

# A Novel *PANK2* Gene Mutation with Sudden-Onset Dystonia

JiSun Kim, Hyeun Shin, Jinyoung Youn, Chang-Seok Ki, Ah Ra Cho, Jin Whan Cho

Can J Neurol Sci. 2012; 39: 395-397

Pantothenate kinase-associated neurodegeneration (PKAN), formerly known as Hallervorden–Spatz syndrome, is an autosomal recessive disorder typically caused by mutations in the pantothenate kinase 2 gene (*PANK2*) on chromosome 20p13. The *PANK2* gene encodes pantothenate kinase, a key regulatory enzyme in the biosynthesis of coenzyme A. Classic PKAN presents in the first decade of life with extrapyramidal dysfunction, dystonia, and retinopathy, and progresses rapidly with loss of ambulation and restriction of activities by mid-adolescence.<sup>1</sup> Atypical PKAN presents in the second or third decade of life with variable clinical phenotype including speech-related issues or psychiatric problems. All reported cases have featured insidious onset with progressive course regardless of subtype.

In this report, we describe a compound heterozygous *PANK2* mutation in a patient with sudden-onset and stationary course of dystonia mimicking a psychogenic movement disorder.

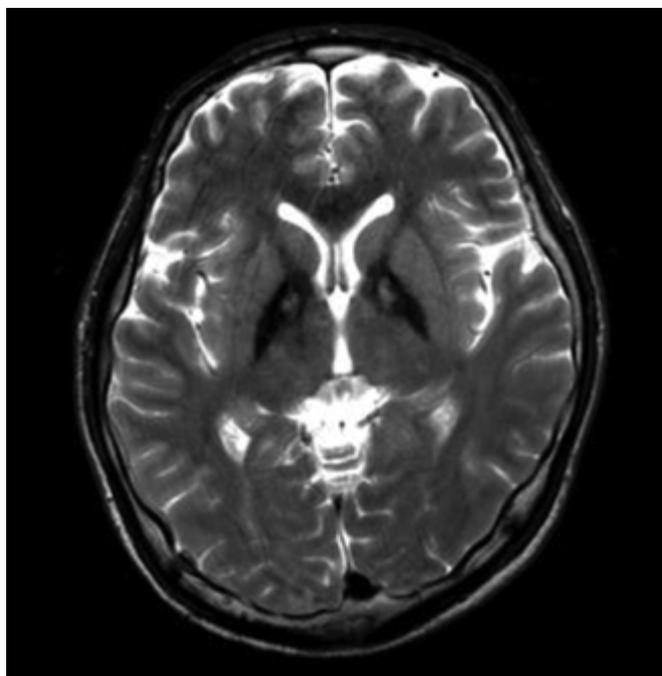
## CASE REPORT

### Clinical findings

A 29-year-old man visited our movement disorder clinic due to generalized dystonia which had developed abruptly. He first experienced sudden difficulty with mouth closure while eating at age 23. Subsequently, he had to push his lower jaw with his hands to chew food. The patient visited another hospital and was diagnosed with a psychogenic movement disorder. According to his medical records at the other hospital, he did not feel anxious about his symptoms, which had appeared suddenly. Additionally his jaw opening dystonia was reduced when he was distracted such as watching TV. At the age of 29, he noticed another involuntary movement in his left toe and visited our clinic to get a second opinion.

He denied a history of drug exposure, trauma, other medical problems, or relevant family history. His general appearance was gaunt due to chewing difficulty that had led to a 10 kg weight loss.

Initial neurological examination revealed jaw opening and plantar flexing dystonia of the left toe, and task specific dystonia of the right hand while writing. (see video on-line). Dystonia of the jaw was noted during rest and speech. Dystonia of the toe was observed in the resting state and disappeared while walking and sleeping. Although task specific dystonia of right hand was observed while writing, he did not recognize it and feel discomfort. He had no problems in the left upper or right lower extremities, and his gait and balance were normal. There were no other focal neurologic signs. He did not have any cognitive or psychiatric problems such as depression or obsessive-compulsive disorder.

