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Novel *SPG4* Mutation in a Patient with Sporadic Hereditary Spastic Paraplegia and Elevated Cerebrospinal Fluid Protein

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Dear Editor,

Hereditary spastic paraplegia (HSP) is a clinically and genetically heterogeneous group of inherited neurological disorders.[1] We report a sporadic patient with HSP who carried a novel *SPG4* mutation (c.1141T>G) in a highly conserved region of the gene. The patient presented with a typical pure form of HSP with progressive lower extremity weakness and spasticity, but he also developed lower limb amyotrophy, spinal cord atrophy, and progressive CSF protein elevation, which has not previously been described in *SPG4* HSP.

The patient was a 58-year-old right-handed Chinese male who had experienced progressive lower limb weakness and stiffness since the age of 29 years. He was first seen at the age of 46 years, at which time he was still able to walk independently. An examination revealed symmetric diffuse muscle atrophy and weakness [Medical Research Council (MRC) grade 4] in the lower limbs, spasticity of both legs with hyperreflexia, positive bilateral Babinski sign, and a scissors gait. Needle electromyography showed fibrillation potentials and a mixed pattern of motor-unit potentials in the rectus femoris, medial thigh, and gastrocnemius muscles suggesting a chronic neurogenic process. The findings of motor and sensory nerve conduction studies were normal. Cerebrospinal fluid (CSF) showed a mildly elevated protein level of 53 mg/dL (normal 15−45 mg/dL), but otherwise the CSF findings were normal. MRI of the spine and brain performed at that time produced unremarkable findings.

The lower limb weakness of the patients continued to deteriorate, and he started walking with crutches at the age of 49 years. At 57 years of age his lower limb muscle strength had decreased to MRC grade 3. His score on the Spastic Paraplegia Rating Scale was 30. A repeat CSF examination again showed protein elevation (77 mg/dL), but the findings were otherwise normal, with no oligoclonal bands or AQP4 antibodies. He was negative for serum antibodies to human T-lymphotropic virus type-1 (HTLV-1). Repeat MRI brain produced unremarkable findings, while spinal MRI showed atrophy of the thoracic cord between T7 and T8 (Fig. 1A).

Genetic screening using next-generation sequencing identified a heterozygous missense mutation in the *SPAST* gene in exon 8: c.1141T>G, p.(Phe381Val), NM_014946.3. The novel mutation was confirmed by Sanger sequencing in the Guangzhou Kingmed Laboratory (Fig. 1B). This mutation was not present in the Human Gene Mutation Database. We then predicted the pathogenicity of this mutation in silico using the following software: MutationTaster (http://www.mutationtaster.org/), Provean protein analysis tool (http://provean.jcvi.org/index.php), and PolyPhen-2 (http:// genetics.bwh.harvard.edu/pph2/index.shtml). The *SPAST* amino acid sequence (Genbank ID CAB60208.1) was entered into the analysis tool in the standard FASTA format. The variant F381V generated a Provean score of -6.767, indicating that such a change from phenylalanine at amino acid 381 to valine would be deleterious. Further evidence from Clustal analysis (https://www.uniprot.org/align/) revealed that *SPAST* F381 resides in a region that is highly conserved across species (human, mouse, chicken, ze-

