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A Novel *KCNA1* Variant Manifesting as Persistent Limb Myokymia Without Episodic Ataxia

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Dear Editor,

We read with great interest the article by Lee et al.[1] describing the first Korean episodic ataxia (EA) type 1 patient with a novel *KCNA1* mutation. We report another novel *KCNA1* variant with a rare phenotype: isolated myokymia without either EA or seizure. We also make additional comments on the phenotypic variability in *KCNA1* mutations.

A 39-year-old female presented with continuous muscle twitches involving both thighs with intermittent right-foot dystonia. The muscle twitching had initially started in the right thigh and spread to the left side 1 year later. Her previous medical history included bronchial asthma and several orthopedic surgeries of both ankles and knees after a traffic collision 7 years previously. The family history was unremarkable. A neurologic examination identified continuous involuntary undulating muscle movements in both thighs that was worse on the right side (Supplementary Video 1 in the online-only Data Supplement). She had difficulty walking due to persistent muscle spasms. Muscle weakness, dysarthria, limb dysmetria, and spasticity were not observed. A nerve conduction study revealed normal sensory and motor responses. Needle electromyography showed myokymic discharges in several muscles (including rectus femoris) bilaterally in the lower extremities (Fig. 1A). Overnight polysomnography confirmed persistent muscle twitching during sleep. Routine laboratory testing showed normal creatine kinase and inflammatory markers. Thyroid-stimulating hormone, thyroxine, magnesium, and vitamin D levels were normal. Serologic studies were negative for human immunodeficiency virus and syphilis. An additional evaluation for the differential diagnosis of peripheral nerve hyperexcitability was performed. Paraneoplastic antibodies, tumor markers, and anti-glutamic-acid decarboxylase antibodies were not detected, nor were autoantibodies to leucine-rich glioma inactivated-1 and contactin-associated protein-2. Chest and abdomen computed tomography was unrevealing. An electroencephalogram (EEG) showed occasional frontally predominant generalized delta slowing, which is usually considered a nonspecific EEG pattern. Brain magnetic resonance imaging findings were normal. Given the unremarkable initial workup, genetic testing was conducted. Diagnostic exome sequencing identified a novel variant, c.724G>A (p.Ala242Thr), in *KCNA1* (NM_000217.3) (Fig. 1B). This *KCNA1* variant was predicted to be likely pathogenic based on the American College of Medical Genetics and Genomics guidelines (PM1, PM2, PM5, PP2, and PP3).[2]

KCNA1 mutations are known to be associated with EA1, which is a potassium channelopathy characterized by brief attacks of ataxic gait with interictal myokymia.[3] While the broad clinical spectrum includes EA1 with epilepsy and also epilepsy without EA1,[3] isolated myokymia without EA1 or epilepsy is extremely rare: only two cases of isolated myokymia have been reported,[4,5] and to our knowledge the present case is the first Korean one.

Our case illustrates not only the phenotypic variability but also the complex relationship between phenotype and genotype. The *KCNA1* mutation in our patient is a novel missense mutation (p.Ala242Thr) that is located in the S2 segment of the Kv1.1 (voltage-gated potas-

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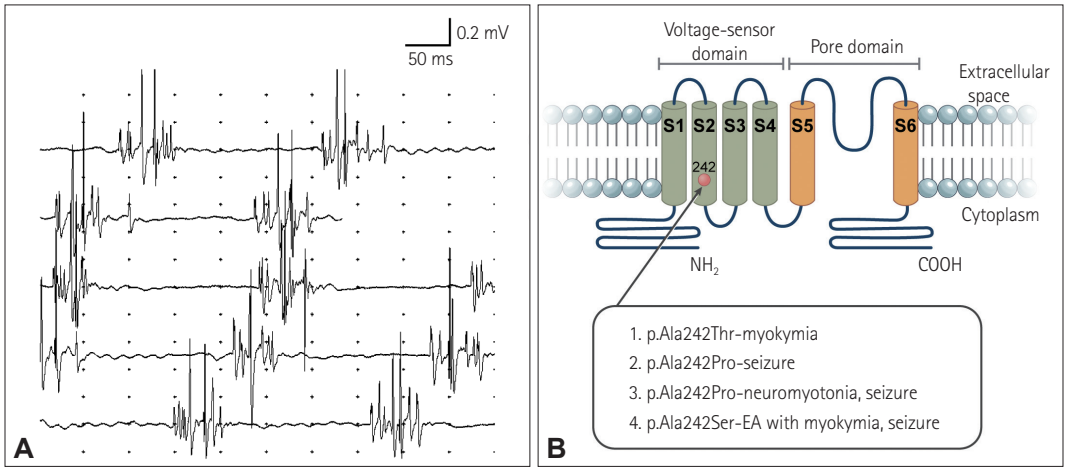

Fig. 1. Needle electromyography findings and schematic representation of the voltage-gated potassium channel (Kv1.1). A: Multiplets and myokymic discharges firing with an intraburst frequency of 40–80 Hz and an interburst frequency of 4 Hz in a patient with persistent thigh-muscle spasms. B: Schematic view of the Kv1.1 alpha subunit. The alpha subunit encoded by *KCNA1* consists of six transmembrane segments (S1–S6). Four segments (S1–S4) comprise the voltage-sensor domain, and two segments (S5 and S6) form an ion-conduction pore domain. Reported cases with mutation at amino acid position 242 are listed in the rounded rectangle (1: current case). More than 47 different *KCNA1* mutations have been identified along the entire length of the protein.[3] EA, episodic ataxia.

sium channel) alpha subunit (Fig. 1B). While four cases (including our case) have been identified as having mutation at the same amino acid position, their phenotypes have differed (Fig. 1B).[5-7] It is noteworthy that substitution at the same amino acid location can lead to different phenotypes. The property of the substituted amino acid, genetic modifier, and non-genetic factors as well as the location of mutation may be involved in determining the phenotypic presentation of the mutation.[3]

This report describes a rare phenotype associated with a novel point mutation in *KCNA1*. Patients harboring *KCNA1* mutations may present with peripheral nerve hyperexcitability syndrome, and isolated myokymia without EA or epilepsy may be the only clinical manifestation. We believe that the present case broadens current perspectives on the phenotypic variability and the complex genotype-phenotype correlation in *KCNA1* mutations.

Supplementary Video Legend

Video 1. Continuous involuntary muscle movements of the patient.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.2.235.

Ethics Statement

Written informed consent was obtained from the patient.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to potentially sensitive personal information but are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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