



HAL
open science

Hereditary spastic paraplegia and prominent sensorial involvement: think MAG mutations!

Agathe Roubertie, Majida Charif, Pierre Meyer, Gaël Manes, Isabelle Meunier, Guillaume Taieb, Raul Juntas Morales, Agnès Guichet, Cécile Delettre, Emmanuelle Sarzi, et al.

► To cite this version:

Agathe Roubertie, Majida Charif, Pierre Meyer, Gaël Manes, Isabelle Meunier, et al.. Hereditary spastic paraplegia and prominent sensorial involvement: think MAG mutations!. *Annals of Clinical and Translational Neurology*, 2019, 6 (8), pp.1572-1577. <10.1002/acn3.50860>. <hal-04956737>

HAL Id: hal-04956737

<https://hal.science/hal-04956737v1>

Submitted on 25 Mar 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.


L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC-ND 4.0 - Attribution - Non-commercial use - No Derivative Works - International License

BRIEF COMMUNICATION

Hereditary spastic paraplegia and prominent sensorial involvement: think *MAG* mutations!

Agathe Roubertie^{1,2,3} , Majida Charif⁴, Pierre Meyer^{1,5}, Gael Manes², Isabelle Meunier^{2,3}, Guillaume Taieb⁶, Raul Junta Morales⁶, Agnès Guichet⁷, Cecile Delettre², Emmanuelle Sarzi², Nicolas Leboucq⁸, François Rivier^{1,5} & Guy Lenaers⁴

¹Département de Neuropédiatrie, CHU Gui de Chauliac, Montpellier, France

²Institut des Neurosciences de Montpellier, INSERM U1051, Université de Montpellier, France

³Centre of Reference for Genetic Sensory Diseases, CHU Gui de Chauliac, Montpellier, France

⁴MitoLab, UMR CNRS 6015, INSERM 1083, Université d'Angers, 49933, Angers, France

⁵PhyMedExp, Université de Montpellier, INSERM, CNRS, Montpellier, France

⁶Département de Neurologie, CHU Gui de Chauliac, Montpellier, France

⁷Department of Biochemistry and Genetics, Angers University Hospital, Angers, France

⁸Département de Neuroradiologie, CHU Gui de Chauliac, 34 295, Montpellier, France

Correspondence

Agathe Roubertie, Département de Neuropédiatrie, CHU Gui de Chauliac, 80 Avenue Fliche, 34295 Montpellier, France. Tel: 33 4 67 33 01 82; Fax: 33 4 67 33 01 83; E-mail: a-roubertie@chu-montpellier.fr

Funding Information

None declared.

Received: 4 May 2019; Revised: 9 July 2019;

Accepted: 9 July 2019

Annals of Clinical and Translational Neurology 2019; 6(8): 1572–1577

doi: 10.1002/acn3.50860

Introduction

Hereditary spastic paraplegias (HSP) are a heterogeneous group of neurodegenerative diseases clinically characterized by progressive lower extremity weakness and spasticity, which may be isolated (pure HSP) or combined to other neurological or non-neurological signs (complex HSP).^{1,2} More than 70 genes have been implicated, involved in interconnected biological processes including axonal transport, reticulum endoplasmic function, mitochondrial metabolism, vesicle formation, membrane trafficking and myelin formation and maintenance.³ The Myelin-Associated Glycoprotein MAG is a membrane-bound adhesion protein implicated in myelin function and glial-axon interactions,⁴ which interacts with SPG2-related membrane proteolipid-1.⁵ Recently, homozygous mutations in *MAG* have been reported in patients with complex HSP^{6–8}; here, we describe a patient with

Abstract

Homozygous mutations in *MAG*, encoding the myelin-associated glycoprotein, a transmembrane component of the myelin sheath, have been associated with SPG 75 recessive spastic paraplegia. Here, we report the first patient with two compound heterozygous novel *MAG* mutations (p.A151V and p.S373R) and early developmental delay with a progressive complex phenotype characterized by spastic paraplegia, peripheral sensorimotor neuropathy, intellectual disability, and sensorial dysfunctions with severe optic atrophy and hearing involvement. Brain imaging showed progressive global cerebellar atrophy. We propose that complex hereditary spastic paraplegia, with axonal and demyelinating polyneuropathy, sensorial impairment and intellectual disability might suggest *MAG* mutations.

heterozygous composite *MAG* mutations and a complex HSP phenotype associated to severe sensorial symptoms.

