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Genetic Brief

Clinical and Genetic Study of a Brazilian Family With Spastic Paraplegia *(SPG6 locus)*

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Abstract: We describe a Brazilian family in which inheritance of a G106R mutation in the *SPG6* gene (also know as *NIPA1*) resulted in an autosomal dominant form of hereditary spastic paraplegia (ADHSP). Clinical investigations indicated that this family has a pure form of spastic paraplegia. All patients presented with gait difficulty in their twenties, progressing to frank spastic paraplegia during the next decade. Our report further supports evidence that mutations in *SPG6* cause ADHSP. © 2005 Movement Disorder Society

Key words: missense mutation; hereditary spastic paraplegia; *SPG6*

The gene SPG6 (also know as *NIPA1*) was identified to be responsible for an autosomal dominant hereditary spastic paraplegia (ADHSP).[1] To date, two missense mutations, T45R and G106R, were identified in four *SPG6* families originating from Irish, Iraqi, Chinese, and British populations.[1–3] Here, we report on the clinical and genetic findings of a Brazilian ADHSP family.

PATIENTS AND METHODS

Informed consent for research purposes was obtained from all individuals involved in the study approved by the research ethics board. Standard neurological clinical examination was performed on all participants recruited from the Movement Disorders Unit, Neurology Service, Hospital de Clínicas, Federal University of Paraná, Brazil. The diagnosis of spastic paraplegia was based on published criteria.[4] Cognitive impairment was assessed with a Mini-Mental State Examination.[5]

Genomic DNA from the proband was extracted from whole blood as previously described.[6] Sequence analyses of the entire open reading frame and exon–intron boundaries of the *SPG4*, *SPG3A*, and *SPG6* genes were conducted as described elsewhere.[1,2,7]

RESULTS

Clinical Findings

The SPG-BRZ family is composed of a nuclear family with four members affected by ADHSP (Fig. 1). Their remote ancestors were originally from Portugal; however, it remains unknown whether they had the disease.

Drs. Munhoz and Kawarai contributed equally to this work.

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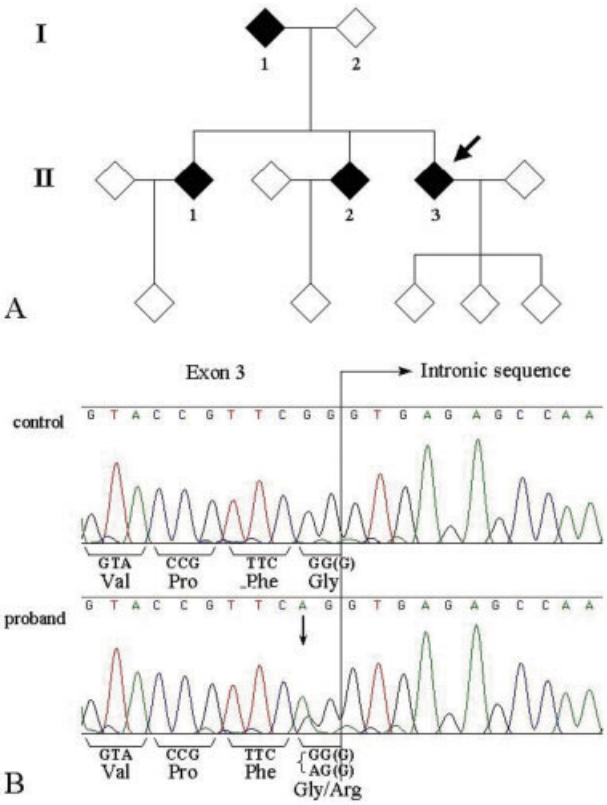

FIG. 1. A: The pedigree structure of SPG-BZL family: the arrow points to the proband on which complete sequencing analysis was performed. The gender of all individuals has been masked to protect family confidentiality (affected individuals are shown as filled symbols). **B:** The DNA sequence fluorescent chromatograms. The top panel illustrates the normal *SPG6* sequence, and the bottom panel shows the missense G106R mutation in exon 3 (sequence around the mutation site is shown with the corresponding amino acids; the arrow points to the heterozygous substitution). The third guanine in codon 106 is coded in exon 4 and is indicated in parentheses.

