



Pathogenic Variant of *REEP1* in a Korean Family with Autosomal-Dominant Hereditary Spastic Paraplegia

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Dear Editor,

Hereditary spastic paraplegia (HSP) encompasses a heterogeneous group of genetic disorders characterized by progressive lower-limb spastic paralysis due to degeneration of the corticospinal tract. HSP has been classified into pure and complicated forms according to the existence of mental retardation, epilepsy, cerebellar ataxia, optic atrophy, and peripheral neuropathy. To date 66 causative genes for HSP have been reported, of which 20 are associated with autosomal-dominant inheritance (www.musclegenetable.fr). Three genes account for up to 50% of the pathogenic variants in families with autosomal-dominant HSP: the causative gene is *SPAST* in 40%, *ATL1* in 10%, and *REEP1* in 4.5% to 6%.¹ However, pathogenic variants in *REEP1* have not been reported in Korea.² Here we report a pathogenic variant of *REEP1* in a Korean family with autosomal-dominant HSP.

The proband in the HSP family (an 8-year-old boy) (Fig. 1A, III-8) presented to our clinic with gait disturbance. He first noticed an unstable gait at an age of 5 years, since when his gait disturbance had progressed slowly. When we examined him at the age of 8 years, he was still able to ambulate independently. A neurological examination demonstrated muscle weakness and brisk reflexes of the lower extremities. His ankle joints were affected by contracture. However, the motor function of the upper extremities was normal, and he did not exhibit cognitive decline, sensory deficits, or bladder dysfunction. Magnetic resonance images of the brain and spinal cord were normal, as were the findings of electrophysiological studies.

His family history showed that HSP was inherited in an autosomal-dominant manner (Fig. 1A). His mother (a 45-year-old woman, II-10) and oldest aunt (a 52-year-old woman, II-4) also showed spastic paraplegia and ankle contracture. The findings of electrophysiological studies were normal for both of these relatives. His younger brother (a 5-year-old boy, III-10) did not complain of gait disturbance, but showed mild spasticity and hyperreflexia of the lower extremities. However, his younger sister (a 5-year-old girl, III-11) did not show any abnormal neurological deficits.

To identify pathogenic variants, whole-exome sequencing was performed on the proband (III-8) (Supplementary Material in the online-only Data Supplement). Our screening of HSP-related genes revealed a heterozygous pathogenic variant (c.337C>T) (p.Arg113*) in *REEP1* (nomenclature refers to NM_022912) (Supplementary Table 1 in the online-only Data Supplement). This variant was previously reported as the pathogenic variant in complicated HSP (Supplementary Table 2 in the online-only Data Supplement).³ DNA sequencing by capillary electrophoresis of samples from extended family members identified the *REEP1* variant in four affected family members and one asymptomatic family member (Fig. 1).

REEP1 is the third most common cause of autosomal-dominant HSP, but it is also a causative gene of distal hereditary motor neuropathy.⁴ The *REEP1* protein is located in mitochondria and the endoplasmic reticulum, and it enhances the transport of G-protein-coupled re-

