


BRIEF COMMUNICATION

Multigeneration family with dominant SPG30 hereditary spastic paraplegia

Ricardo H. Roda^{1,2} , Alice B. Schindler² & Craig Blackstone²¹Department of Neurology, Neuromuscular Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland²Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

Correspondence

Ricardo H. Roda, Department of Neurology, Johns Hopkins University School of Medicine, Meyer 5-119A, 600 N. Wolfe Street, Baltimore, MD 21287. Tel: 410 614 9402; Fax: 410 955 1961; E-mail: rroda1@jhmi.edu

Funding Information

This work was supported by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke, National Institutes of Health.

Received: 5 July 2017; Revised: 1 August 2017; Accepted: 5 August 2017

Annals of Clinical and Translational Neurology 2017; 4(11): 821–824

doi: 10.1002/acn3.452

Introduction

Members of the large kinesin protein superfamily (KIFs) are microtubule-based mechanoenzymes that use ATP hydrolysis to power the transport of cargoes such as organelles, protein complexes, and mRNAs within cells. They are distinguished by a motor domain, which may be localized throughout the protein, as well as other domains which allow for selectivity of the materials transported.¹ Given this crucial role in cellular transport, it is not surprising that alterations in KIFs have been implicated in a variety of inherited disorders, particularly affecting the nervous system. For instance, mutations in the gene encoding the brain-specific kinesin KIF1A – involved in anterograde axonal transport and learning enhancement² – lead to a variety of neurological syndromes, including hereditary sensory neuropathy (HSN2C, OMIM 614213), intellectual disability (MRD9, OMIM 614255), and hereditary spastic paraplegia (HSP) (SPG30, OMIM 610357).³

The KIF1A protein comprises a motor domain at the N-terminus (residues 1–361), a forkhead-associated (FHA) domain (residues 516–572), and a pleckstrin

Abstract

Autosomal recessive *KIF1A* missense mutations cause hereditary spastic paraplegia (HSP) type SPG30, while recessive truncations lead to sensory and autonomic neuropathy (HSN2C) and many de novo missense mutations are associated with cognitive impairment. Here, we describe family members across three generations with pure HSP. A heterozygous p.Ser69Leu *KIF1A* mutation segregates with those afflicted. The same variant was previously reported in a Finnish father and son with pure HSP as well as four members of a Sicilian kindred with more intrafamilial phenotypic variability. This further validates the pathogenicity of the p.Ser69Leu mutation and suggests that it may represent a mutation hot spot.

homology (PH) domain (residues 1676–1774). Patients presenting with cognitive impairment often exhibit a relatively severe phenotype with a range of additional symptoms including optic atrophy, cerebellar ataxia, and neuropathy; they frequently carry heterozygous missense mutations in the motor domain, suggestive of a dominant-negative pathogenic mode of action.^{3–5} Several different families presenting with neuropathy alone, characterized by common features of profound sensory loss and ulcero-mutilation, have harbored recessive truncating mutations in the alternatively spliced exon 25b.⁶

In the initial report of HSP caused by *KIF1A* mutations (SPG30), Klebe and colleagues described two consanguineous families with autosomal recessive HSP due to homozygous mutations in *KIF1A*.⁷ The HSPs are a group of progressive gait disorders characterized by lower extremity spasticity in their “pure” form, along with cognitive symptoms, optic atrophy, and other neurologic findings in their “complex” form. They are among the most genetically diverse neurologic disorders, with almost 90 distinct genetic loci (SPG1–78, plus others).⁸ Although >60 HSP genes within these loci have been identified, a

relatively small number of common cellular pathogenic themes have emerged, among them is the disruption of the proper morphology and distribution of organelles within the long axons of corticospinal neurons.⁹ In addition to spasticity, some of the originally described patients and those identified subsequently also displayed cerebellar ataxia, axonal neuropathy, or both.¹⁰

More recently, dominantly inherited *KIF1A* mutations resulting in a HSP phenotype have been reported. Ylikallio et al.¹¹ uncovered a c.206C>T, p.Ser69Leu variant in *KIF1A* in a Finnish father and son with early-onset pure HSP. This same variant was also observed in a multigeneration Sicilian family with a more variable phenotype, complicated in some members by psychomotor delay, hand amyotrophy, and sensory abnormalities.¹² Finally, Iqbal et al.¹³ found that both c.80T>C, p.Ile27Thr and c.22G>A, p.Val8Met were associated with pure HSP in multigeneration families.

Here, we present a three-generation family whose afflicted members each carry the heterozygous c.206C>T, p.Ser69Leu mutation in *KIF1A*. The phenotype is most reminiscent of early-onset pure HSP, although one affected member had only mild symptoms in childhood before developing more prominent spasticity and gait abnormalities in adulthood. This firmly establishes p.Ser69Leu as a pathogenic *KIF1A* variant, with typically early-onset symptoms.

