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Abstracts

Papers appearing in the October 2019 issue

A family with spinocerebellar ataxia and retinitis pigmentosa attributed to an *ELOVL4* mutation

Objective To identify the genetic cause of autosomal dominant spinocerebellar ataxia and retinitis pigmentosa in a large extended pedigree.

Methods Clinical studies were done at 4 referral centers. Ten individuals in the same extended family participated in at least a portion of the study. Records were obtained from an 11th, deceased, individual. Neurologic and dermatological examinations were performed. Ophthalmologic evaluation including funduscopic examination and in some cases ocular coherence tomography were used to identify the presence of retinal disease. Whole exome sequencing (WES), in conjunction with Sanger sequencing and segregation analysis, was used to identify potential genetic mutation.

Results Affected individuals reported slowly progressive cerebellar ataxia with age at onset between 38 and 57. Imaging demonstrated cerebellar atrophy (3/3). WES identified a novel heterozygous mutation in the elongation of very long chain fatty acids 4 (*ELOVL4*) gene (c.512T > C, p.Ile171Thr) that segregated with ataxia in 7 members tested. Four of 8 members who underwent ophthalmologic evaluation were found to have retinitis pigmentosa. No skin findings were identified or reported. Ocular movement abnormalities and pyramidal tract signs were also present with incomplete penetrance.

Conclusions We report a family with both spinocerebellar ataxia and retinal dystrophy associated with an *ELOVL4* mutation. In addition, to supporting prior reports that *ELOVL4* mutations can cause spinocerebellar ataxia, our findings further broaden the spectrum of clinical presentations associated with spinocerebellar ataxia 34.

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Homozygous pathogenic variant in *BRAT1* associated with nonprogressive cerebellar ataxia

Objective To investigate the pathogenicity of a novel homozygous *BRAT1* variant in 2 siblings with nonprogressive cerebellar ataxia (NPCA) through functional studies on primary and immortalized patient cell lines.

Methods BRAT1 protein levels and ataxia-telangiectasia mutated (ATM) kinase activity in patient-derived and control cell lines were assessed by Western blotting. The impact of the novel *BRAT1* variants on mitochondrial function was also assessed, by comparing patient and control cell lines for rates of oxygen consumption and for phosphorylation (S293) of the E1α subunit of pyruvate dehydrogenase (PDH).

Results Two male siblings with NPCA, mild intellectual disability, and isolated cerebellar atrophy were found to be homozygous for a c.185T>A (p.Val62Glu) variant in *BRAT1* by WES. Western blotting revealed markedly decreased BRAT1 protein levels in lymphocytes and/or fibroblast cells from both affected siblings compared to control cell lines. There were no differences between the patient and control cells in ATM kinase activation, following ionizing radiation. Mitochondrial studies were initially suggestive of a defect in regulation of PDH activity, but there was no evidence of increased phosphorylation of the E1α subunit of the PDH complex. Measurement of oxygen consumption rates similarly failed to identify differences between patient and control cells.

Conclusions Biallelic pathogenic variants in *BRAT1* can be associated with NPCA, a phenotype considerably milder than previously reported. Surprisingly, despite the molecular role currently proposed for BRAT1 in ATM regulation, this disorder is unlikely to result from defective ATM kinase or mitochondrial dysfunction.

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