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Mutations in the m-AAA proteases AFG3L2 and SPG7 are causing isolated dominant optic atrophy

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Abstract

Objective
To improve the genetic diagnosis of dominant optic atrophy (DOA), the most frequently inherited optic nerve disease, and infer genotype-phenotype correlations.

Methods
Exonic sequences of 22 genes were screened by new-generation sequencing in patients with DOA who were investigated for ophthalmology, neurology, and brain MRI.

Results
We identified 7 and 8 new heterozygous pathogenic variants in *SPG7* and *AFG3L2*. Both genes encode for mitochondrial matricial AAA (m-AAA) proteases, initially involved in recessive hereditary spastic paraplegia type 7 (HSP7) and dominant spinocerebellar ataxia 28 (SCA28), respectively. Notably, variants in *AFG3L2* that result in DOA are located in different domains to those reported in SCA28, which likely explains the lack of clinical overlap between these 2 phenotypic manifestations. In comparison, the *SPG7* variants identified in DOA are interspersed among those responsible for HSP7 in which optic neuropathy has previously been reported.

Conclusions
Our results position *SPG7* and *AFG3L2* as candidate genes to be screened in DOA and indicate that regulation of mitochondrial protein homeostasis and maturation by m-AAA proteases are crucial for the maintenance of optic nerve physiology.

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Glossary

DOA = dominant optic atrophy; **HSP7** = hereditary spastic paraplegia; **OCT** = optical coherence tomography; **RGC** = retinal ganglion cell; **RNFL** = retinal nerve fiber layer; **SCA28** = spinocerebellar ataxia.

Dominant optic atrophy (DOA, MIM*605290) is the most commonly inherited optic neuropathy, leading to irreversible loss of retinal ganglion cells (RGCs), optic nerve degeneration, and central visual loss.[1,2] More than 400 *OPA1* variants were identified in DOA individuals,[3–6] resulting in excess of mitochondrial fission.[7,8] Surprisingly, a similar clinical presentation was also reported in individuals with dominant *DNM1L* mutations[9] (MIM603850) and mitochondrial network hyperfusion, thus providing evidence that alterations of both fusion and fission compromise RGC survival. This hypothesis was further supported by the identification in syndromic DOA families of dominant mutations in *MFN2* (MIM608507)[10] and *OPA3* (MIM606580),[11] 2 additional genes acting on mitochondrial dynamics. More recently, a single *SPG7* (MIM602783) mutation and a single *AFG3L2* (MIM604581) mutation were reported in DOA families,[12–14] although mutations in these genes are commonly known to be responsible for the recessive hereditary spastic paraplegia type 7 (HSP7)[15] and dominant spinocerebellar ataxia 28 (SCA28),[16] respectively. In addition, the occurrence of heterozygous variants in *SPG7* and *AFG3L2* was identified in a patient affected with DOA and parkinsonism,[17] a clinical presentation found in few patients with *OPA1*.[18] *SPG7* and *AFG3L2* are paralogue genes encoding mitochondrial matricial AAA (m-AAA)-proteases involved in protein homeostasis and the cleavage of the OMA1 and YME1L mitochondrial proteases, which control the shift between profusion long and profission short OPA1 isoforms.[19]

This prompted us to screen *SPG7* and *AFG3L2* exonic sequences in patients with DOA without molecular diagnosis. We report the identification of pathogenic variants in these 2 genes in nonsyndromic patients with DOA.

Methods

Standard protocol approvals, registrations, and patient consents

Written informed consent to perform genetic analyses was obtained from each subject involved in this study or from the parents of individuals younger than 18 years of age, according to the protocols approved by the ethical committees of the different institutes involved in this study and in agreement with the Declaration of Helsinki (Institutional Review Board Committee of the University Hospital of Angers, Authorization number: AC-2012-1507).

Genetic analysis

Genomic DNA was extracted from peripheral blood cells from multinational cohorts of DOA and sporadic cases of optic atrophy, initially screened for *OPA1*, *OPA3*, and *WFS1* exonic sequences and the 3 primary Leber hereditary optic neuropathy mutations. Cases negative after this primary screening were analyzed by resequencing a panel of 22 genes (table e-1, links.lww.com/NXG/A260) involved in inherited optic neuropathies or in mitochondrial dynamics. Library preparation for each sample was performed using an Ion AmpliSeq Library Kit 2.0 (Cat. no. 4480441) according to the manufacturer's protocol (Thermo Fisher Scientific, MAN0006735). Sample emulsion PCR, emulsion breaking, and enrichment were performed using the Ion 540 Kit–Chef (Cat. no. A27759) according to the manufacturer's instructions (Thermo Fisher Scientific, MAN0010851). Sequencing was performed using a 540 ChIPs on an Ion S5 Sequencer using the barcoded samples. Sequencing data were processed using our own dedicated bioinformatics pipeline, as described elsewhere.[20] Candidate pathogenic variants were validated by Sanger sequencing, and their segregation was assessed in DNAs from other members of the families, when available.

