OBJECTIVE: Neurodegeneration with brain iron accumulation (NBIA) is a group of disorders characterized by magnetic resonance imaging (MRI) changes in basal ganglia. Both missense and nonsense mutations have been found in such patients in a gene encoding the mitochondrial pantothenate kinase (PANK2).

METHODS: We completed a mutation screen in 72 patients with the diagnosis NBIA based on clinical findings and radiological imaging. The entire coding region of the PANK2 gene (20p12.3) was investigated for point mutations and deletions.

RESULTS: We uncovered both mutant alleles in 48 patients. Deletions accounted for 4% of mutated alleles. Patients with two loss-of-function alleles (n = 11) displayed symptoms always at an early stage of life. In the presence of missense mutations (n = 37), the age of onset correlated with residual activity of the pantothenate kinase. Progression of disease measured by loss of ambulation was variable in both groups. We did not observe a strict correlation between the eye-of-the-tiger sign and PANK2 mutations. In 24 patients, no PANK2 mutation was identified.

INTERPRETATION: Deletion screening of PANK2 should be part of the diagnostic spectrum. Factors other than enzymatic residual activity are
determining the course of disease. There are strong arguments in favor of locus heterogeneity.