The clinical features of each affected member are summarized in Table 1.

Mean age at onset was 23.75 ± 2.98 years (±SD). Common initial symptoms were lower limb stiffness and weakness. Gait disturbances progressed insidiously, and spasticity occurred, tending to assume a posture with femoral adduction, leg extension, and plantar flexion of the feet during the next decade. Ten years after the initial symptoms, 2 affected siblings were able to walk unassisted for relatively long distances (~100 m), whereas the third required a cane due to repeated falls. Urinary incontinence occurred in 2 affected members after 5 to 7 years. Examination of 3 affected siblings showed increased muscle tone at the hamstrings, quadriceps, and ankles. Deep tendon reflexes were brisk in the upper and lower extremities. Plantar reflexes were extensor, with Babinski's sign bilaterally.

Motor evoked potentials (MEPs) performed on the proband showed reduced conduction velocity in the corticospinal tract with reduced amplitude in muscles innervated by lumbar spinal segments. The MEPs of the arms were normal. Other than the upper motor neurons, no evidence of nervous system involvement was observed. Tropical spastic paraplegia, subacute combined degeneration, tabes dorsalis, and multiple sclerosis were excluded.

Genetic Findings

The three genes known to cause ADHSP were screened for the proband (II-3) of the SPG-BZL family. Mutations in *SPG4* and *SPG3A* were excluded, however, analysis of *SPG6* revealed a heterozygous G-to-A mutation at nucleotide position 316 in exon 3 (accession no. NM_144599; numbering using the A of the translation initiation codon as +1), resulting in an amino acid substitution of glycine to arginine at codon 106 (G106R; Fig. 1).

DISCUSSION

Our mutation survey uncovered a nonsynonymous G106R substitution in *SPG6* in the SPG-BZL family. This substitution was reported previously in two unrelated Chinese families where nucleotide position 316

Table 1 *Summary of clinical features*

	Patient no.			
	I-1	II-1	II-2	II-3
Age at examination (yr)	57	37	36	33
Age at onset (yr)	27	20	25	23
Disease duration (yr)	30	17	11	10
Disability stage	5	3	3	4
Spastic gait	+	+	+	+
Upper limb hyperreflexia	3+	2+	3+	3+
Lower limb hyperreflexia	4+	3+	3+	4+
Lower limb weakness	3	4	4	4
Lower limb wasting	Mild	Mild	-	-
Lower limb decreased vibration sense	-	-	-	-
Babinski signs	+	+	+	+
Pes cavus	+	-	-	+
Sphincter disturbances (urinary problems)	3	0	1	3
Motor evoked potentials (normal, msec)	Not done	Not done	Not done	
Central motor conduction times; first dorsal interosseous (<9.2)				9.1
Central motor conduction times; tibialis anterior (<18.8)				21.6
Somatosensory evoked potentials	Not done	Not done	Not done	Normal
Epilepsy	-	-	-	-
Tremor	-	-	-	-
Cognitive impairment	-	-	-	-

was mutated with G-to-A or G-to-C[2] and in a British family where a G-to-A substitution at the same nucleotide position was also identified.[3] Our finding further confirms that the G106R mutation causes ADHSP and indicates that the 106 codon may be a mutational hotspot in *SPG6*, because the same nucleotide position is affected by different mutations in several families of different ethnic origin.

Clinical investigation of the SPG-BZL family revealed a pure form of ADHSP without any distinct intrafamilial phenotypic heterogeneity. Similarly, the Chinese *SPG6* families also showed a pure form HSP phenotype. However, one of the families showed a broad range of age-at-onset (ranging between 17 and 40 years) with a much earlier onset observed in younger generations.[2] In contrast, a British *SPG6* family demonstrated phenotypic variations between affected family members. In addition, an impression of anticipation was mentioned in the report.[3] The SPG-BZL family is too small to address the existence of anticipation. Further accumulation of data on the correlation between genotype and phenotype would help to understand the pathogenesis of spastic paraplegia and prioritize which genes should be screened in different ADHSP families.

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