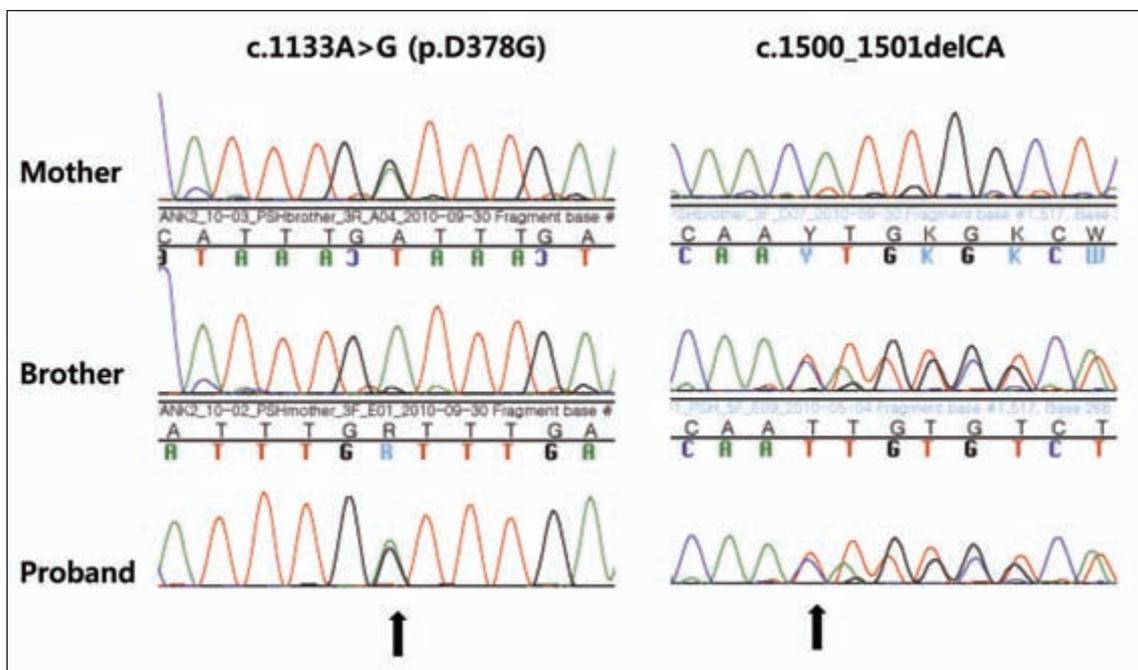


**Figure 1:** Symmetrical low signal intensity in the pallidum with a slight anteromedial core of high signal intensity, i.e., the “eye-of-the-tiger” sign, was evident on T2-weighted brain magnetic resonance imaging (MRI).

Ophthalmologic evaluation did not reveal any abnormalities. The results of initial laboratory testing including thyroid and parathyroid hormone tests, a peripheral blood smear test, and gene studies for torsion dystonia (*DYT1* gene) were normal. T2-weighted brain magnetic resonance imaging (MRI) showed symmetrical low signal intensity in the pallidum with a slight anteromedial core of high signal intensity; the “eye-of-the-tiger” sign (Figure 1).

From the Department of Neurology (JSK, JWC, HS, JY), Department of Laboratory Medicine and Genetics (CSK, ARC), Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

RECEIVED SEPTEMBER 26, 2011. FINAL REVISIONS SUBMITTED NOVEMBER 8, 2011. Correspondence to: Jin Whan Cho, Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50, Irwon-Dong, Gangnam-Gu Seoul 135-710, Korea. Email: jinwhan.cho@samsung.com



**Figure 2:** Electropherograms of the *PANK2* gene. The proband was compound heterozygous for *c.1133A>G* (p.D378G) in exon 5 and *c.1500\_1501delCA* (p.I501WfsX10) in exon 7.

### Genetic analysis

Genetic analyses were performed after obtaining informed consent from the proband, his only elder brother and his mother. Blood sample of his deceased father was not available. Direct sequencing of the *PANK2* gene (GenBank ID: NM\_153638.2) revealed two heterozygous mutations (Figure 2). One mutation was an A-to-G change at nucleotide 1133 in exon 5, which resulted in the substitution of aspartate for glycine at amino acid 378 (D378G). The other mutation was a deletion of isoleucine at nucleotides 1500-1501 in exon 7, which resulted in a frameshift at amino acid 501 (I501WfsX10). The mother was heterozygous for the D378G variation, and the brother of the proband was heterozygous for the I501WfsX10 variation.

