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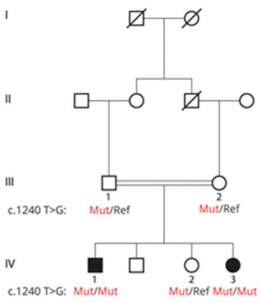
Abstracts

Articles appearing in the April 2018 issue

ACO2 homozygous missense mutation associated with complicated hereditary spastic paraplegia



Objective To identify the clinical characteristics and genetic etiology of a family with hereditary spastic paraplegia (HSP).

Methods Clinical, genetic, and functional analyses involving genome-wide linkage coupled to whole-exome sequencing in a consanguineous family with complicated HSP.

Results A homozygous missense mutation was identified in the *ACO2* gene (c.1240T>G p.Phe414Val) that segregated with HSP complicated by intellectual disability and microcephaly. Lymphoblastoid cell lines of homozygous carrier patients revealed significantly decreased activity of the mitochondrial aconitase enzyme and defective mitochondrial respiration. *ACO2* encodes mitochondrial aconitase, an essential enzyme in the Krebs cycle. Recessive mutations in this gene have been previously associated with cerebellar ataxia.

Conclusions Our findings nominate *ACO2* as a disease-causing gene for autosomal recessive complicated HSP and provide further support for the central role of mitochondrial defects in the pathogenesis of HSP.

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Rare *ABCA7* variants in 2 German families with Alzheimer disease

Objective To identify variants associated with familial late-onset Alzheimer disease (AD) using whole-genome sequencing.

Methods Several families with an autosomal dominant inheritance pattern of AD were analyzed by whole-genome sequencing. Variants were prioritized for rare, likely pathogenic variants in genes already known to be associated with AD and confirmed by Sanger sequencing using standard protocols.

Results We identified 2 rare *ABCA7* variants (rs143718918 and rs538591288) with varying penetrance in 2 independent German AD families, respectively. The single nucleotide variant (SNV) rs143718918 causes a missense mutation, and the deletion rs538591288 causes a frameshift mutation of *ABCA7*. Both variants have previously been reported in larger cohorts but with incomplete segregation information. *ABCA7* is one of more than 20 AD risk loci that have so far been identified by genome-wide association studies, and both common and rare variants of *ABCA7* have previously been described in different populations with higher frequencies in AD cases than in controls and varying penetrance. Furthermore, ABCA7 is known to be involved in several AD-relevant pathways.

Conclusions Both SNVs might contribute to the development of AD in the examined family members. Together with previous findings, our data confirm *ABCA7* as one of the most relevant AD risk genes.

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B. Rhead, M. Bäärnhielm, M. Gianfrancesco, et al. 2016;2: e97. doi: 10.1212/NXG.0000000000000097

A novel *DYNC1H1* mutation causing spinal muscular atrophy with lower extremity predominance

Q. Niu, X. Wang, M. Shi, and Q. Jin. 2015;1:e20. doi: 10.1212/NXG.0000000000000017

***CHCHD10* variant p.(Gly66Val) causes axonal Charcot-Marie-Tooth disease**

M. Auranen, E. Ylikallio, M. Shcherbii, et al. 2015;1:e1. doi: 10.1212/NXG.0000000000000003

The Clinical Outcome Study for dysferlinopathy: An international multicenter study

E. Harris, C.L. Bladen, A. Mayhew, et al. 2016;2:e89. doi: 10.1212/NXG.0000000000000089

Complete callosal agenesis, pontocerebellar hypoplasia, and axonal neuropathy due to AMPD2 loss

A.P.L. Marsh, V. Lukic, K. Pope, et al. 2015;1:e16. doi: 10.1212/NXG.0000000000000014