Case Report

Subjects provided informed consent to participate in a clinical research protocol (00-N-0043), approved by the NIH Combined NeuroScience Institutional Review Board, and were evaluated at the NIH Clinical Research Center.

Patient II.5 is the index subject (Fig. 1A). He was the product of a normal pregnancy but developed abnormal gait and frequent falls at 3 years of age. His gait abnormalities gradually progressed. By the age of 40, he was using a cane to steady himself, and by his late 50s he required a wheel chair. By report, evaluation at age 52 revealed hyperreflexia, a pyramidal pattern of weakness, and spastic gait. Serum studies including vitamin B₁₂, folate, ceruloplasmin, RPR, HTLV I/II serologies, and ANA titers were unrevealing. MRI of the brain was normal, while cervical spine MRI was notable for stenosis from C3 to C6, without spinal cord impingement. On examination in our clinic at age 61, he exhibited normal cognition and language. Motor examination revealed full power in the upper extremities. However, in the lower extremities, he was symmetrically weak on hip flexion (MRC grade 5-/5), dorsiflexion (2/5), and plantar flexion (4-/5); foot eversion and inversion were immobile (0/5). He had prominent scoliosis. Sensory examination was notable for decreased vibratory sensation at the great toes. There was diffuse hyperreflexia, with sustained clonus at

the ankles and extensor plantar responses. There was no dysmetria. He was nonambulatory.

Patient III.2 is a daughter of II.5, and she was 35 years old at evaluation. She developed normally throughout childhood. However, in her teenage years, her running became strained. By her early 20s, she noted cramps in her legs and feet as well as trouble walking upstairs. On examination, she had normal cognition and exhibited full strength. Reflexes were increased only at the patella and ankles, but plantar responses were extensor bilaterally. There were no sensory abnormalities, and her coordination was normal. Her gait was mildly spastic, with toe walking. Head MRI was normal (Fig. 1B).

Patient IV.2 is a 6-year-old daughter of III.2 conceived via in vitro fertilization. During her mother's pregnancy, there was in utero demise of a twin. She walked at 13 months, but by 3 years of age, she preferred walking on her toes. She also complained of pain in the back of her legs, and has four developmentally absent spinous processes in her back. On examination, she had full muscle power but tone was increased in her lower extremities. Reflexes in the lower extremities were brisk, with cross adductors and extensor plantar responses. She walked on her toes with a mildly spastic gait. By report, head MRI was normal, with the exception of a possibly low-lying cerebellum (without Chiari malformation).

Patient IV.2 underwent commercial genetic testing for common autosomal dominant HSPs including SPG3A, SPG4 (deletion/duplication and sequencing), SPG6, SPG8, SPG17, and SPG31, which was negative. Blood was drawn for DNA isolation and exome sequencing from the patient described above as well as II.5 and III.2. Two clearly unaffected, first-degree relatives (II.6 and III.3, ages 56 and 33, respectively) of different generations were also selected for targeted testing to facilitate segregation analysis of possible pathogenic variants. Subject IV.1, who was 4 years old at evaluation and unaffected clinically, was not tested for the *KIF1A* variant.

Exome sequencing was performed after target capture using an Agilent SureSelect or Illumina TruSeq kit and run on an Illumina HiSeq2000 or HiSeq2500 per the manufacturer's instructions, employing 101-bp paired-end read sequencing. Reads were mapped to the reference genome using the Burrows-Wheeler Aligner and processed using the Genome Analysis Toolkit. Missense variants were sought in public databases to determine minor allele frequencies (ExAC, EVS) and interrogated in silico to predict any damaging effects (SIFT, PolyPhen-2, Mutation Taster, and CDPred) as described previously.¹⁴ Sanger sequencing was performed for confirmation of mutations (GeneDx, Gaithersburg, MD). Genes screened via exome sequencing included: *ABCD1*, *ACOX1*, *AP4B1*, *AP4E1*, *AP4M1*, *AP4S1*, *AP5Z1*, *ATL1*, *B4GALNT1*, *BSCL2*, *C12orf65*, *CCT5*, *CLPP*, *CYP2U1*, *CYP7B1*, *DDHD1*, *DDHD2*,

Discussion

We present a family with pure HSP and an autosomal dominant pattern of inheritance. Furthermore, we have demonstrated segregation of the c.206 C>T, p.Ser69Leu mutation among affected family members spanning three generations, as well as its absence in two unaffected subjects. All other candidate genes examined either did not show pathogenic mutations or else the identified variants did not segregate among affected members. In silico analysis of this mutation in the N-terminal motor domain of KIF1A suggests that it may affect the L2 loop which forms part of the ATP-binding pocket, possibly by breaking the interaction between Tyr67 and ATP.¹¹ Importantly, our identification of an additional family with this mutation is informative because unlike many residues mutated within the motor domain, Ser69 is not as highly conserved, with some variation across species at this position and at neighboring residues (Fig. 1C).

