CORRESPONDENCE

Mutations in *PLA2G6* and the riddle of Schindler disease

S K Westaway, A Gregory, S J Hayflick

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We would like to draw attention to a recent discovery that may explain the striking discordance between the clinical and biochemical phenotypes observed in Schindler disease. This disorder was originally reported in siblings with deficiency of α-N-acetylgalactosaminidase (α-NAGA) and early-onset, rapidly progressive psychomotor regression.[1] Whereas α-NAGA deficiency underlies the abnormal oligosaccharidiuria found in Schindler disease, its causal role in the neurological phenotype has been questioned. Other patients with α-NAGA deficiency show a puzzling spectrum of clinical findings that range from angiokeratoma to no abnormalilties.[2 3] In two families, NAGA deficiency did not segregate with clinical abnormalities.[3–5] Bakker *et al*[2] and Keulemans *et al*[3] have suggested that a second disease locus may explain these observations.

We recently identified mutations in the calcium-independent phospholipase A_2 gene, *PLA2G6*, in infantile neuroaxonal dystrophy (INAD).[4] INAD is characterised by progressive motor and sensory impairment, with pathological evidence of distended axons, termed ''spheroids'', in the central and peripheral nervous systems. Spheroids are also seen in Schindler disease but in only a subset of patients. Indeed, Schindler disease has been categorised as a neuroaxonal dystrophy. On the basis of their common clinical and pathological features and the proximity of *PLA2G6* to *NAGA* on chromosome 22, we hypothesise that mutations in *PLA2G6* account for the childhood neurodegenerative phenotype that occurs in a subset of patients with Schindler disease.

How might mutations in two genes arise in multiple patients with NAGA deficiency and neuroaxonal dystrophy? Only three patients with Schindler disease are documented to have both spheroids and *NAGA* mutations, and all are related. Schindler original patients had consanguineous parents, and the third is ''consanguineous with the first patients''.[3] All three are homozygous for the same *NAGA* mutation[5]; thus, these patients are homozygous through identity by descent. We hypothesise that they carry two chromosomes 22 that bear deleterious mutations in both the *NAGA* and *PLA2G6* genes. Deficiency of α-NAGA accounts for their biochemical phenotype. Defective *PLA2G6* underlies their neurodegenerative disease, which is clinically and pathologically indistinguishable from that of patients with classic INAD. Most patients with α-NAGA deficiency do not show early psychomotor regression because their disease is caused by mutations in *NAGA* only.

Testing of the samples from patients with Schindler disease (which are unavailable to us) for mutations in *PLA2G6* should resolve the question of whether Schindler disease is, as Bakker *et al*[3] suggest, an ''accidental occurrence of two monogenic diseases''. We propose that it is.

Authors' affiliations
S K Westaway, A Gregory, S J Hayflick, Departments of Molecular and Medical Genetics, School of Medicine, Oregon Health and Science University, Portland, Oregon, USA

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