

Hereditary spastic paraplegia:  
a novel mutation and  
expansion of the phenotype  
variability in SPG10

**INTRODUCTION**

Hereditary spastic paraplegias (HSPs) are a group of disorders characterised by slow progressive weakness and spasticity of the lower limbs. HSPs have been divided into pure and complicated forms, depending

on the absence or presence of additional neurological or non-neurological features. To date, 72 loci and 55 spastic paraplegia genes (SPGs) have been identified.<sup>1</sup> SPG10 is caused by mutations in the *KIF5A* gene encoding neuron-specific kinesin heavy chain 5A (NK-HC5A), a member of the kinesin-1 family of motor proteins. In mammals, NK-HC5A is necessary for the anterograde axonal transport of neurofilament subunits, and it has a role in the transport of other anterograde cargoes, such as membrane vesicles. SPG10 is an autosomal dominant HSP (ADHSP), accounting for about 10% of the complicated forms. Peripheral neuropathy and cognitive impairment are the most common additional clinical features.<sup>1</sup> This report describes a novel *KIF5A* genetic defect in a large Italian ADHSP family with exclusive clinical features.

## METHODS

The currently living family members were examined by movement disorder specialists (TLG, GAM, RM and AO). Neurological assessments, including the Spastic Paraplegia Rating Scale (SPRS)<sup>2</sup> Mental Deterioration Battery (MDB)<sup>3</sup> electrophysiology of peripheral nerves, and neuroimaging analyses, were carried out. After informed consent was given, genomic DNA was extracted from peripheral lymphocytes. Genetic analyses were conducted as described in online supplementary data, including linkage studies at the currently known ADHSP loci, PCR-direct sequencing, PCR-restriction fragment length polymorphism (PCR-RFLP) assay, and *in silico* analysis.

## RESULTS

The RM 551 family is composed of a three-generation kindred with AD inheritance. Eleven individuals were diagnosed as 'certainly affected' and classified as having complicated HSP.<sup>1</sup> At examination, the age range of the affected individuals was 19–77 years (mean±SD=40.4±17.9 years). Spastic paraparesis was the primary symptom in the clinical course of each patient; age at onset ranged between 12 and 55 years (mean±SD=32.2±15.0 years). The decrease of age at onset between successive generations ranged from 4 to 39 years per generation. The disease was slowly progressive and urinary urgency was a common symptom. Electroneurography of both motor and sensory nerves, as well as electromyography, were normal. MDB did not show cognitive impairment. Other clinical features associated with SPG10<sup>1</sup> were absent.

Interestingly, this variant form of HSP was associated in all affected individuals of the family with varicose veins (VV) of the legs, as well as bilateral Dupuytren's disease (DD) at various stages, according to Clinical-Etiology-Anatomy-Pathophysiology (CEAP)<sup>4</sup> and Tubiana<sup>5</sup> classifications, respectively (table 1 and online supplementary figure S1). DD and VV were absent in all members of the family who did not have gait difficulty. The environmental associations of DD, such as alcohol consumption, tobacco exposure, manual activities, retractile capsulitis, epilepsy, diabetes, HIV and dyslipidemia,<sup>5</sup> were absent in all patients. Obesity and lower limb deep vein thrombosis examined by venous ultrasonography were also absent, suggesting a primary form of VV.<sup>4</sup>

Significant logarithm of odds (LOD) scores were obtained at the SPG10 locus only ( $Z_{\max}=4.56$  at  $\theta=0.0$  at the microsatellite marker D12S1724, online supplementary table S1) and a novel heterozygous change in exon 6 (c.484C>T) was found, resulting in amino acid substitution of arginine to tryptophan at codon 162 (p.R162W). The PCR-RFLP analysis demonstrated a complete cosegregation of the mutation with the disease and the

nucleotide change is predicted to cause the disease, as well as influence the protein function by *in silico* analysis (see online supplementary figure S2 and table S2).

