SCP2 MUTATIONS AND NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

Mutations in PANK2, PLA2G6, C19orf12, FA2H, ATP13A2, WDR45, COASY, FTL, CP, and DCAF17 cause neurodegeneration with brain iron accumulation (NBIA), but the genetic etiology remains undefined in many patients. We report the second patient with sterol carrier protein x (SCPx) deficiency presenting with adult-onset spinocerebellar ataxia and brain MRI characteristic of NBIA.

Case report. A 51-year-old man developed hand clumsiness in his 30s, followed by gait disturbance and deafness. He was the first child of healthy, nonconsanguineous parents with no relevant family history. On examination, he had normal cognition, speech, vision, and optic fundi. He had slow ocular saccades but no nystagmus or ophthalmoparesis. Lower cranial nerve examination was normal. There was no muscle wasting or weakness, but tone was increased with brisk deep tendon reflexes throughout. Plantar responses were normal. Proprioception was impaired. He had mild dysmetria, dysdiadochokinesis, and a wide-based gait. There were no extrapyramidal signs.

Routine biochemical analyses showed increased alanine transaminase (88 U/L, normal <40), gamma glutamyl transferase (78 U/L, normal <70), alpha-fetoprotein (63 kU/L, normal <10), creatine kinase (777 U/L, normal <40–320), and ferritin (539 μg/L, normal <300 in men). Copper and ceruloplasmin were normal, as was the blood count, vitamin B12, and folate. Free carnitine (65 μmol/L, normal <52) and total carnitine (85.6 μmol/L, normal <63) were increased, and there was a nonspecific increase in long chain hydroxyacylcarnitines. Electrophysiology showed no evidence of polyneuropathy.

3T MRI brain revealed abnormal T2 signal (figure, A–E). Susceptibility-weighted sequences suggested increased mineral deposition in the basal ganglia (figure, F–H). Spine imaging showed no significant abnormality. Genetic testing for SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, DRPLA, FA, FTL, and HFE/p. Cys282Tyr was negative. Illumina TruSeq 62 Mb exome capture, sequencing (100 bp paired-end reads, HiSeq 2000), and alignment (UCSC hg19) was performed. Variants with a minor allele frequency >0.01 in local and international databases were filtered out. Potentially deleterious recessive variants were identified using QIAGEN Ingenuity Variant Analysis, and validated by Sanger sequencing (ABI 3130XL, Life Technologies, Carlsbad, CA), also used for the segregation analysis. Immunoblotting was performed on 12.5 μg protein using standard protocols.

Results. No pathogenic mutations were identified in genes known to cause NBIA despite 92% of bases being covered >20-fold. Potentially pathogenic mutations were identified in SCP2 (c.349C>T/p.Glu41 Tyr, c.121G>T/p.Glu41* figure, I), both predicted to introduce premature stop codons and truncate SCPx. Segregation analysis (unaffected mother and sister) confirmed that the patient was a compound heterozygote. Immunoblotting showed undetectable levels of the SCPx protein in fibroblasts (figure, J). Very long chain fatty acid analysis revealed high pristanic acid (34.1 μmol/L, normal range 0–1.5) and mildly increased phytanic acid (13.8 μmol/L, normal <11.5). Free carnitine (65 μmol/L, normal <52) and total carnitine (85.6 μmol/L, normal <63) were increased.

Discussion. The SCP2 mutations are likely to be pathogenic because (1) c.349C>T has only been described in heterozygotes in <1/10,000 healthy controls, and c.121G>T has never been previously reported; (2) the predicted functional consequences of the nonsense mutations were confirmed on Western blot, with no detectable SCPx protein likely due to nonsense-mediated decay of truncated transcripts; (3) serum branched-chain pristanic and phytanic acid levels were increased consistent with the biochemical consequences of SCPx deficiency; and (4) the only other patient described with SCPx deficiency presented was similar to the patient we describe here. Although our patient does not have a leukodystrophy at present, there was striking thalamic and pontine T2 hypointensity as in the previous case (figure).

SCPx is a peroxisomal enzyme with thiolase activity required for the breakdown of branched chain fatty acids (figure, K), and the pathogenic effects are likely to be mediated by the accumulation of branch chain fatty acids, as in other peroxisomal disorders. Mice with SCPx deficiency develop normally, but develop ataxia and...
peripheral neuropathy when fed phytanic acid. After 2 months on a Refsum diet, our patient reported an improvement of his symptoms, pristanic acid (14.0 μmol/L) and phytanic acid (2.5 μmol/L) levels were reduced, and acyl-carnitines were within the normal range, but the examination findings are unchanged so far.

Our patient had abnormal fatty-acid acyl-CoA metabolism, which has emerged as a common disease mechanism in NBIA (PANK2, FA2H, COASY). FA2H mutations cause a wide spectrum of phenotypes encompassing the ataxia and spastic paraplegia, and overt brain iron accumulation is not always
point towards other potential treatments.

The findings we report broaden the neurometabolic basis to include peroxisomal disorders, and point towards other potential treatments.

*These authors contributed equally to this work.

From the Institute of Genetic Medicine (R.H., D.L.-S., K.D., J.D., M.K., A.P., P.F.C.), Newcastle University, Newcastle upon Tyne, and The Walton Centre NHS Trust (N.F.), Liverpool, UK.

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SCP2 mutations and neurodegeneration with brain iron accumulation
Rita Horvath, David Lewis-Smith, Konstantinos Douroudis, et al.
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