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Abstracts

Articles appearing in the April 2018 issue

Ataxia-telangiectasia: A new remitting form with a peculiar transcriptome signature

Objective Ataxia-telangiectasia (AT) is a rare, severe, and ineluctably progressive multisystemic neurodegenerative disease. Variant AT phenotypes have been described in patients with mild and late-onset neurologic deterioration and atypical features (dystonia and myoclonus). We report on the clinical characteristics and transcriptome profile of patients with a typical AT presentation and genotype who experienced an unexpected favorable course.

Methods A 24-year-old woman developed, by the age of 3 years, all the classic symptoms of AT associated with increased α-fetoprotein levels, a compound AT-mutated (*ATM*) genotype with an in-frame deletion c.2250G>A (p.Glu709_Lys750del42) and a missense mutation c.8122G>A (p.Asp2708Gln), and no residual ATM protein expression. By the age of 12 years, ataxia slowly disappeared, and a very mild choreic disorder was the only neurologic feature in adulthood. Brain MRI was normal. The blood transcriptome profile was assessed and compared with that of healthy controls and patients with the classic AT phenotype.

Results The atypical clinical course of the patient was associated with a transitional transcriptome profile: while 90% of transcripts were expressed as in patients with the classic AT presentation, 10% of transcripts were expressed as in healthy controls.

Conclusions The unexpected mild clinical outcome and transcriptome profile of this patient with AT suggest the existence of individual resilience to the altered ATM synthesis. Because of their possible prognostic and therapeutic implications, the identification of modifier factors affecting the phenotype would deserve further studies.

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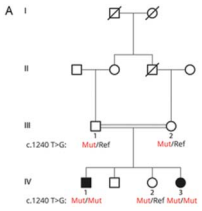
ACO2 homozygous missense mutation associated with complicated hereditary spastic paraplegia



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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