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Hereditary spastic paraplegia caused by compound heterozygous mutations outside the motor domain of the KIF1A gene.

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Abstract

BACKGROUND AND PURPOSE: Hereditary spastic paraplegia is a clinically and genetically heterogeneous group of rare, inherited disorders causing an upper motor neuron syndrome with (complex) or without (pure) additional neurological symptoms. Mutations in the **KIF1A** gene have already been associated with recessive and dominant forms of hereditary spastic paraplegia (SPG30) in a few cases.

METHODS: All family members included in the study were examined neurologically. Whole-exome sequencing was used in affected individuals to identify the responsible candidate gene. Conventional Sanger sequencing was conducted to validate familial segregation.

RESULTS: A family of Macedonian origin with two affected siblings, one with slowly progressive and the other one with a more complex and rapidly progressing hereditary spastic paraplegia is reported. In both affected individuals, two novel pathogenic mutations outside the motor domain of the **KIF1A** gene were found (NM_001244008.1:c.2909G>A, p.Arg970His and c.1214dup, p.Asn405Lysfs*40) that segregate with the disease within the family establishing the diagnosis of autosomal recessive SPG30.

CONCLUSIONS: This report provides the first evidence that mutations outside the motor domain of the gene can cause (recessive) SPG30 and extends the genotype-phenotype association for **KIF1A**-related diseases.

KEYWORDS: **KIF1A** ; SPG30; hereditary spastic paraplegia; spastic paraparesis; whole-exome sequencing

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