Cell studies

Fibroblasts from *AFG3L2* individuals P1: III:2 and P2: II:1 from family 9 and 15, respectively, were generated from skin biopsies and cultured in 2/3 Dulbecco's Minimum Essential Medium (DMEM, Gibco) supplemented with 1/3 AmnioMAX (Gibco), 10% fetal calf serum (Lonza), and 1% Penicillin-Streptomycin-Amphotericin B (Lonza). Mitochondrial network analysis, respiratory chain enzymatic activities, and mtDNA copy number were assessed as described.[9]

Data availability

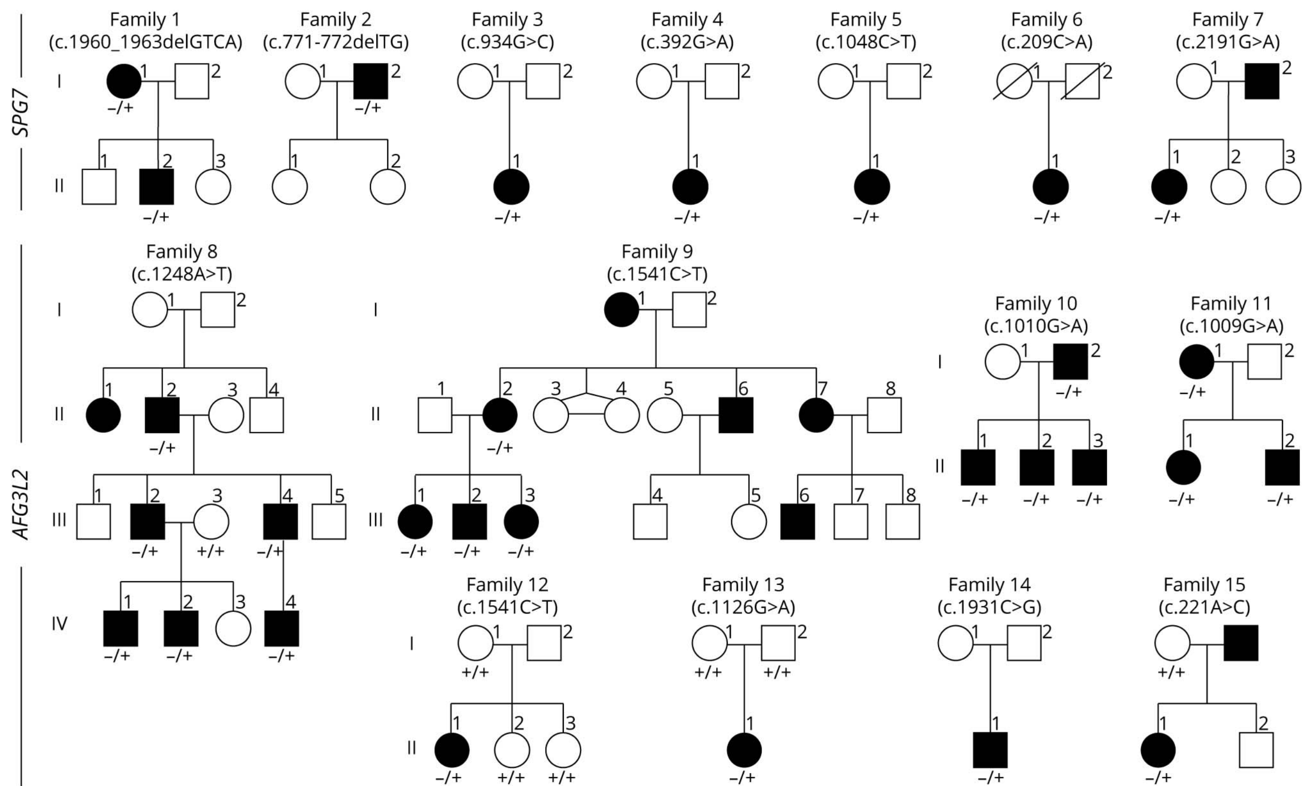
All data relevant to this study are contained within the article.