Material and Methods

Standard protocol approvals, registrations, and patient consents

The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethical committee. Informed consent was obtained from the patient's legal representative.

Genetic analyses

Analysis of single-nucleotide polymorphism with a mean resolution of 18 kilo-bases⁹ was performed on the

proband DNA. Whole exome sequencing (WES) was performed on the same DNA sample by Aros Company-LTD. Variants with a frequency higher than 1% were discarded. Special attention was focused on variants in the *SPG*, *COG*, and *ALG* genes and all other genes reported to be involved in inherited Spastic Paraplegia, Congenital Disorders of Glycosylation and Friedreich Ataxia.

Brain imaging

CT scan was performed on a 64-section CT scanner (Discovery750 HD; GE Healthcare, Milwaukee, Wisconsin). Magnetic resonance images were acquired on a 1.5-T system (AVENTO, Siemens medical solutions, Erlangen, Germany) as follows: axial slices T2-weighted, T2*-weighted, FLAIR, SWI sequences and sagittal slices T1-weighted sequences.

Results

Case report

The patient is a girl of an unrelated couple from North Africa. Her three brothers are healthy (Fig. 1A). Pregnancy and delivery were uneventful. Slow progression of the psychomotor achievements was noticed from the first months of life. The girl was able to sit unaided at 10 months and managed to walk at 21 months, with an unsteady and spastic gait. Clinical examination at the age of 4 showed a broad-based gait, upper limbs dysmetria, and coordination impairment. Lower limbs examination revealed spasticity with exaggerated osteotendinous reflexes. From the age of 7, the parents reported distal lower limbs vegetative disturbances, with frequent cold feet or pale blue feet. Mild atrophy of the calf muscles and diminished ankle reflexes were noticed. Distal weakness of the lower limbs progressed slowly resulting in gait worsening; from the age of 9, the girl needed support to walk and falls occurred occasionally. At the age of 10, clinical examination showed ataxic drop-foot gait, with knee flossum; lower limbs pyramidal tract signs were less obvious. Distal sensory assessment, as vibration and pin-prick sensations, could not be performed due to the patient understanding difficulties. Upper limbs dysmetria was improved, and the patient could eat and drink alone; nevertheless, her gestures were still very slow and uncoordinated. Some degree of facial akinesia was noticed. Height, weight, and cranial perimeter growth were normal. The patient had a severe intellectual disability; she could produce three words sentences and needed help for most of the daily living activities; she was admitted in an institution for disabled children.

Peripheral motor and sensory nerve conduction studies were normal at 4 years of age, and revealed a mild mixed axonal and demyelinating sensorimotor polyneuropathy at the age of 6, without worsening at the age of 10 (Table S1).

Fundusoscopic examination performed at 4 years disclosed bilateral severe optic atrophy that remained stable (Fig. 2A). Visual acuity was 4.5/10 on both eyes. Color vision, visual field, and pattern visual evoked potentials were not performed as the patient was uncooperative. Flash visual evoked potentials were normal. Brainstem auditory evoked potentials showed reduced amplitudes of waves I, III, and V on both sides, without prolonged latencies.

Brain MRI performed at 4 years of age showed increased visibility of the cerebellar sulci (data not shown). Brain MRI performed at 6 years showed severe global cerebellar atrophy, with mild medullar and severe optic tract atrophy; discrete hyper signal of the periventricular white matter were also noticed. Brain imaging at 10 years showed progression of the cerebellar atrophy, while the other findings remained unchanged (Fig. 2B–F). Spectroscopic MRI of the brain was normal.

Metabolic investigations including amino acid screening, urine organic acid screening, serum lipid profile, vitamin E dosage, acyl carnitine and long-chain fatty acid screening, cerebrospinal fluid analysis (cell count, protein level, glycorrhachia/glycemia ratio, neurotransmitter screening), lysosomal enzyme activities and biochemical Congenital Disorder of Glycosylation testing in plasma were normal. Mitochondrial enzymatic activities on a muscle biopsy were normal.

