

## BRIEF COMMUNICATION

**A novel mutation in *KIF5A* in a Malian family with spastic paraplegia and sensory loss**

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**Introduction**

Hereditary spastic paraplegias (HSPs) are clinically and genetically heterogeneous neurologic disorders that manifest with progressive lower extremity hypertonia and hyperreflexia along with typically more mild lower limb weakness in "pure" forms and with other associated neurologic or non-neurologic symptoms in "complicated" (or "complex") forms.<sup>1</sup> HSP is often due to a progressive, length-dependent degeneration of the corticospinal tracts and posterior columns of the spinal cord, though abnormal development may play a role as well. All modes of inheritance are seen, and the clinical presentations can show striking inter- and intra-family variability. While dominant HSPs are prevalent in northern Europe and North America, recessive cases are mostly seen in North

**Abstract**

Hereditary spastic paraplegias (HSPs) are well-characterized disorders but rarely reported in Africa. We evaluated a Malian family in which three individuals had HSP and distal muscle atrophy and sensory loss. HSP panel testing identified a novel heterozygous missense mutation in *KIF5A* (c.1086G>C, p.Lys362Asn) that segregated with the disease (SPG10). Lys362 is highly conserved across species and Lys362Asn is predicted to be damaging. This study shows that HSPs are present in sub-Saharan Africa, although likely underdiagnosed. Increasing efficiency and decreasing costs of DNA sequencing will make it more feasible to diagnose HSPs in developing countries.

Africa, the Middle East, and Mediterranean regions.<sup>1–3</sup> Although prevalent in other populations, genetically confirmed HSP cases in sub-Saharan Africa in general, and West Africa in particular, are rare.<sup>4</sup> Here, we report here a novel mutation in an HSP gene in a previously unstudied population in Mali.

**Methods**

All patients were evaluated by a group of neurologists after giving informed consent. Brain MRI plus HTLV-1 and HIV serologies were performed to exclude common causes of spasticity in this population. Nerve conduction studies (NCS) and ophthalmologic examinations were performed to assess peripheral nerve or ocular involvement. DNA was extracted from peripheral blood in all

available family members for genetic analysis. Next-generation DNA sequencing assessing 58 HSP genes was performed commercially (Medical Neurogenetics, Atlanta, GA). DNA from all available family members was sequenced for segregation analyses.

## Results

The index subject, of Khasonka ethnicity, was admitted for an ischemic stroke of the right superficial Sylvian artery that caused weakness in his left limbs. During examination, upper motor neuron signs were noticed on the right side as well. Further investigation revealed that he had experienced problems with walking at around 20 years of age, and two of his sons had the same symptoms. Other family members were subsequently evaluated. The disease distribution within the family was consistent with autosomal dominant inheritance (Fig. 1).

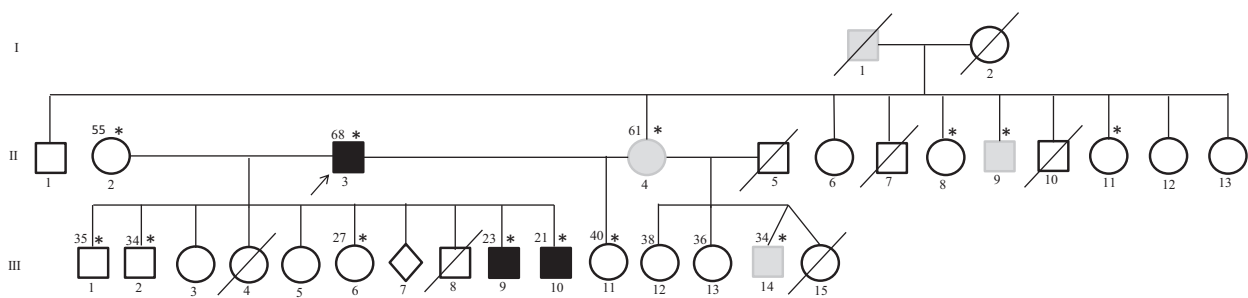
Three subjects were found to be affected based on clinical examination, with spastic gait, extensor plantar responses, and brisk reflexes in all those affected (Table 1). There were no visual or hearing complaints, but the eldest patient had dysarthria, possibly due to his concurrent stroke. In addition, patients had muscle atrophy and weakness in lower extremities along with decreased pin-prick and vibration sense. NCS showed slightly decreased conduction velocities in both tibial nerves at 39 m/sec with increased F-wave latency at 63.5 msec in the 23-year-old patient (shown in *italic* in Table 1). The youngest patient also had an increased F-wave latency. *SPG4* deletion and duplication testing was negative, and targeted HSP next-generation sequencing of one affected individual identified a heterozygous missense variant in the *KIF5A* gene at position c.1086G>C (Fig. 2A and B), leading to the amino acid change p.Lys362Asn. The Lys362 residue is located in a highly conserved, Lys-rich domain of the protein (Fig. 2C), and mutation in the neighboring Ala361 residue has been reported in autosomal dominant “pure” SPG10.

