falls caused by *KCNA1* mutations. We report the first Korean EA1 patient with a novel *KCNA1* mutation. Understanding the pathomechanism of unusual clinical features in this case will require more research into the genotype–phenotype correlation.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.2.333.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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