Genetics

Analysis of single-nucleotide polymorphisms, performed with a mean resolution of 18 kilo-bases on the DNA from the index case did not disclose loss of heterozygosity, excluding consanguinity between the parents.⁹ Exome sequencing was then performed, using routine experimental protocols and pipeline analyses.¹⁰ Variants were screened for unknown damaging dominant mutations and for rare (frequency lower than 1/100) heterozygous bi-allelic mutations. No pertinent dominant mutation was found in genes related to inherited neurological diseases, and in particular in the *SPG*, *COG*, and *ALG* genes, while two mutations c.452C > T (p.A151V) and c.1117A > C (p.S373R) were found in *MAG*. They co-segregate in the index case, while both parents were carrying a single heterozygous variant, and none was found in the healthy brother (Fig. 1A and B). No alternative pair of relevant heterozygous mutations was found in another gene.

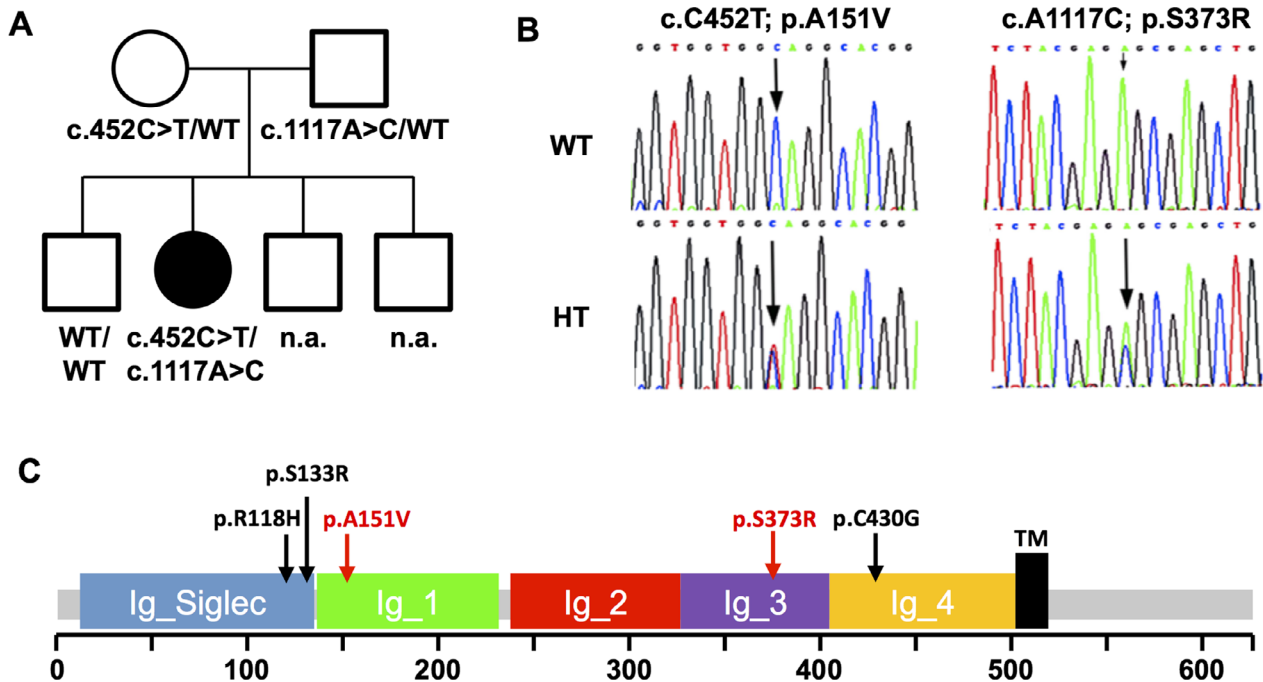


Figure 1. (A) Pedigree showing the index case and the segregation of the two heterozygous mutations in the family. (B) Electropherograms showing the wild-type (WT) and heterozygous mutated (HT) sequences for both mutations. (C) Schematic representation of the human MAG structure (626 aa), including the remarkable domains: Ig-Siglec V-Type: Immunoglobulin domain at the N terminus of Siglec (sialic acid-binding Ig-like lectins) (aa 22–139); Ig_1: C2 type 1 immunoglobulin domain (aa 141–223); Ig_2: C2 type 2 immunoglobulin domain (aa 239–309); Ig_3: C2 type 3 immunoglobulin domain (aa 339–409); Ig_4: C2 type 4 immunoglobulin domain (aa 413–508) and TM: the transmembrane domain separating the N-terminal extra-cellular region from the cytoplasmic C-terminal region. Homozygous mutations already reported in the literature are denoted in black, while the two heterozygous composite mutations identified in this work are noted in red.

