OP 15 PLA2G6

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Mutations in the PLA2G6 gene cause infantile neuroaxonal dystrophy (INAD), a subgroup of neurodegeneration with brain iron accumulation (NBIA). INAD affects the central and peripheral nervous system and is defined pathologically by the presence of neuroaxonal spheroids containing accumulated membranes in distal axons. The PLA2G6 gene encodes the protein known as group VIA calcium-independent phospholipase A2 (PLA2G6). Our studies demonstrate that human PLA2G6 hydrolyzes both phospholipids and lysophospholipids to produce free fatty acids, and that disease-associated mutations dramatically impair the catalytic function of the protein. These results indicate that PLA2G6 plays an important role in the production of fatty acids from phospholipids, and predict two pathological pathways in INAD: accumulation of PLA2G6 substrates (phospholipids) and deficiency of products (free fatty acids). Accumulation of PLA2G6 substrates explains membrane accumulation within neuroaxonal spheroids in INAD. The corresponding defect in free fatty acid production caused by loss of PLA2G6 function in INAD likely restricts rates of new lipid synthesis and remodeling, but could also restrict the availability of fatty acids for other processes such as beta oxidation. Neuroaxonal spheroids are recapitulated in a Pla2g6-KO mouse model and accompany the progressive neurological impairment observed in these mice. The defect in free fatty acid and subsequent acyl CoA production caused by PLA2G6 mutations could be addressed by approaches that increase acyl CoA production through increased activity of fatty acid synthase and acyl CoA synthetase enzymes. Studies in the Pla2g6-KO mouse line support this hypothesis and ongoing studies are evaluating this therapeutic approach in INAD by characterizing the ability of drug-like compounds to increase acyl CoA production and improve neurological impairment in Pla2g6-KO mice.