Results

Identification of *SPG7* and *AFG3L2* pathogenic variants in individuals with DOA or isolated optic atrophy using a targeted sequencing panel

Six hundred cases without positive result after screening *OPA1, OPA3,* and *WFS1* exonic sequences and the 3 primary Leber hereditary optic neuropathy mutations were included in a resequencing program focused on 22 genes, among which were those already firmly established for DOA and recessive optic atrophy and candidate genes encoding actors of the mitochondrial dynamics. After eliminating frequent (>1/10.000) and nonpathogenic variants, according to the SIFT, PolyPhen, MutationTaster, and LRT prediction tools, we identified 7 and 8 individuals harboring a *SPG7* or an

Figure 1 *SPG7* and *AFG3L2* pedigrees



Description of the pedigrees with *SPG7* (top) and *AFG3L2* (middle and bottom) mutations and their segregation among the DOA families. DOA = dominant optic atrophy.

AFG3L2 pathogenic heterozygous variant, respectively. These variants were confirmed by Sanger sequencing and analyzed for segregation whenever possible in the respective families. Segregation of the 15 variants fitted with the clinical features of affected individuals for whom DNA samples were available (Figure 1). In family 13, the c.1126G > A variant in *AFG3L2* was not found in both parents, suggesting that it occurred de *novo*.

Phenotypic manifestations of *SPG7* and *AFG3L2* mutation carriers

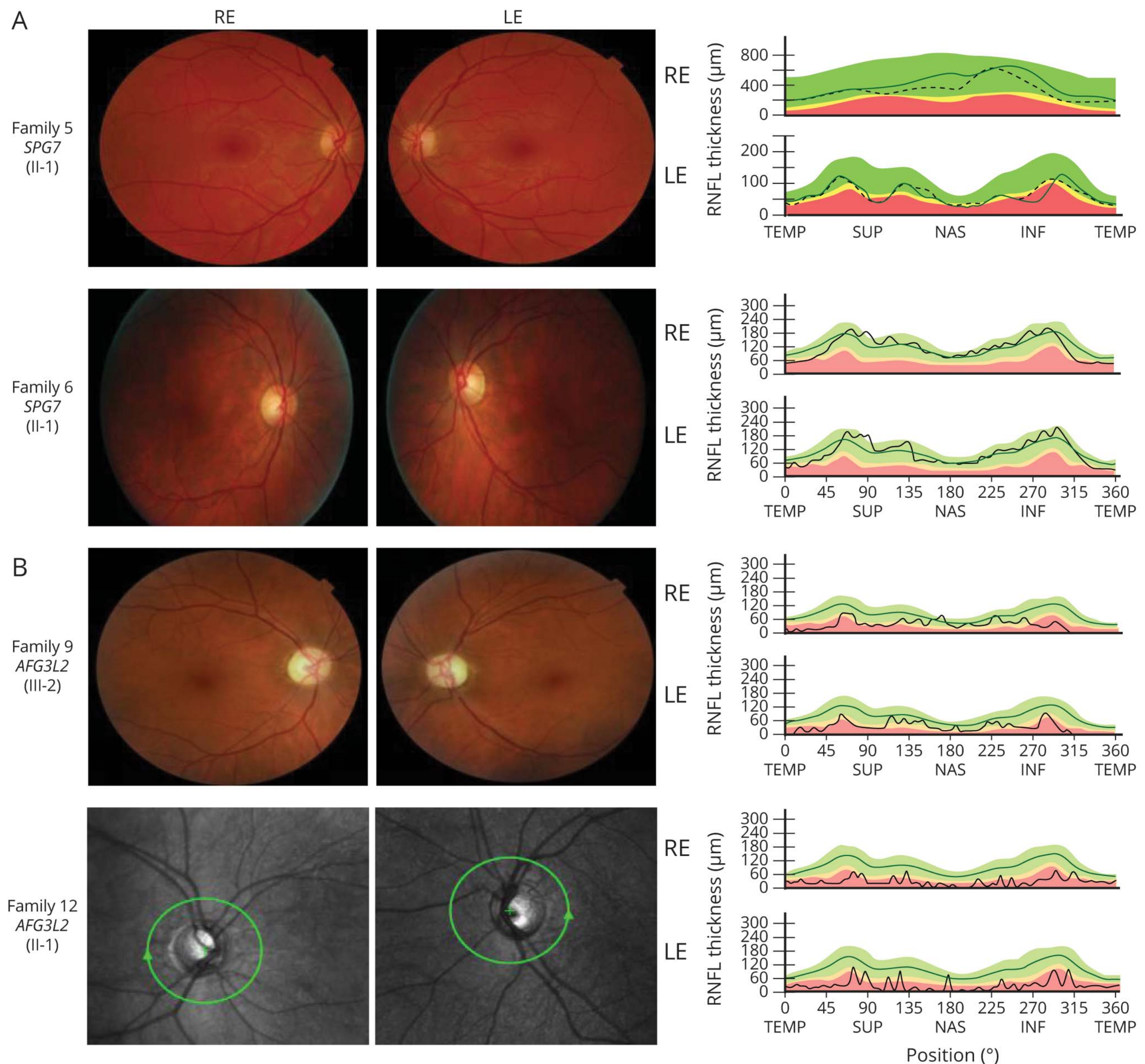
All individuals included were referred to ophthalmology departments for visual acuity impairment. At inclusion, none of them complained of spastic paraplegia or SCA, and in all cases but one, the brain MRI was normal. All patients with *SPG7* presented optic disk pallor and accordingly, reduced retinal nerve fiber layer (RNFL) at optical coherence tomography (OCT) scanning, mainly on the temporal side (figure 2A). Nevertheless, their visual acuity alterations were mild, with scores ranging from 3/10 to 10/10 (table 1) and occurring during midlife for all individuals except one (family 3, II-1). Patient II.1 from family 4 with the best visual acuity only presented a significant reduction of the RNFL at the OCT examination. No additional symptom was observed for the index cases and their relatives when the clinical data were available, except for a hearing impairment in family 5 (table 1).