Both mutations affect one of the five extracellular immunoglobulin-related domains, but different from those altered by the pathogenic homozygous mutations identified so far in *MAG* (Fig. 1C).^{6–8} The c.452C > T mutation (rs144553163) is reported with a frequency of 3.8×10^{-3} and 4.4×10^{-3} in Gnomad exomes and genomes respectively, and leads to the p.A151V amino-acid change in the second immunoglobulin domain. The c.1117A > C mutation (rs142375870) is reported with a frequency of 2.4×10^{-4} and 9.7×10^{-5} in Gnomad exomes and genomes respectively, and leads to the p.S373R amino-acid change in the fourth immunoglobulin domain. Both mutations are predicted to be damaging by the Sift, Polyphen, Mutation-Taster and LRT prediction tools and were reported as variant with uncertain clinical significance in a heterozygous state in three patients with hereditary spastic paraplegia.¹¹

Discussion

We describe a young girl with the first compound heterozygous mutations in *MAG*, who presented a complex form of HSP. The clinical picture described here

fits with the previous seven reported cases with *MAG* homozygous mutations (1) development delay noticed in the first 2 years in all but one patients (2) spastic paraplegia with sensorial visual and hearing involvements and peripheral neuropathy; (3) progressive motor deterioration; (4) variable cognitive impairment with cognitive function ranging from normal to severe mental disability; and (5) cerebellar atrophy and white matter abnormal signal concordant with myelin disorder according to the Knapp leukodystrophy classification.¹² Nevertheless, the severity and some singularities of the case reported here must be highlighted: only two patients, including this one, managed to walk independently; among the four of five patients with available follow-up information, all experienced motor deterioration after adolescence, while the one described here had earlier loss of motor autonomy at 7 years. In addition, our patient exhibited a severe cognitive impairment compared to the mild intellectual disability reported for all the others (Table S2).

This clinical presentation is due to compound heterozygous mutations affecting the second and fourth immunoglobulin domains of the *MAG* protein. *MAG*