The p.Lys362Asn substitution of a positively charged with an uncharged amino acid is predicted to be damaging by an *in silico* method (Mutation Taster). Sequencing of DNA from eight other family members demonstrated that the Lys362Asn mutation co-segregates perfectly with disease status, and this variant was not seen in various SNP databases (ExAC Browser: 0.00000, dbSNP, 1000genome). Another branch of the family (individual II.4 and relatives) had a genetically confirmed spinocerebellar ataxia (SCA2) characterized by ataxia and slurred speech.

## Discussion

More than 90 HSP-related genes (SPG1-78, plus others) have been reported worldwide, and mutations in about 60 identified genes have been associated with these clinical variants.<sup>5</sup> However, reports of genetically confirmed HSPs in the African population are scant and involve a limited number of these genes, mostly recessive forms.<sup>6</sup> In Africa, a majority of spinal disorders appears due to injury or other known causes such as infectious or tumor,<sup>7</sup> but genetic forms are likely underdiagnosed because of the cost and limited availability of genetic testing. Mutations in *KIF5A* have been associated with both HSP (SPG10) and CMT2.<sup>8</sup> Previous reports of autosomal dominant HSP caused by *KIF5A* mutations have shown a clinical variability within and between families, but complicated cases are more frequent, especially in some populations.<sup>9</sup> In addition to spasticity, some patients have peripheral neuropathy manifesting with muscle atrophy and weakness, and sensory loss in extremities.<sup>8</sup> Furthermore, a small number of cases are characterized by infantile onset with myoclonus, hypotonia, optic nerve abnormalities, dysphagia, and apnea.<sup>10</sup> To our knowledge, mutation in *KIF5A* has not been previously reported in Africa.

In the family we describe here, the age of onset ranged from about 14–40 years, with a wide range of clinical variability. *KIF5A* encodes a member of the kinesin family