Conversely, all *AFG3L2* mutated individuals disclosed a severe optic atrophy with visual acuities ranging from 0.2/10 to 2/10, except for the 3 members of family 7 who had visual acuity scores above 4/10 (table 1). First ophthalmologic examination occurred in a broad range of age, with some individuals being affected early during the first 2 decades, as reported for patients with *OPA1*.[1] All patients disclosed optic nerve pallor and highly reduced RNFL at OCT scanning (figure 2B). Similar to *SPG7*, no brain MRI abnormality was reported in investigated patients, except for patient II.1 from family 14, who had a pituitary adenoma without cerebellar atrophy. This individual had a hearing impairment in addition to a very low visual acuity (table 1).

Functional consequences of *SPG7* and *AFG3L2* mutations

SPG7 and *AFG3L2* encode highly similar proteins with 5 conserved domains (figure 3). Four of the DOA mutations in *SPG7* are referenced with a frequency close to 1e-05 in the GnomAD database, whereas the 3 others were not referenced. All *SPG7* variants responsible for DOA are interspersed with the recessive variants responsible for HSP7, and 2 of them are deletions leading to a frameshift at positions 258 and 654. These latter data suggest that SPG7 haploinsufficiency might be the primary causal pathologic process in DOA. Surprisingly, other heterozygote composite frameshift mutations were

Figure 2 Ophthalmologic exploration of *SPG7* and an *AFG3L2* affected individuals



Left: Eye fundus pictures of individuals with *SPG7* (A, family 5, II.1 and family 6 II.1) and individuals with *AFG3L2* (B, family 9, III:2 and family 12, II.1) revealing the temporal pallor of the optic discs in both REs and LEs. Right: RNFL by optic coherence tomography in individuals, disclosing the mild reduction of RNFL thickness in the individuals with *SPG7* (A) and the severe one in the individuals with *AFG3L2* (B). The green area defines the 5th to 95th, the yellow area the 1st to 5th, and the red area below the 1st percentiles. INF = inferior quadrants; LE = left eye; NAS = nasal; RE = right eye; RNFL = retinal nerve fiber layer assessment; SUP = superior; TEMP = temporal.

reported to cause HSP7, even at an earlier position toward the N-end of the protein (figure 3A). Unfortunately, no individual with a *SPG7* variant accepted to provide a skin biopsy to infer fibroblasts for functional validation.