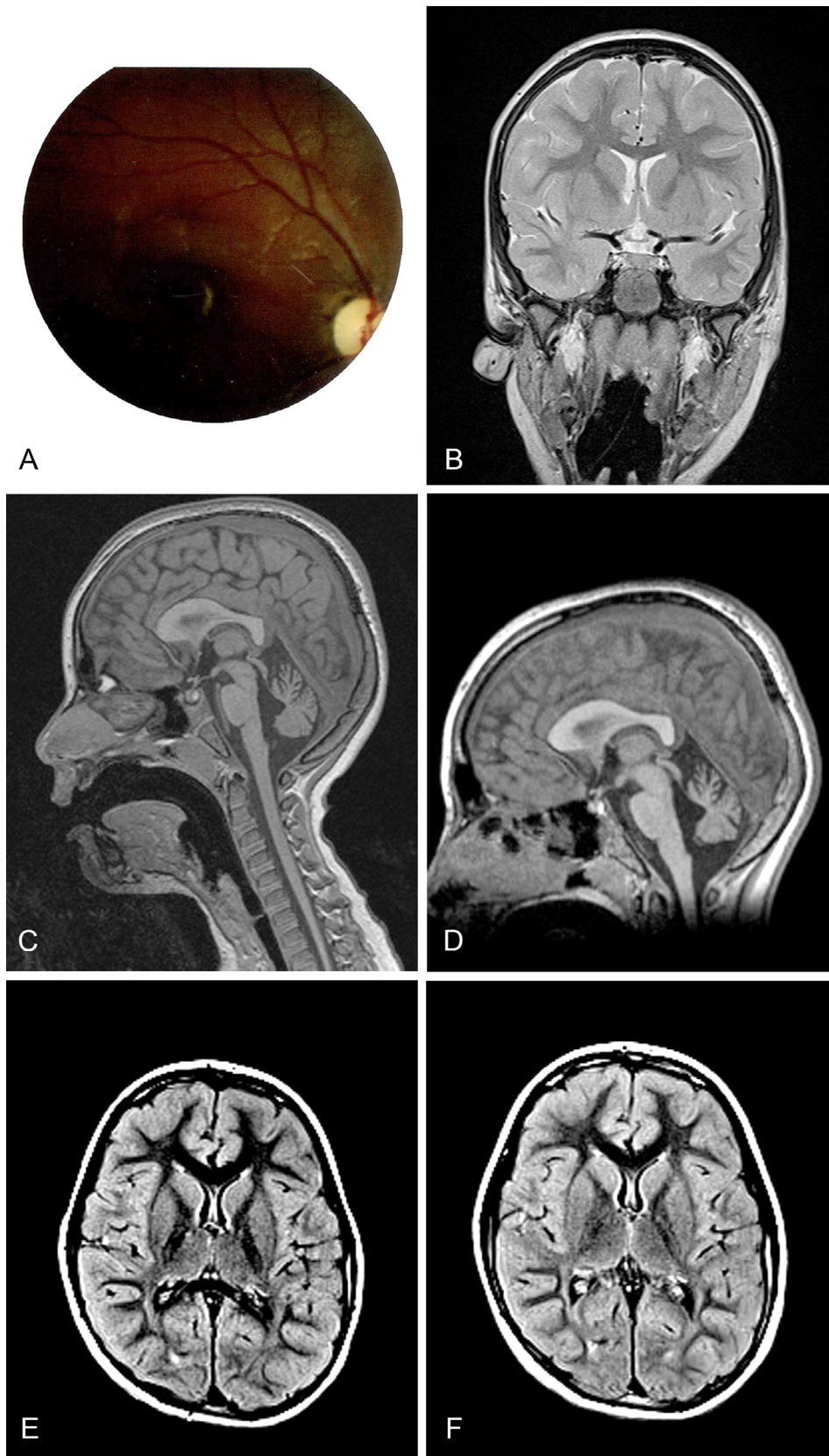


Figure 2. Eye fundus and brain magnetic resonance imaging. (A) Right eye. Note the profound pallor of the optic nerve head in line with the bilateral visual loss related to the optic nerve disorder. In contrast, the retina and the vessels are preserved. (B) T2 weighted images, axial section imaging showing optic nerve atrophy (age 10). (C and D) T1 weighted image sagittal section imaging performed at 6 (C) and 10 (D) years of age, showing progressive cerebellar atrophy. (E and F) Flair images, performed at 6 (E) and 10 (F) years of age showing stable leukopathy.

functions are associated with the control of myelin production and maintenance, and to the adhesion and signaling between myelinating oligodendrocyte and Schwann cells and axons.⁴ These functions are related to the binding of sialic acid moieties on the neuronal surface by the Siglec first immunoglobulin domain, to the interaction of the first three immunoglobulin domains with the RTN4R protein, and to homo-dimerization through the fourth and fifth immunoglobulin domains.¹³ Thus, the two *MAG* mutations identified here should disorganize the adhesion and signaling processes between myelinating cells and the axons, and affect the dimer stability, but this remains to be challenged in silico by structural modeling of the amino-acid changes, and demonstrated in vivo. Importantly, although these mutations affect different domains than the ones affected by the former 3 *MAG* mutations yet identified, the reported clinical presentations share strong similarities, suggesting a common conserved pathophysiological mechanism. In this respect, the phenotype of the *MAG* KO mice disclosed progressive peripheral neuropathy, central nervous system myelin deterioration with aging, and abnormal optic nerve myelination,^{4,14} a combination of symptoms very consistent with the ones disclosed in our patient.

To conclude, hereditary spastic paraplegia comprises a wide group of inherited neurodegenerative and neurodevelopmental disorders, resulting from primary retrograde dysfunction of the long descending fibers of the corticospinal tract. Given the growing number of HSP genetic forms and their overlapping features, clinical characterization remains a challenge before genetic testing.³ Combined CNS and PNS involvement, including spastic-ataxic gait, mixed axonal, and demyelinating polyneuropathy, and evidence of visual and auditory tract impairments, should suggest *MAG* mutations.

