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Novel Compound Heterozygous Mutations in the *PANK2* Gene in a Chinese Patient With Atypical Pantothenate Kinase-Associated Neurodegeneration

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Abstract

We investigated the presence of mutations in the pantothenate kinase (*PANK2*) gene in a 27-year-old male Chinese patient with atypical pantothenate kinase-associated neurodegeneration (PKAN), formerly Hallervorden-Spatz syndrome. Automated DNA sequence analyses revealed compound heterozygous mutations in the exon 3 and 5. This patient had a 10-year history of PKAN characterized by a slight tremor of the right hand when writing at onset and a slow progressive rigidity of the neck and the right arm and resting tremor in upper extremities. Dysarthria, dysphagia, and dystonic-athetoid movements of the face and right fingers were marked. Magnetic resonance showed the typical "eye-of-the-tiger" sign.

Keywords

PANK2 gene; pantothenate kinase-associated neurodegeneration; PKAN; Hallervorden-Spatz syndrome; neurodegeneration; magnetic resonance imaging

Hallervorden-Spatz syndrome, also termed neurodegeneration with brain iron accumulation (NBIA), is an autosomal recessive extrapyramidal disorder characterized by dystonia, parkinsonism, iron accumulation in the brain, and progressive course. Rare clinical features include rigidity, choreoathetosis, seizures, optic atrophy, and pigmentary retinopathy.^{1,2}

The locus responsible for NBIA was first mapped to chromosome 20p12.3–13.³ In 2001, a novel gene, designated pantothenate kinase 2 gene (*PANK2*) was identified in this locus and were detected in families with NBIA.⁴ This discovery has led to the introduction of the term pantothenate kinase-associated neurodegeneration (PKAN).^{2,4–6} PKAN can be classified by age at onset and rate of disease progression and occurs in two major forms: (1) the classic form of PKAN characterized by early onset, rapid progression, dysarthria, dystonia, rigidity, and

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pigmentary retinopathy; and (2) atypical PKAN, which presents in the second decade of life with neurobehavioral signs and speech difficulties, and the progression of the disease is slower and more variable.² We report a compound heterozygote for *PANK2* mutations in a Chinese patient with atypical PKAN.

PATIENTS AND METHODS

Diagnosis of NBIA was established according to the criteria of Dooling¹ and Swaiman and colleagues.^{7,8} We studied a Chinese family in which one of two siblings had NBIA. The proband underwent a detailed neurologic examination, cognitive testing, extensive laboratory screening, and neuroimaging.

After informed consent, genomic DNA was extracted from peripheral blood obtained from affected and unaffected family members. DNA from 51 normal Chinese controls was also investigated. The seven exons, including the intron/exon boundaries of the *PANK2* gene, were amplified using primers as described elsewhere.⁴ PCR-amplified DNA was sequenced in both the forward and the reverse directions on an ABI 3100 automated sequencer (Applied Biosystems, Foster City, CA). Alignment and analysis was carried out with DNASTar (DNASTar, Inc., Madison, WI) (*PANK2* GenBank accession number BK000010).

RESULTS

This 27-year-old man at the age of 17 years had developed mild tremor of his right hand when writing, and 1 year later he had slowness and stiffness in his right arm. He exhibited progressive rigidity of the neck and the right arm and resting tremor in the upper limbs. At the age of 19 years, he developed dysarthria and dysphagia, and his speech became slow and slurred. At the age of 24 years, he exhibited dystonic-athetoid movements, especially of the face. There was no progressive intellectual decline.

Neurological examination showed speech was dysarthric. He had dystonia of the face and right fingers, and a marked rigidity with a 4- to 6-Hz resting tremor in the upper extremities. Grasp was poor because of dystonia. The remainder of the neurological and general examination showed normal results. Cognitive and laboratory testing showed no abnormality. T2-weighted brain magnetic resonance imaging (MRI) showed a characteristic “eye-of-the-tiger” sign (Fig. 1).

We identified two compound heterozygous mutations (Asp268Gly, Ile391Asn) involving exons 3 and 5 in *PANK2* of the patient. Neither of the two single-base variants was found in 102 control chromosomes. The mother (age 56 years) was a heterozygote for Asp268Gly mutation, and the father (age 62 years) was a heterozygote for Ile391Asn mutation. The proband's sister carried none of the mutations (Fig. 2). His parents were nonconsanguineous. Both were examined, along with the patient's sister; none exhibited any neurologic abnormality.

DISCUSSION

We identified compound heterozygous mutations in exon 3 (Asp268Gly) and 5 (Ile391Asn) of the *PANK2* gene. To our knowledge, these two mutations are described for the first time in this study. Our results would be the first *PANK2* mutation reported for a Chinese patient with atypical PKAN.

Homozygous, heterozygous, and compound heterozygous mutations in *PANK2* have been identified including deletions, insertions, nonsense, and missense mutations.^{2,4} *PANK2* mutations have been linked not only to typical PKAN, but also to atypical PKAN. Recently,

a large study of 98 families showed that all cases with classic disease had *PANK2* mutations, whereas only 35% of families with atypical disease had such mutations.² This study indicated that a striking one-to-one correlation was found between the MRI “eye-of-the-tiger” pattern and the presence of a *PANK2* mutation. Not all patients with “eye-of-the-tiger” sign had *PANK2* mutations, however, because other diseases such as Karak syndrome⁹ showed similar radiographic features but linkage to *PANK2* was eliminated.

PANK2 mutations in patients with the classic form of PKAN were generally resulting in premature protein termination, whereas most mutations in patients with the atypical PKAN led to amino acid substitutions. Human *PANK2* localizes primarily to mitochondria.¹⁰ The transcript is expressed abundantly in brain⁴ and is predicted to encode a 29-amino acid mitochondrial targeting sequence at the amino terminus.¹⁰ It is likely that the mutant Asp268Gly/ Ile391Asn *PANK2* protein might lose its functional properties but would not alter its location.

Pantothenate kinase is an essential regulatory enzyme in coenzyme A (CoA) biosynthesis from pantothenate (vitamin B₅). CoA plays a central role in intermediary and fatty acid metabolism. In PKAN, a deficiency of *PANK2* is thought to result in mitochondrial accumulation of cysteine and cysteine-containing substrates, which may undergo rapid autooxidation in the presence of iron, leading to free radical production and lipid peroxidation, and resulting in cell death. Further studies on pathological function of mutation *PANK2* protein may help us to understand the mechanism underlying neuronal degeneration in PKAN.

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FIG. 1. T2-weighted brain MRI showing the “eye-of-the-tiger” sign. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIG. 2. Family with compound heterozygous *PANK2* gene mutations. Proband with PKAN is indicated with an arrow. Square, male; circle, female; filled symbol, affected. Individuals with a *PANK2* mutation are indicated below the symbol.