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# Hereditary Spastic Paraplegia with Axonal Sensorimotor Polyneuropathy in a Korean Family Caused by Pathogenic Variant of *KIF5A* (c.611G>A)

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Dear Editor,

Hereditary spastic paraplegia (HSP) is a heterogeneous group of rare neurodegenerative diseases that are characterized by progressive weakness and spasticity of the lower limbs. Spastic paraplegia 10 (SPG10) is a autosomal dominant HSP with early onset that is caused by pathogenic variants of the kinesin family member 5A gene (*KIF5A*) that encodes the kinesin heavy chain (KHC).[1] Here we report two SPG10 patients carrying a pathogenic missense variant (c.611G>A, p.Arg204Gln), which is a novel variation that has not been reported previously in Korea.

The proband was a 48-year-old man who presented with leg weakness and gait disturbance manifesting as tip-toe walking that had slowly progressed over 18 years. Nerve conduction studies (NCS) were performed to evaluate his symptoms at the age of 36 years, which produced no remarkable findings. Urinary dysfunction that developed in his mid-40s was the only concomitant clinical symptom upon presentation at our center. Neurologic examination revealed muscle weakness, spasticity, and brisk deep tendon reflexes in both legs without sensory symptoms or ataxia. Although he did not show relevant symptoms, NCS revealed axonal sensorimotor polyneuropathy (i.e., subclinical polyneuropathy) (Supplementary Table 1 in the online-only Data Supplement). His electromyography and spinal cord MRI findings were normal.

Targeted next-generation sequencing was performed for 172 genes related to neuromuscular disorders (1023.4x average depth with 99.9% of >30x coverage rate), which revealed 9 rare variants (<5% minor allele frequency). A heterozygous pathogenic variant of *KIF5A* (RefSeq NM_004984.4, c.611G>A; p.R204Q, rs387907287) was identified, and further confirmed by Sanger sequencing, while the other eight variants were classified as variants of unknown significance.

A segregation study was applied to the proband's parents and his 14-year-old son, who had experienced clumsy gait since the age of 8 years without other clinical manifestations, and who was found to carry the same heterozygous pathogenic variant (Fig. 1).

Recent advances in genetic analyses have led to increasing reports of HSP caused by pathogenic variants of *KIF5A*. Most previously reported HSP patients related to pathogenic variant c.611G>A have been childhood- or juvenile-onset cases presenting with complex HSP manifestations such as overt sensory symptoms or cognitive dysfunction.[2-4] However, Goizet et al.[5] reported three patients with adult-onset HSP carrying pathogenic variant c.611G>A in *KIF5A*, suggesting that not all c.611G>A variants are childhood- or juvenile-onset cases. Our proband lend support to this report, since he developed symptoms at the age of 30 year, while his son had childhood-onset HSP. We therefore surmise that this variant shows a highly variable age at onset rather than having a preferential age range, implying that a long-term

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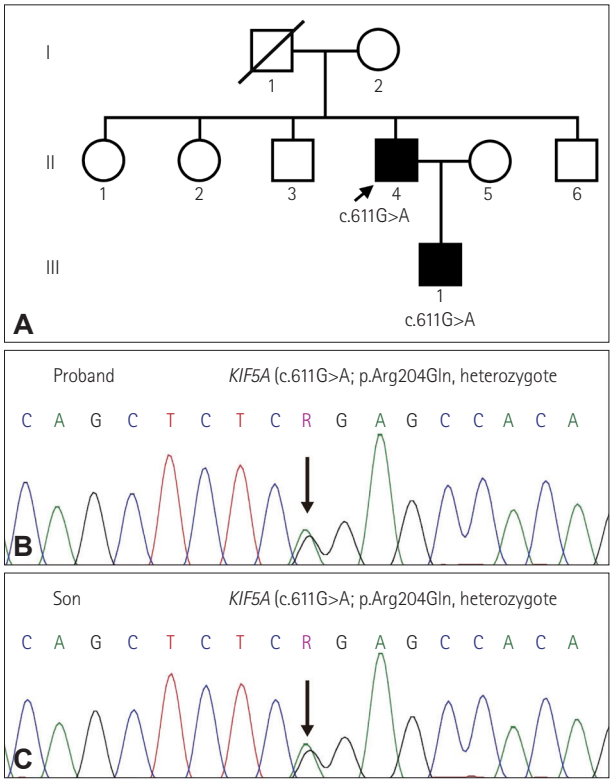


**Fig. 1.** Family pedigree and sequencing chromatogram analysis. (A) Family pedigree of hereditary spastic paraplegia (HSP) with pathogenic variant of the kinesin family member 5A (*KIF5A*) gene. The pedigree indicates an autosomal dominant inheritance pattern (arrow indicates the proband). Both the proband and his son presented with clinical manifestations of HSP, but with differences in their onset ages (30 years vs. 8 years) and disease severities. Confirmatory sequencing chromatograms of the heterozygous missense variant in *KIF5A* (c.611G>A, p.Arg204Gln) of the proband (B) and his son (C). Arrows indicate sites of the pathogenic variant.

follow-up period is required when investigating SPG10 families since some of the members may develop symptoms belatedly.

The axonal sensorimotor polyneuropathy (albeit subclinical) observed in our proband has great clinical implications. There is accumulating evidence that *KIF5A* mutations contribute to the pathogenesis of various neurological disorders, such as HSP[2-5] and axonal Charcot-Marie-Tooth peripheral neuropathy type 2 (CMT2).[4,6] Intriguingly, some patients exhibit mixed features of distinct disease entities. For example, a recent study performed whole exome sequencing in Korean CMT2 families and identified a pathogenic variant p.Arg-204Trp in *KIF5A* that exhibited mixed features suggestive of both CMT2 and HSP.[6] These findings are intriguing in that mutation of a single gene (*KIF5A*) could result in distinct neurological disorders that exhibit distinct selective vulnerabilities: peripheral nerves in CMT2 and corticospinal tract in HSP.[4,6] Given that the KHC proteins play a central role in the microtubule-dependent anterograde axonal transport of neurofilaments, pathogenic variants in *KIF5A* might contribute to the pathogenesis of neuron degeneration,[1,6] thereby producing a wide phenotypic spectrum. This means that the sensorimotor polyneuropathy accompanied in our proband may be at least partly explained by the weak genotype-phenotype correlation of *KIF5A* variants.[4,6]

We have reported the first Korean SPG10 patient carrying the pathogenic variant c.611G>A with an onset age of 30 years who exhibited generally mild neurological manifestations with subclinical sensorimotor polyneuropathy, mimicking "pure" HSP based on clinical symptoms. Genomic sequencing including that of *KIF5A* should be considered for HSP patients with or without other neurological features.

## Supplementary Material

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.2.347.

### Author Contributions

Conceptualization: Young-Chul Choi. Data curation: Hyungwoo Lee, Yunkyung La, Han Kyu Na, Hongkyung Kim, Saeam Shin. Formal analysis: Hongkyung Kim, Saeam Shin. Methodology: Hongkyung Kim, Saeam Shin, Young-Chul Choi. Supervision: Young-Chul Choi. Visualization: Han Kyu Na. Writing—original draft: Hyungwoo Lee. Writing—review & editing: Yunkyung La, Han Kyu Na, Hongkyung Kim, Saeam Shin, Young-Chul Choi.

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### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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