Acknowledgments

We are indebted to INSERM, CNRS, the University of Montpellier, the University of Angers, the CHU of Angers, the region Pays de la Loire, Angers Loire Metropole, the Fondation pour les Maladies Rares and Fondation pour la Recherche Médicale, and the following patient associations: Retina France, UNADEV, Ouvrir Les Yeux, foundation VISIO. We thank Lagavulin for constructive discussions.

Authors' Contributions

A. Roubertie and G. Lenaers conceptualized and designed the study, interpreted clinical and genetic data, drafted the initial manuscript, reviewed, and revised the manuscript.

M. Charif, A. Guichet and G. Manes carried out genetic analysis and critically reviewed the manuscript.

P. Meyer and N. Leboucq collected brain imaging data and revised the manuscript.

I. Meunier collected ophthalmological data and reviewed the manuscript.

G. Taieb, R. Junta Morales and F. Rivier collected clinical data and reviewed the manuscript.

C. Delettre and E. Sarzi interpreted the data and substantially revised the manuscript.

All authors read and approved the final manuscript.

Conflict of Interest

The authors have no conflict of interest to disclose.

References

1. Fink JK. Hereditary spastic paraplegia: clinico-pathologic features and emerging molecular mechanisms. *Acta Neuropathol* 2013;126:307–328.
2. Finsterer J, Löscher W, Quasthoff S, et al. Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance. *J Neurol Sci* 2012;318:1–18.
3. Souza P, Pinto W, Batistella G, et al. Hereditary spastic paraplegia: clinical and genetic hallmarks. 2017;1–27.
4. Quarles RH. Myelin-associated glycoprotein (*MAG*): past, present and beyond. *J Neurochem* 2007;100:1431–1448.
5. Cai Z, Sutton-Smith P, Swift J, et al. Tomacula in *MAG*-deficient mice. *J Peripher Nerv Syst* 2002;7: 181–189.
6. Novarino G, Fenstermaker AG, Zaki MS, et al. Exome sequencing links corticospinal motor neuron disease to common neurodegenerative disorders. *Science* 2014;343:506–511.
7. Lossos A, Elazar N, Lerer I, et al. Myelin-associated glycoprotein gene mutation causes Pelizaeus-Merzbacher disease-like disorder. *Brain* 2015;138(Pt 9):2521–2536.

8. Roda RH, FitzGibbon EJ, Boucekkin H, et al. Neurologic syndrome associated with homozygous mutation at *MAG* sialic acid binding site. *Ann Clin Transl Neurol* 2016;3:650–654.
9. Fradin M, Colin E, Hannouche-Bared D, et al. Run of homozygosity analysis reveals a novel nonsense variant of the *CNGB1* gene involved in retinitis pigmentosa 45. *Ophthalmic Genet* 2016;37:357–359.
10. Gerber S, Charif M, Chevrollier A, et al. Mutations in *DNM1L*, as in *OPA1*, result in dominant optic atrophy despite opposite effects on mitochondrial fusion and fission. *Brain* 2017;140:2586–2596.
11. Morais S, Raymond L, Mairey M, et al. Massive sequencing of 70 genes reveals a myriad of missing genes or mechanisms to be uncovered in hereditary spastic paraplegias. *Eur J Hum Genet* 2017;25:1217–1228.
12. KnaapMS, BugianiM. Leukodystrophies: a proposed classification system based on pathological changes and pathogenetic mechanisms. 2017:1–32.
13. Pronker MF, Lemstra S, Snijder J, et al. Structural basis of myelin-associated glycoprotein adhesion and signalling. *Nat Commun* 2016;7:13584.
14. Bartsch S, Montag D, Schachner M, Bartsch U. Increased number of unmyelinated axons in optic nerves of adult mice deficient in the myelin-associated glycoprotein (*MAG*). *Brain Res* 1997;762:231–234.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Nerve conduction studies concordant with mixed axonal and demyelinating sensorimotor polyneuropathy. (ms: millisecond; mV: millivolt, m/s: meter per second).

Table S2. Main clinical findings in published patients and in the present case harboring *MAG* mutations. NK: not known.