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Abstracts

Articles appearing in the October 2019 issue

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 whole exome sequencing. 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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Next-generation sequencing approach to hyperCKemia: A 2-year cohort study

Objective Next-generation sequencing (NGS) was applied in molecularly undiagnosed asymptomatic or paucisymptomatic hyperCKemia to investigate whether this technique might allow detection of the genetic basis of the condition.

Methods Sixty-six patients with undiagnosed asymptomatic or paucisymptomatic hyperCKemia, referred to tertiary neuromuscular centers over an approximately 2-year period, were analyzed using a customized, targeted sequencing panel able to investigate the coding exons and flanking intronic regions of 78 genes associated with limb-girdle muscular dystrophies, rhabdomyolysis, and metabolic and distal myopathies.

Results A molecular diagnosis was reached in 33 cases, corresponding to a positive diagnostic yield of 50%. Variants of unknown significance were found in 17 patients (26%), whereas 16 cases (24%) remained molecularly undefined. The major features of the diagnosed cases were mild proximal muscle weakness (found in 27%) and myalgia (in 24%). Fourteen patients with a molecular diagnosis and mild myopathic features on muscle biopsy remained asymptomatic at a 24-month follow-up.

Conclusions This study of patients with undiagnosed hyperCKemia, highlighting the advantages of NGS used as a first-tier diagnostic approach in genetically heterogeneous conditions, illustrates the ongoing evolution of molecular diagnosis in the field of clinical neurology. Isolated hyperCKemia can be the sole feature alerting to a progressive muscular disorder requiring careful surveillance.

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