Seven out of the 8 *AFG3L2* variants identified in this study were not referenced in any database. They result in missense amino acid changes (table 1), and all but one (p.Thr644Ser from family 14) are located in domains different from the one involved in SCA28 individuals, suggesting that they affect another AFG3L2 function than the one responsible for the SCA28 phenotype (figure 3B). Two fibroblast cell lines were established from individuals III:2 from family 9 and II:1 from family 15 to assess their mitochondrial shape and physiology. A tendency toward mitochondrial fragmentation was observed in *AFG3L2* fibroblasts (figure e-1, links.lww.com/NXG/A261), together with a significant reduction of CI, CIII, and CIV enzymatic activities, which correlated with a significant citrate synthase decreased activity, suggesting a reduction of the mitochondrial mass. This prompted the analysis of mitochondrial DNA copy number (figure e-1), which showed a significant 50% reduction in *AFG3L2* cells.

Table 1 Clinical data of the patients with *SPG7* and *AFG3L2*

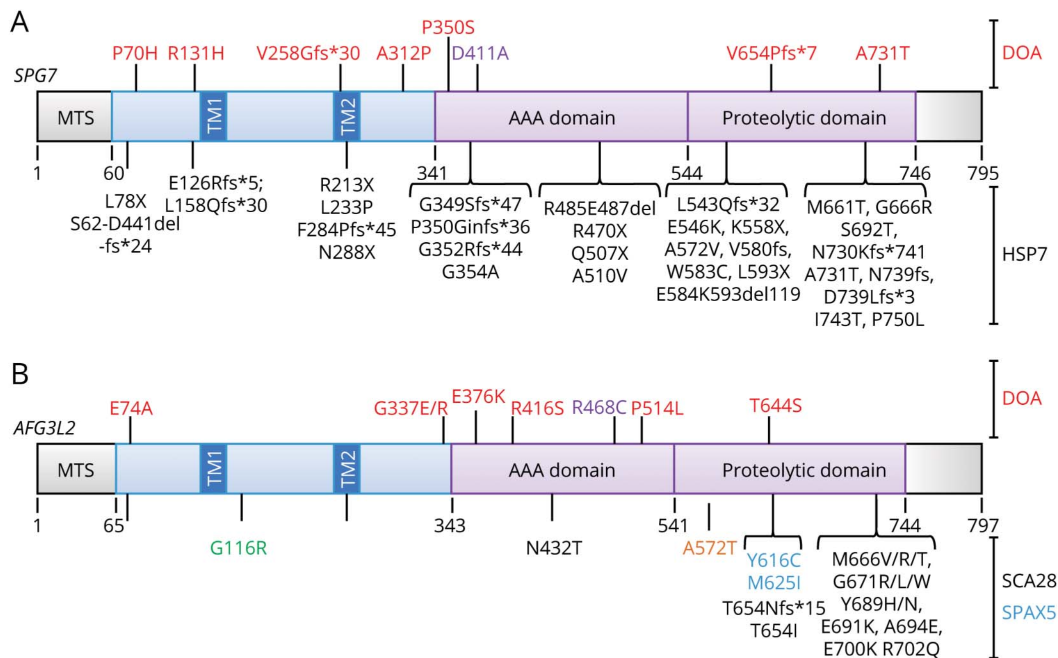
Family	Patient	Sex	Age	VA	Other symptoms	Brain MRI	Gene	ORF mutation	Protein change	rs #	GnomAD Freq.
1	I.1	F	42	4/10	—	Normal	*SPG7*	c.1960_ 1963delGTCA	p.Val654Profs*7	Unknown	
2	II.1	M	43	3/10	Liver cirrhosis	ND	*SPG7*	c.773-774delTG	p.Val258Glyfs*30	rs768136171	8.03e-06
3	II.1	F	8	5/10	—	Normal	*SPG7*	c.934G>C	p.Ala312Pro	Unknown	
4	II.1	F	66	10/ 10	—	Normal	*SPG7*	c.392G>A	p.Arg131His	rs985921704	7.99e-06
5	II.1	F	31	9/10	Hearing impairment	ND	*SPG7*	c.1048C>T	p.Pro350Ser	rs199789849	2 e-05
6	II.1	F	64	5/10	—	Normal	*SPG7*	c.209C>A	p.Pro70His	Unknown	
7	II.1	F	62	2&9/ 10	—	Normal	SPG7	c.2191G>A	p.Ala731Thr	rs747521455	3.19e-5
8	III.2	M	36	5/10	—	Normal	*AFG3L2*	c.1248A>T	p.Arg416Ser	Unknown	
	IV.1	M	7	5/10	—	Normal	*AFG3L2*	c.1248A>T	p.Arg416Ser		
	IV.4	M	8	4/10	—	Normal	*AFG3L2*	c.1248A>T	p.Arg416Ser		
9	II.2	F	47	2/10	—	Normal	*AFG3L2*	c.1541C>T	p.Pro514Leu	Unknown	
	III.1	F	26	1/10	—	Normal	*AFG3L2*	c.1541C>T	p.Pro514Leu		
	III.2	M	22	1/10	—	Normal	*AFG3L2*	c.1541C>T	p.Pro514Leu		
	III.3	F	15	1/10	—	Normal	*AFG3L2*	c.1541C>T	p.Pro514Leu		
10	I.2	M	80	1/10	—	ND	*AFG3L2*	c. 1010 G>A	p.Gly337Glu	Unknown	
	II.1	M	61	1.6/ 10	—	ND	*AFG3L2*	c. 1010 G>A	p.Gly337Glu		
	II.2	M	60	1.6/ 10	—	ND	*AFG3L2*	c. 1010 G>A	p.Gly337Glu		
	II.3	M	58	1.6/ 10	—	ND	*AFG3L2*	c. 1010 G>A	p.Gly337Glu		
11	I.1	F	46	0.5/ 10	—	Normal	*AFG3L2*	c.1009G>A	p.Gly337Arg	Unknown	
	II.1	F	13	0.5/ 10	—	Normal	*AFG3L2*	c.1009G>A	p.Gly337Arg		
	II.2	M	7	0.8/ 10	—	Normal	*AFG3L2*	c.1009G>A	p.Gly337Arg		
12	II.1	F	25	0.2/ 10	—	Normal	*AFG3L2*	c.1541C>T	p.Pro514Leu	Unknown	
13	II.1	F	9	1.3/ 10	—	Normal	*AFG3L2*	c.1126G>A	p.Glu376Lys	Unknown	
14	II.1	M	59	1.6/ 10	—	Normal	*AFG3L2*	c.1931C>G	p.Thr644Ser	rs1226952405	3.98e-06
15	II.1	F	19	0.5/ 10	Hearing impairment	Pituitary adenomas	*AFG3L2*	c.221A>C	p.Glu74Ala	Unknown	

