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Abstracts

Articles appearing in the June 2020 issue

Cerebellar ataxia, neuropathy, hearing loss, and intellectual disability due to AIFM1 mutation

Objective To describe the clinical and molecular genetic findings in a family segregating a novel mutation in the *AIFM1* gene on the X chromosome.

Methods We studied the clinical features and performed brain MRI scans, nerve conduction studies, audiometry, cognitive testing, and clinical exome sequencing (CES) in the proband, his mother, and maternal uncle. We used in silico tools, X chromosome inactivation assessment, and Western blot analysis to predict the consequences of an *AIFM1* variant identified by CES and demonstrate its pathogenicity.

Results The proband and his maternal uncle presented with childhood-onset nonprogressive cerebellar ataxia, hearing loss, intellectual disability (ID), peripheral neuropathy, and mood and behavioral disorder. The proband's mother had mild cerebellar ataxia, ID, and mood and behavior disorder, but no neuropathy or hearing loss. The 3 subjects shared a variant (c.1195G>A; p.Gly399Ser) in exon 12 of the *AIFM1* gene, which is not reported in the exome/genome sequence databases, affecting a critical amino acid for protein function involved in NAD(H) binding and predicted to be pathogenic with very high probability by variant analysis programs. X chromosome inactivation was highly skewed in the proband's mother. The mutation did not cause quantitative changes in protein abundance.

Conclusions Our report extends the molecular and phenotypic spectrum of *AIFM1* mutations. Specific findings include limited progression of neurologic abnormalities after the first decade and the coexistence of mood and behavior disorder. This family also shows the confounding effect on the phenotype of nongenetic factors, such as alcohol and drug use and side effects of medication.

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

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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