## DISCUSSION

To date, 21 mutations have been reported in SPG10/*KIF5A*. Most of the mutations locate within the kinesin motor domain and are missense mutations, except from one in-frame deletion mutation N256del. The residues p.R204, p.N256 and p.R280 are mutational hot spots (see online supplementary figure S3). Neither nonsense nor frameshift mutations leading to truncated proteins are reported. These data suggest that SPG10 pathogenesis is not simply due to haploinsufficiency. A dominant negative effect has been postulated in SPG10 pathogenesis. The novel missense mutation, p.R162W, would lead to altering the conformation of the kinesin-1 complex and disrupting cargo transportation along the axon.

Other kinesin isoforms, *KIF1A* and *KIF1C*, have been reported as causative genes of SPG30 and spastic ataxia 2 (SAX2 or SPG58), respectively. This indicates that the underlying pathological mechanism in spastic paraplegia caused by

**Table 1** Clinical findings in family members with the *KIF5A* mutation

	I:2	II:1	II:4	II:5	II:6	III:1	III:4	III:5	III:7	III:8	III:10
Sex	F	F	M	F	M	F	M	F	M	M	M
Age at examination	77	58	54	49	43	40	31	28	25	21	19
Age at onset*	55	49	51	39	36	32	26	18	21	16	12
Disease duration (years)	22	9	3	10	7	8	5	10	4	5	7
Disability stage†	2	2	2	3	2	3	3	4	3	3	3
SPRS‡	14	16	16	21	18	25	26	38	26	25	28
LL pyramidal weakness	+	+	+	+	+	++	++	++	++	++	++
LL hyper-reflexia	+	+	++	++	+	+	++	++	++	++	++
LL spasticity	+	+	+	+	+	++	+	++	++	+	++
Babinski reflex	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+
<i>Pes cavus</i>	–	–	–	–	–	–	–	+	–	–	–
Sensory deficits	+	–	+	–	–	+	–	+	–	–	–
VV	R/L	R/L	L	R/L	R/L	R/L	L	R	R/L	L	R/L
VV stage§ (affected or worst side)	C <sub>2</sub>	C <sub>2</sub>	C <sub>4a</sub>	C <sub>2</sub>	C <sub>2</sub>	C <sub>6</sub>	C <sub>4b</sub>	C <sub>4a</sub>	C <sub>3</sub>	C <sub>3</sub>	C <sub>2</sub>
Bilateral DD	+	+	+	+	+	+	+	+	+	+	+
DD stage¶ (worst side)	1	1	2	N	1	3	3	2	4	3	3
Sphincter disturbances	+	+	+	–	+	+	–	+	+	–	–

\*Age at onset was calculated approximately as the time when difficulty in walking first appeared in the affected individuals.

†Disability stages: 1, no mobility problems or slight stiffness of the legs; 2, moderate gait stiffness; 3, problems running, but able to walk alone; 4, problems walking; 5, wheelchair user.

‡SPRS, Spastic Paraplegia Rating Scale.<sup>2</sup>

§Clinical section from CEAP classification of chronic venous disease:<sup>4</sup> C<sub>0</sub>, no visible or palpable signs of venous disease; C<sub>1</sub>, telangiectasies or reticular veins; C<sub>2</sub>, varicose veins; C<sub>3</sub>, oedema; C<sub>4a</sub>, pigmentation or eczema; C<sub>4b</sub>, lipodermatosclerosis or atrophie blanche; C<sub>5</sub>, healed venous ulcer; C<sub>6</sub>, active venous ulcer.

¶Tubiana classification:<sup>5</sup> 0, no lesion; N, palmar nodule without the presence of contracture; 1, TFD between 0° and 45°; 2, TFD between 45° and 90°; 3, TFD between 90° and 135°; 4, TFD greater than 135°.