Abbreviations: GnomAD Freq. = frequency in the genome aggregation database; ND = not done; ORF = open reading frame; rs # = reference sequence number; VA = visual acuity.

Discussion

Dominant *SPG7* and *AFG3L2* mutations can result in isolated optic nerve involvement with a clinical phenotype indistinguishable from that seen in patients with DOA harboring dominant *OPA1* mutations. As in *OPA1*-positive DOA, *SPG7* and *AFG3L2* mutation carriers can present with a broad spectrum of visual impairment ranging from asymptomatic

Figure 3 Structural representation of SPG7 and AFG3L2 amino acid changes related to mutations in individuals with DOA, HSP7, and SCA28/SPAX5



(A): Structure and domains of the SPG7 protein with the amino acid changes associated with DOA (top) and HSP7 (bottom); red, mutations identified in this study; purple, a DOA mutation previously reported; and black: HSP7 published mutations. (B): Structure and domains of the AFG3L2 protein with the amino acid changes associated with DOA (top) and to other diseases (bottom); red, mutations identified in this study; purple, a previously reported DOA mutation; black, published mutations responsible for SCA28; blue, published mutations responsible for recessive spastic ataxia SPAX5; in green, myoclonus and pyramidal signs; and in orange, microcephaly, early onset seizures, spasticity, and basal ganglia atrophy. DOA = dominant optic atrophy; SCA28 = spinocerebellar ataxia; SPAX5 = spastic ataxia-neuropathy syndrome.

mutation carriers to legal blindness and, in some of them, to a more severe syndromic manifestation with sensorineural deafness.[21]