When taken together with the two previous reports of HSP patients with p.Ser69Leu mutation in KIF1A,^{11,12} these additional cases strongly support pathogenicity of p.Ser69Leu autosomal dominant SPG30 and furthermore suggest that this may represent a mutation hot spot. Intriguingly, most of these cases differ substantially from typical presentations of patients with heterozygous missense mutations in the motor domain, as these patients typically have a far more severe phenotype with prominent cognitive impairment and other associated neurological findings.^{3–5,16} Perhaps, the fact that Ser69 is not invariant and occurs within a small segment of the motor domain that appears relatively divergent (Fig. 1C) mitigates the functional effects of this mutation. The identification of additional patients with missense mutations in this critical domain will likely facilitate more precise genotype–phenotype correlations.

Acknowledgments

We thank Elizabeth Hartnett for assistance with patient scheduling. The Exome Aggregation Consortium provided exome variant data for comparison; a full list of contributing groups can be found at <http://exac.broadinstitute.org/about>.

Conflict of Interest

None declared.

References

1. Hirokawa N, Tanaka Y. Kinesin superfamily proteins (KIFs): various functions and their relevance for important

- phenomena in life and diseases. *Exp Cell Res* 2015;334:16–25.
2. Kondo M, Takei Y, Hirokawa N. Motor protein KIF1A is essential for synaptogenesis and learning enhancement in an enriched environment. *Neuron* 2012;73:743–757.
3. Lee J-R, Srour M, Kim D, et al. De novo mutations in the motor domain of KIF1A cause cognitive impairment, spastic paraparesis, axonal neuropathy, and cerebellar atrophy. *Hum Mutat* 2015;36:69–78.
4. Ohba C, Hagiya K, Osaka H, et al. De novo *KIF1A* mutations cause intellectual deficit, cerebellar atrophy, lower limb spasticity and visual disturbance. *J Hum Genet* 2015;60:739–742.
5. Okamoto N, Miya F, Tsunoda T, et al. *KIF1A* mutation in a patient with progressive neurodegeneration. *J Hum Genet* 2014;59:639–641.
6. Rivière J-B, Ramalingam S, Lavastre V, et al. *KIF1A*, an axonal transporter of synaptic vesicles, is mutated in hereditary sensory and autonomic neuropathy type 2. *Am J Hum Genet* 2011;89:219–230.
7. Klebe S, Azzedine H, Durr A, et al. Autosomal recessive spastic paraplegia (SPG30) with mild ataxia and sensory neuropathy maps to chromosome 2q37.3. *Brain* 2006;129:1456–1462.
8. de Souza PVS, de Rezende Pinto WBV, de Rezende Batistella GN, et al. Hereditary spastic paraplegia: clinical and genetic hallmarks. *Cerebellum* 2017;16:525–551.
9. Blackstone C. Cellular pathways of hereditary spastic paraplegia. *Annu Rev Neurosci* 2012;35:25–47.
10. Klebe S, Lossos A, Azzedine H, et al. *KIF1A* missense mutations in SPG30, an autosomal recessive spastic paraplegia: distinct phenotypes according to the nature of the mutations. *Eur J Hum Genet* 2012;20:645–649.
11. Ylikallio E, Kim D, Isohanni P, et al. Dominant transmission of de novo *KIF1A* motor domain variant underlying pure spastic paraplegia. *Eur J Hum Genet* 2015;23:1427–1430.
12. Citterio A, Arnoldi A, Panzeri E, et al. Variants in *KIF1A* gene in dominant and sporadic forms of hereditary spastic paraparesis. *J Neurol* 2015;262:2684–2690.
13. Iqbal Z, Rydning SL, Wedding IM, et al. Targeted high throughput sequencing in hereditary ataxia and spastic paraplegia. *PLoS ONE* 2017;12:e0174667.
14. Roda RH, Schindler AB, Blackstone C. De novo *REEP2* missense mutation in pure hereditary spastic paraplegia. *Ann Clin Transl Neurol* 2017;4:347–350.
15. Kircher M, Witten DM, Jain P, et al. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet* 2014;46:310–315.
16. Hotchkiss L, Donkervoort S, Leach ME, et al. Novel de novo mutation in *KIF1A* as a cause of hereditary spastic paraplegia with progressive central nervous system involvement. *J Child Neurol* 2016;31:1114–1119.