A novel missense mutation (I344K) in the SPG4 gene in a Korean family with autosomal-dominant hereditary spastic paraplegia

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Abstract  Hereditary spastic paraplegia (HSP) is a group of clinically and genetically heterogeneous neurodegenerative disorders characterized by slowly progressive spasticity and weakness of the lower extremities. Among eight loci linked with autosomal-dominant (AD)-HSP, the SPG4 locus on chromosome 2p22 accounts for about 40% of all patients. Recently, mutations in a new member of the AAA protein family, called spastin, have been identified as responsible for SPG4-linked AD-HSP. Here, we describe a novel missense mutation (c.1031T>A; I344K) in exon 7 of the SPG4 gene identified in a Korean family with typical clinical features of pure AD-HSP. The mutation affects the third amino acid of the highly conserved AAA cassette domain, which is the most fore part of the domain altered by a missense mutation reported so far. Clinical presentations of affected individuals carrying the I344K mutation were not different from those of pure AD-HSP with SPG4 mutations reported previously. However, it is noteworthy that neither urinary dysfunction nor involvement of upper extremities was noticed in this family. To our knowledge, this is the first report of genetically confirmed AD-HSP in Korea.

Key words  Autosomal dominant hereditary spastic paraplegia · SPG4 · Korean · Missense mutation · Spastin · AAA cassette domain

Introduction  
Familial or hereditary spastic paraplegia (HSP) is a group of clinically and genetically heterogeneous neurodegenerative disorders that share the primary features of slowly progressive spasticity and weakness of the lower limbs. Traditionally, HSP has been classified on the basis of the inheritance pattern, the age of onset, and the presence (complicated HSP) or absence (pure HSP) of additional neurological abnormalities such as mental retardation, dementia, ataxia, optic neuropathy, retinopathy, and so on. Although both forms can be inherited in an autosomal-dominant (AD-HSP), autosomal-recessive (AR-HSP) or X-chromosome-linked (X-HSP) manner, pure AD-HSP is the most common form of HSP (Fink et al. 1996; Harding 1983; Tallaksen et al. 2001).

To date, seven genetic loci for pure AD-HSP have been mapped: chromosomes 14q (SPG3), 2p (SPG4), 15q (SPG6), 8q (SPG8), 12q (SPG10), 19q (SPG12), and 2q (SPG13). Among these loci, SPG4 is the most common and represents approximately 40% or more of pure AD-HSP cases (Casari and Rugarli 2001; Fink et al. 1996; Tallaksen et al. 2001). Recently, Hazen et al. (1999) identified the spastin (SPG4) gene, which encodes a new member of the AAA (ATPase associated with diverse cellular activities) protein family. After this discovery, more than 70 mutations of the SPG4 gene have been reported, including missense, nonsense, and splice-site mutations, as well as insertions and deletions (Bürger et al. 2000; de Bantel et al. 2001; Fonknechten et al. 2000; Hazan et al. 1999; Hentati et al. 2000; Jiggins et al. 2001; Lindsey et al. 2000; Namekawa et al. 2001; Santorelli et al. 2000; Svenson et al. 2001). Here, we present a novel missense (I344K) mutation in the SPG4 gene in a large Korean family with pure AD-HSP.
Subjects and methods

Case report

A 40-year-old male visited the neurology department complaining of weakness and spasticity in the lower extremities. He first noted stiffness of both legs and gait unsteadiness at age 33, and it had progressed over the years. His father and all of his siblings as well as many relatives on his father’s side had similar problems (Fig. 1). On neurological examination, his gait was spastic but independent. He was well oriented and had normal cognitive function without evidence of decreased visual acuity, optic neuropathy, retinopathy, pigmental macular degeneration, nystagmus, or dysarthria. Deep tendon reflex, muscle strength, tone, sensation, and coordination of upper extremities were normal. The lower extremity showed proximal and distal weakness, marked increase in tone, pathologically brisk reflexes, ankle clonus, and extensor planter reflex, but normal sensation.

Clinical evaluation

After we had obtained informed consent, a detailed neurological examination including evaluation of the cranial nerves, deep tendon reflexes, motor, and sensory systems was performed on 14 additional family members of the proband. Information on deceased family members as well as on other family members who were not evaluated neurologically was obtained from the proband and other senior members of the family. Subjects were classified into four groups: (1) “definitely affected” if they had spasticity, increased reflexes, and extensor planter response; (2) “possibly affected” if they had only increased reflexes or extensor plantar response; (3) “probably affected” if they had brisker reflexes in the lower limbs compared with the upper limbs; and (4) “normal” if they had no neurological abnormalities, as described previously (Fonknechten et al. 2000). Disability was assessed on a five-point scale: 1, normal gait or very slight stiffness in the legs; 2, moderate gait stiffness; 3, unable to run but able to walk alone; 4, walk with help; 5, wheelchair bound (Fonknechten et al. 2000).

Molecular genetic study

All 15 neurologically examined and 5 additional family members (4 were suspected to be affected and 1 was normal, based on the histories) were included in the molecular genetic study, after we obtained informed consent. Genomic DNA was isolated from peripheral blood leukocytes by using a Wizard Genomic DNA Purification kit following the manufacturer’s instruction (Promega, Madison, WI, USA). Since SPG4 is the most common cause of pure AD-HSP and because it was the only locus with an identified gene, we decided to perform direct sequencing analysis of the SPG4 gene [during preparation of this article, however, Zhao et al. (2001) identified a second gene, SPG3A, causing early-onset AD-HSP]. By using the proband’s DNA, all 17 exons of the SPG4 gene were amplified by polymerase chain reaction (PCR), as described previously (Hazan et al. 1999). Cycle sequencing was performed with a BigDye Terminator Cycle Sequencing Ready Reaction kit, version 2.0. (Applied Biosystems, Foster City, CA, USA) on an automated ABI Prism 3100 genetic analyzer (Applied Biosystems).