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Abstracts

Papers appearing in the August 2020 issue

COX deficiency and leukoencephalopathy due to a novel homozygous APOPT1/COA8 mutation

Objective To describe the long-term follow-up and pathogenesis in a child with leukoencephalopathy and cytochrome c oxidase (COX) deficiency due to a novel homozygous nonsense mutation in *APOPT1/COA8*.

Methods The patient was clinically investigated at 3, 5, 9, and 25 years of age. Brain MRI, repeat muscle biopsies with biochemical, morphologic, and protein expression analyses were performed, and whole-genome sequencing was used for genetic analysis.

Results Clinical investigation revealed dysarthria, dysphagia, and muscle weakness following pneumonia at age 3 years. There was clinical regression leading to severe loss of ambulation, speech, swallowing, hearing, and vision. The clinical course stabilized after 2.5 years and improved over time. The MRI pattern in the patient demonstrated cavitating leukoencephalopathy, and muscle mitochondrial investigations showed COX deficiency with loss of complex IV subunits and ultrastructural abnormalities. Genetic analysis revealed a novel homozygous mutation in the *APOPT1/COA8* gene, c.310T>C; p.(Gln104*).

Conclusions We describe a novel nonsense mutation in APOPT1/COA8 and provide additional experimental evidence for a COX assembly defect in human muscle causing the complex IV deficiency. The long-term outcome of the disease seems in general to be favorable, and the characteristic MRI pattern with cavitating leukoencephalopathy in combination with COX deficiency should prompt for testing of the *APOPT1/COA8* gene.

NPub.org/NG/959a

Brainstem ischemic syndrome in juvenile NF2

Objective A new case of brainstem ischemic necrosis in a young woman with de novo neurofibromatosis type 2 (NF2) is reported, and given notable similarities to 7 prior cases of brainstem stroke in the literature, features defining a possible syndrome were sought.

Methods Case review including detailed clinical assessment, neuroimaging analysis, genetic testing, and brain biopsy, followed by a multicase analysis.

Results Brainstem ischemia in juvenile NF2 typically occurs in teenagers without previously known NF2 as an acute, monophasic presentation with restricted diffusion in the midbrain or pons following a recent hypoperfusion event, normal vascular imaging, obvious intracranial imaging features of NF2, typical inactivating *NF2* alterations, biopsy showing necrosis without small vessel pathology, and subsequent aggressive NF2 lesion progression.

Conclusions Brainstem ischemia in juvenile NF2 is a rare syndrome of unclear etiology, possibly reflecting an unknown underlying vascular abnormality; a digenic effect is not excluded.

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J.J. Millichap, K.L. Park, T. Tsuchida, et al. 2016;2:e96. doi.org/10.1212/NXG.0000000000000096

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

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

Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk

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

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G.W. Beecham, J.C. Bis, E.R. Martin, et al. 2017;3:e194. doi.org/10.1212/NXG.0000000000000194

