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 mildly increased phytanic acid (13.8 µmol/L, normal <40), gamma-glutamyltransferase (78 U/L, normal <70), alpha-fetoprotein (63 kU/L, normal <40–320), and ferritin (539 µg/L, normal <300 in men). Copper and ceruloplasmin were normal, as was the blood count, vitamin B<sub>12</sub>, 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.Gln117* 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 \( \mu \text{mol/L} \)) and phytanic acid (2.5 \( \mu \text{mol/L} \)) 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 (\( \text{PANK2}^4 \), \( \text{FA2H}^5,6 \), \( \text{COASY}^11 \)). \( \text{FA2H} \) mutations cause a wide spectrum of phenotypes encompassing the ataxia and spastic paraplegia, and overt brain iron accumulation is not always

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Figure Brain MRI and molecular and biochemical findings in the patient

(A–E) T2-weighted imaging shows signal change in the (A) subcortical white matter, (B) thalamus, (C) globus pallidus, (D) cerebral peduncles, and (E) pons. (F–H) Susceptibility-weighted imaging shows signal dropout in the globus pallidus, substantia nigra, red nuclei, and dentate nuclei. (I) Confirmatory Sanger sequencing shows heterozygous mutations in \( \text{SCP2} \). (J) Western blot shows no detectable levels of steroid carrier protein x (SCPx) in fibroblasts from the patient using 12.5 \( \mu \text{g} \) protein and monoclonal antibodies against SCPx and \( \beta \)-actin as a loading control. (K) Schematic representation of the localization of the enzyme defect and the biochemical pathways affected by the mutations in \( \text{SCP2} \). CoA = coenzyme A; FA = fatty acid; VLCFA = very long-chain fatty acids.
apparent on T2 brain imaging, even in severely affected cases. This suggests that the brain iron accumulation is secondary to the underlying metabolic defect for FA2H and SCP2 patients, questioning the role of iron chelation as a treatment in all forms of NBIA.

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

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