+ and –, indicate the presence and absence of a feature, respectively; DD, Dupuytren's disease; F, female; L, left leg; LL, lower limbs; M, male; R, right leg; TFD, total flexion deformity; VV, varicose veins.

mutations in the *kinesin* gene family varies depending on the basis of the isotype. Moreover, HSP-related proteins interact with each other, including myelin proteolipid protein 1, atlastin-1, kinesin-HC5A, kinesin-3, REEP1, KIF1C and reticulon proteins. Mutations in *KIF5A* might further affect the biological pathway revealed by such interactions leading to motoneuron degeneration, as described in the *Drosophila* model.<sup>6</sup>

Additional clinical features observed in the family, such as VV and DD, might be explained by two potential pathological mechanisms. The genetic factor(s) for developing VV and/or DD might exist within the approximately 7.5 cM interval encompassed by the two microsatellite markers, D12S270 and D12S1601. Developmental abnormalities, including vessel malformation, were observed in an individual with chromosomal deletion of 1.76-Mb comprising the SPG10 locus<sup>7</sup> suggesting that there might be genetic predisposing factor(s) for fragility of the blood vessel within the region. Considering the histopathology in DD, genes involved in myofibroblast regulation, extracellular matrix or collagen might be a candidate for developing the disease. The *OS-9* gene, encoding osteosarcoma amplified 9, has been mapped 143-kb away from *KIF5A* [National Center for Biotechnology Information (NCBI) website at <http://www.ncbi.nlm.nih.gov/>]. The gene expression was coamplified with the cyclin-dependent kinase 4 (*CDK4*) gene in sarcoma tissues.<sup>8</sup> Dysregulation of the gene might be involved in DD observed in the patients. The other possibility is that the combined phenotypic features might be due to the coexistence of the *KIF5A* mutation and other genetic variation(s) mapped to region(s) away from the SPG10 locus. There is a growing body of evidence that expression of the transforming growth factor  $\beta$  (TGF $\beta$ ) is elevated in Dupuytren's fibroblasts.<sup>9</sup> Further investigation of genetic variations at the promoter region of TGF $\beta$  is needed to confirm the genetic model.

In conclusion, this study demonstrates further allelic heterogeneity, thus expanding the clinical-genetic spectrum of SPG10.

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## REFERENCES

- Lo Giudice T, Lombardi F, Santorelli FM, et al. Hereditary spastic paraplegia: clinical-genetic characteristics and evolving molecular mechanisms. *Exp Neurol* 2014;261C:518–39.
- Schüle R, Holland-Letz T, Klümpe S. The Spastic Paraplegia Rating Scale (SPRS): a reliable and valid measure of disease severity. *Neurology* 2006;67:430–4.
- Carlesimo GA, Caltagirone C, Gainotti G. The mental deterioration battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The group for the standardization of the mental deterioration battery. *Eur Neurol* 1996;36:378–84.
- Meissner MH, Gloviczki P, Bergan J, et al. Primary chronic venous disorders. *J Vasc Surg* 2007;46:545–67S.
- Hindocha S, John S, Stanley JK, et al. The heritability of Dupuytren's disease: familial aggregation and its clinical significance. *J Hand Surg Am* 2006;31:204–10.
- Bayat V, Jaiswal M, Bellen HJ. The BMP signaling pathway at the *Drosophila* neuromuscular junction and its links to neurodegenerative diseases. *Curr Opin Neurobiol* 2011;21:182–8.
- Firth HV, Richards SM, Bevan AP, et al. DECIPHER: database of chromosomal imbalance and phenotype in humans using ensembl resources. *Am J Hum Genet* 2009;84:524–33.
- Su YA, Hutter CM, Trent JM, et al. Complete sequence analysis of a gene (*OS-9*) ubiquitously expressed in human tissues and amplified in sarcomas. *Mol Carcinog* 1996;15:270–5.
- Krause C, Kloen P, Ten Dijke P. Elevated transforming growth factor  $\beta$  and mitogen-activated protein kinase pathways mediate fibrotic traits of Dupuytren's disease fibroblasts. *Fibrogenesis Tissue Repair* 2011;4:14.



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