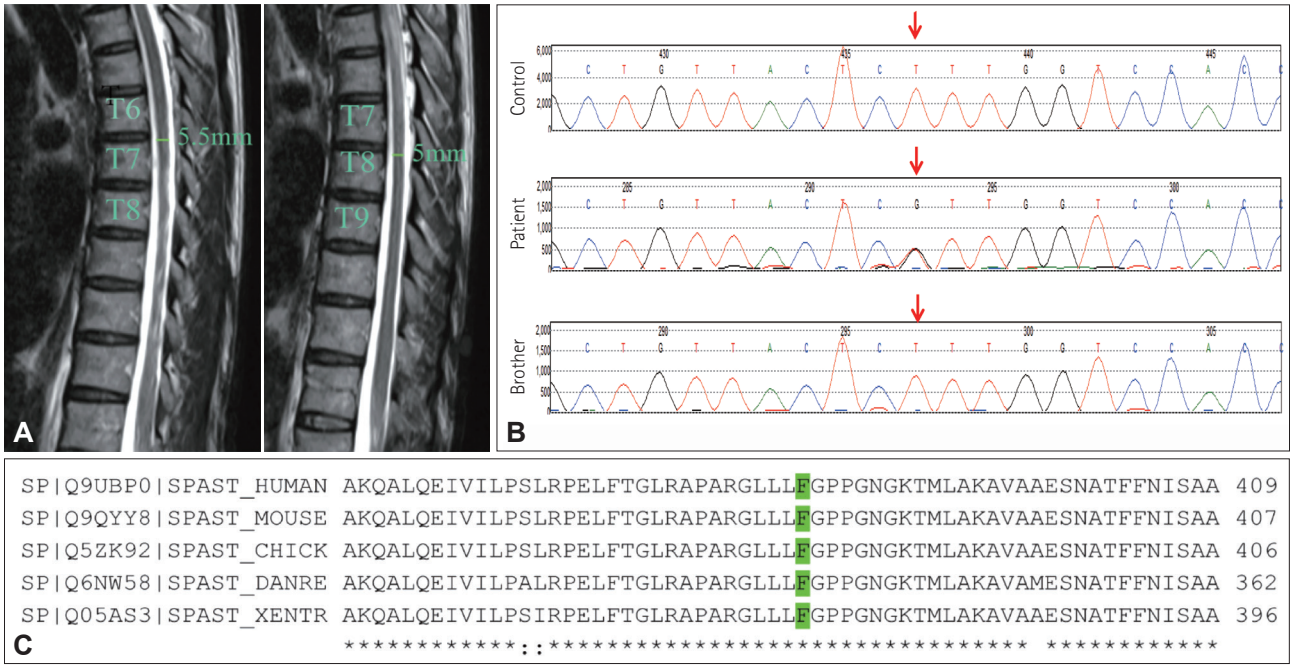

Fig. 1. MRI imaging of thoracic spine, Sanger sequencing and Clustal analysis of the novel mutation. A: T2-weighted MRI of the thoracic sagittal plane. B: The novel mutation (arrows) confirmed by Sanger sequencing. C: The SPAST protein, including the phenylalanine 381 region (highlighted in green) where the mutation to valine was identified, was aligned using Clustal analysis across several species, implying that a mutation change is highly likely to cause disease.

bra fish, and clawed frog) (Fig. 1C) and appears to be bound by strong selective constraints and likely to impact protein structure and function. Other studies have also found that a phenylalanine-to-valine substitution, or vice versa, can cause disease.[2]

The patient worked as an architect, had never married, and had no offspring. He had two brothers aged 55 and 53 years, and the *SPAST* mutation had not been detected in his 53-year-old brother. His mother was alive at the age of 83 years, and his father had died at 72 years of age. None of his family members reported any neurological motor symptoms, and they had all passed the average age at which the onset of HSP occurs, suggesting that this was a sporadic case of HSP.

The finding of spinal cord atrophy on MRI is not uncommon in cases of complicated *SPG4* due to axonal degeneration; however, the progressive increase in CSF protein over a 11-year disease period has not been reported previously. Elevation of CSF protein in HSP is rare, having only been reported in two SPG11 cases with clinical presentations mimicking multiple sclerosis.[3,4] Similar to our case, CSF oligoclonal bands and AQP4 antibody were absent in those cases. The present report further extends the spectrum of *SPAST* mutations and the genotype–phenotype correlation in *SPG4* HSP, and highlights the finding of elevated CSF protein levels in some cases.

Author Contributions

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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