It is intriguing that *SPG7* mutations can behave both dominantly and recessively with variable tissue specificity. Of interest, in a previous work reporting novel *SPG7* mutations, 10 affected individuals underwent an ophthalmologic examination and all of them had evidence of a mild optic neuropathy with bilateral optic disc pallor and thinning of the peripapillary RNFL on OCT imaging.[12] Conversely, the neurologic examination by the same team of the first-identified *SPG7*-related DOA family did not evidence any gait or walking difficulties in mutation carriers. In addition, the *SPG7* variants that we identified in individuals with DOA are interspersed with the recessive variants resulting in HSP7, and in both diseases frameshift variants are contributing to the pathophysiologic mechanism. Altogether, these data suggest a clinical overlap related to *SPG7* mutations between DOA on one end and HSP7 on the other end and all possible mixed phenotype inbetween. These observations should prompt to perform a systematic neuroophthalmological examination of individuals with HSP7 and their heterozygous parents. Similarly, DOA individuals with a *SPG7* variant should have a neurologic follow-up, particularly older than the age of 40 years, to evaluate the eventual occurrence of spasticity and also cognitive impairment, epilepsy, and cerebellar atrophy.

Dominant mutations in *AFG3L2* were initially found in individuals affected with SCA28 and do localize in exons 15 and 16, in addition to one in exon 10.[22] Recessive consanguineous *AFG3L2* mutations in exon 15 were also identified in a spastic ataxia-neuropathy syndrome[23] (SPAX5), whereas 2 additional dominant *AFG3L2* variants were identified in an individual affected with myoclonus and pyramidal signs[24] and a recessive mutation in another family affected with microcephaly, early onset seizures, spasticity, and basal ganglia atrophy.[25] Of interest, the 8 missense *AFG3L2* variants that we identified in individuals with DOA are involving other domains than those identified earlier, thus explaining the absence of clinical overlap between all the symptoms previously described for *AFG3L2* mutations and the optic atrophy found in this study. This is reinforced by the normality of the brain MRI and the absence of ataxia in *AFG3L2*-related patients with DOA. Nevertheless, we suggest that the ophthalmologic follow-up of these individuals should be accompanied by a neurologic examination to eventually diagnose early manifestations of cerebellar ataxia or any other clinical symptoms.

The 2 m-AAA proteases encoded by *SPG7* and *AFG3L2* genes have been described as promoting OPA1 cleavage to its short profission isoforms.[19] This activity is under the control of OMA1 and YME1L proteases that directly process

the cleavage of OPA1.[26] Our data suggest that this mechanism might be affected by the dominant variants in both genes, although at different levels, depending on the mutated gene. Indeed, AFG3L2 forms both homopolymers and heteropolymers with SPG7; therefore, pathogenic variants should affect the activity of both types of polymers. Conversely, SPG7 can only form heteropolymers with AFG3L2, but not homopolymers, implying that pathogenic variants should only affect the activity of the AFG3L2-SPG7 heteropolymers. This might explain the relatively mild visual deficits in individuals with *SPG7* variants, contrasting with the more severe visual loss observed in individuals with *AFG3L2* variants and the syndromic DOA plus phenotype found in a patient harboring concurrent mutations in both genes. It further questions the possible specificity of these mutations for the regulation of *OPA1* processing. In this respect, mitochondrial dynamic might be affected by the other *SPG7* mutations but overwhelmed by the severe HSP7 phenotype, whereas it is apparently not affected by the *AFG3L2* variants involved in SCA28. This reflect the fact that no optic atrophy has been yet reported in the mouse models harboring *Spg7* or *Afg3l2* mutations.

Thus, we provide compelling evidence that heterozygous *SPG7* and *AFG3L2* mutations should be considered in the cases of isolated DOA, more so when already found to be *OPA1*-negative. Our findings stress the central role mediated by m-AAA proteases in the regulation of mitochondrial dynamics and how dysfunction of these pathways compromise the RGC integrity and survival, resulting in optic neuropathy.

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David Goudenège, PhD	University and Hospital of Angers, France	Acquisition and analysis of the data
Valérie Desquiret-Dumas, PhD	University and Hospital of Angers, France	Acquisition and analysis of the data
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Audrey Meunier, MD	University and Hospital of Brussels, Belgium	Clinical investigation and phenotyping
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Continued

Appendix *(continued)*

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Pascal Reynier, MD, PhD	University and Hospital of Angers, France	Clinical investigation and phenotyping; Acquisition and analysis of the data
Dominique Bonneau, MD, PhD,	University and Hospital of Angers, France	Clinical investigation and phenotyping and revised the manuscript for intellectual content
Patrizia Amati-Bonneau, MD, PhD	University and Hospital of Angers, France	Conception and design of the study and acquisition and analysis of the data
Guy Lenaers, PhD	University and Hospital of Angers, France	Conception and design of the study and drafting a significant portion of the manuscript and figures

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