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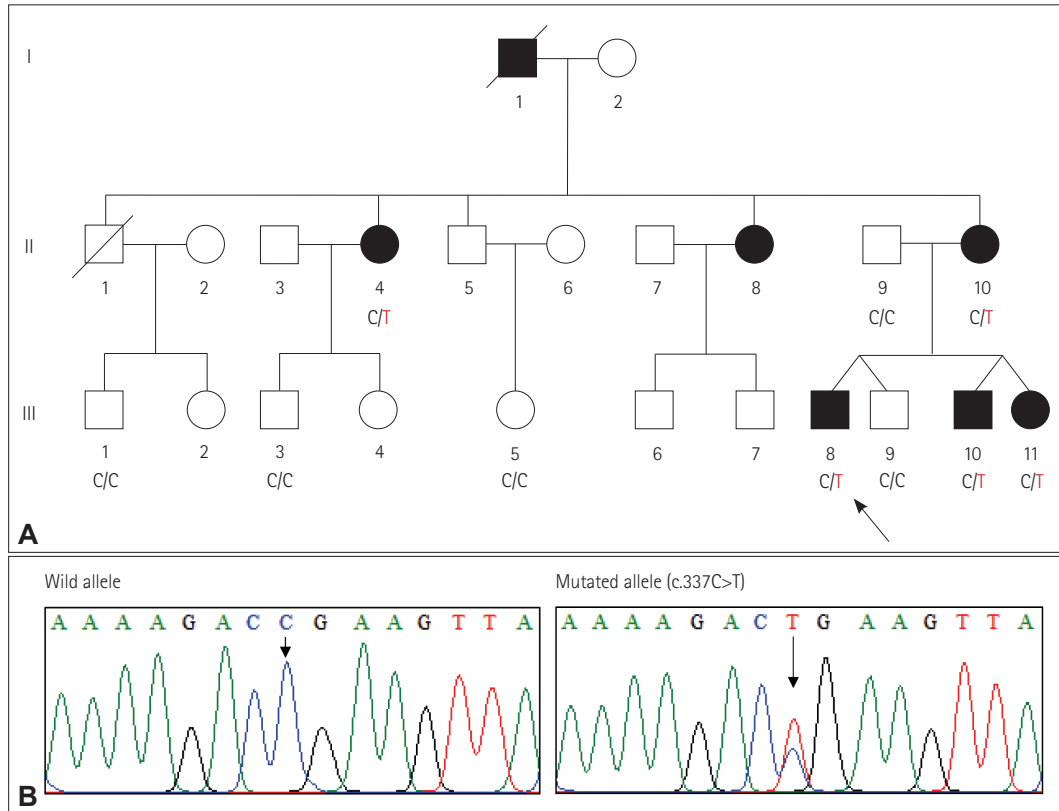


Fig. 1. Pedigree and sequencing chromatograms in a family with autosomal-dominant hereditary spastic paraplegia. A: Pedigree of the family with a heterozygous pathogenic variant in *REEP1*. Arrow indicates the proband, whose DNA was used for exome sequencing. Genotypes of *REEP1* (c.337C>T) are indicated under each subject (square: male, circle: female, filled: affected, and nonfilled: unaffected). B: Sequencing chromatograms of the c.337C>T (p.Arg113*) pathogenic variant in *REEP1*. The pathogenic variant in *REEP1* detected by whole-exome sequencing was confirmed by capillary sequencing. This heterozygous pathogenic variant completely cosegregated with the affected individuals in this family. Arrows indicate sites of the pathogenic variant.

ceptors to the cell surface membrane. It is therefore presumed that *REEP1*-related diseases are caused by the loss of transport of G-protein-coupled receptors to the cell surface membrane (loss-of-function variants) or accumulation of mutant *REEP1* protein (toxic gain-of-function variants). It was postulated that loss-of-function and toxic gain-of-function variants could cause HSP and lower motor neuron disease, respectively.⁴ The c.337C>T pathogenic variant partially escapes nonsense-mediated mRNA decay and is presumed to result in toxic gain of function. In fact, the previous reported patients with the c.337C>T variant presented with both spastic paraplegia and lower motor neuron signs including pes cavus and motor neuropathy (Supplementary Table 1 in the online-only Data Supplement).³ Additionally, these patients were confined to a wheelchair in their early 30s. However, the present patients did not show any electrophysiological evidence of peripheral neuropathy. In addition, the clinical disease progression was relatively slow, and two adults (II-4 and II-10) could still ambulate independently at ages of 52 and 45 years, respectively.

In conclusion, this is the first report of the pathogenic variant of *REEP1* in a Korean family with autosomal-dominant HSP using whole-exome sequencing.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2018.14.2.248>.

Conflicts of Interest

The authors have no financial conflicts of interest.

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