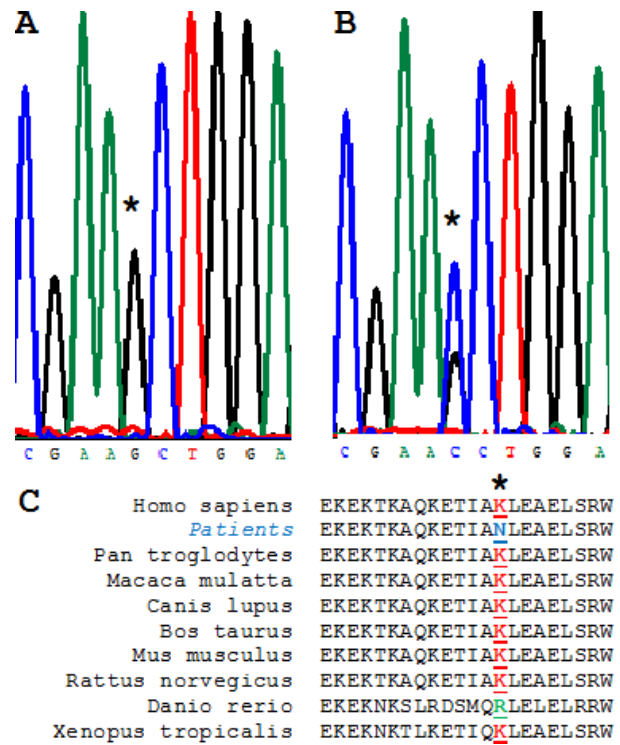


**Figure 1.** Pedigree of the family showing the autosomal dominant inheritance pattern. Individuals with Hereditary spastic paraplegias (HSP) phenotype (solid black) and individuals with SCA (solid gray) are indicated. The arrow identifies the proband. Ages at examination are shown at the top of each symbol, and asterisks (\*) identify those seen in clinic.

**Table 1.** Phenotypic characteristics of subjects with SPG10.

		Nerve conduction studies																			
		Clinical and demographic features					Peroneal					Tibial									
Patient	Age (year)	Sex	Age of onset (year)	First symptom	Spasticity	Distal leg weakness and atrophy	Sensory loss	Left median		Sural		Right		Left		Right		Left			
								CMAP Amp (mV)	CV m/sec	SNAP Amp (mV)	CV m/sec	CMAP Amp (mV)	CV m/sec	CMAP Amp (mV)	CV m/sec	CMAP Amp (mV)	CV m/sec	CMAP Amp (mV)	CV m/sec	CMAP Amp (mV)	CV m/sec
III.3	68	M	~20	Walking difficulty	Yes	Moderate	Moderate	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	
IV.9	23	M	10	Walking difficulty	Yes	Moderate	Moderate	17.5	57	26	26	9.7	45	9	9	5.2	39	5.2	39	6.4	39
IV.10	21	M	11	Walking difficulty	Yes	Mild	Mild	12.1	60	29	29	15	46	13.7	47	10.2	43	10.2	43	11.4	44

Amp, amplitude; SNAP, sensory nerve action potential; CMAP, compound motor action potential; ND, not done; CV, conduction velocity, normal median CMAP>4.5 mV (recorded at abductor pollicis brevis muscle), normal peroneal CMAP>2.5 mV (recorded at extensor digitorus brevis muscle), normal tibial CMAP>6 mV (recorded at abductor hallucis muscle), normal sural SNAP>10 μV, normal F wave<55 msec.



**Figure 2.** Electropherograms of the novel *KIF5A* sequence variant. Sanger DNA sequencing shows an unaffected family member to be homozygous (G/G; panel A), while the affected individual is heterozygous (G/C), for the pathogenic variant (denoted by \*, panel B). Protein sequence alignment of *KIF5A* in various species (amino acid numbers refer to the human sequence). The SPG10 mutation causes an amino acid change at Lys362, a highly conserved residue (in red, asterisk above, panel C).

of proteins that has three structural domains.<sup>11</sup> The mutated residue described here is located in the coiled coil domain and is conserved across species from mammals to fruit flies.

Although dominant HSPs are the most prevalent HSPs worldwide, in Africa (and in North Africa in particular where most HSP cases have been reported), recessive cases predominate. This is likely due to the high rate of consanguinity in these populations. *KIF5A* mutations have been reported in Asia, Europe and North America,<sup>12–14</sup> but no cases have been reported in Africa, probably due to much more limited access to genetic testing.

In summary, our study has identified a novel, autosomal dominant missense mutation in the *KIF5A* gene in a Malian family, broadening the genetic heterogeneity of HSPs in the African population and expanding the geographic spectrum of SPG10. Larger cohort studies in Africa will likely uncover many new HSP cases, representing new genes as well as known genes with mutations described in other populations.

## Acknowledgment

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## Conflict of Interest

The authors declare no conflict of interest.

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