### DISCUSSION

Here, we report a patient with PKAN presenting with an atypical phenotype that showed sudden-onset jaw opening dystonia with a stationary course. The clinical phenotype of patients with *PANK2* mutations has been reported to be heterogeneous and much broader than expected. A previous report<sup>1</sup> found a higher frequency of dystonia, gait disturbance, and tremor in patients with younger age at onset (before 20 years-of-age), whereas parkinsonism appears more commonly in late-onset disease (after 20 years-of-age). In another large study, patients with atypical disease who had *PANK2* mutations were more likely to have prominent speech-related and psychiatric symptoms than patients with classic disease. Symptoms of PKAN develop insidiously regardless of subtype and progress slowly or rapidly according to age at onset.<sup>2</sup>

Our PKAN patient showed unusual and interesting clinical features, presenting with the abrupt onset of focal jaw opening dystonia mimicking psychogenic movement at a later age (after 20 years) and a stationary course over seven years. Sudden onset dystonia as the first symptom of PKAN has not been previously reported. Although a few reports of PKAN have presented with focal or unilateral phenotype at an early stage, many of those cases had progressed within several years and eventually aggravated, presenting with multi-focal variable motor symptoms.<sup>3,4</sup> These clinical courses are different from that of our patient, whose disability was stationary and negligible over seven years and remained restricted to his jaw, left toe and right hand.

We identified compound heterozygous mutations in exon 5 (Asp378Gly) and exon 7 (I501WfsX10) of the *PANK2* gene. Of those, D378G is an established mutation found in PKAN.<sup>5</sup> However, to our knowledge, this is the first report of the I501WfsX10 variation. The deletion of isoleucine at nucleotides 1500-1501 in exon7 result in a frameshift mutation with a premature termination of translation at amino acid 501. This mutation leads to a null allele and causes a loss of function.

To date, numerous mutations underlying PKAN have been reported. *PANK2* mutations in patients with the classic form of PKAN generally result in premature protein termination, whereas most mutations in patients with atypical PKAN led to amino acid substitutions.<sup>2</sup> Our patient, who had an atypical phenotype at late age of onset with slow progression, had a frameshift mutation in exon 7 (I501WfsX10) of the *PANK2* gene. This fact is consistent with the hypothesis that atypical PKAN patients with missense mutations may have residual

*PANK2* activity, and supplemental pantothenate (vitamin B5) compensate for the partial enzymatic deficiency possibly ameliorating or retarding the symptoms.

In this report, we identified a novel mutation in the *PANK2* gene responsible for PKAN and confirmed that PKAN has an unusual spectrum of phenotype. Given the phenotypic variability of PKAN, it is important that physicians consider this disease in the differential diagnosis of patients presenting with a sudden-onset movement disorder and give appropriate caution in diagnosing psychogenic disorders.

#### REFERENCES

1. Thomas M, Hayflick SJ, Jankovic J. Clinical heterogeneity of neurodegeneration with brain iron accumulation (Hallervorden-Spatz syndrome) and pantothenate kinase-associated neurodegeneration. *Mov Disord.* 2004;19(1):36-42.
2. Hayflick SJ, Westaway SK, Levinson B, et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. *N Engl J Med.* 2003;348(1):33-40.
3. Antonini A, Goldwurm S, Benti R, et al. Genetic, clinical, and imaging characterization of one patient with late-onset, slowly progressive, pantothenate kinase-associated neurodegeneration. *Mov Disord.* 2006;21(3):417-8.
4. Chung SJ, Lee JH, Lee MC, Yoo H-W, Kim G-H. Focal hand dystonia in a patient with PANK2 mutation. *Mov Disord.* 2008; 23(3):466-8.
5. Wu YR, Chen CM, Chao CY, Lyu RK, Lee-Chen G-J. Pantothenate kinase-associated neurodegeneration in two Taiwanese siblings: Identification of a novel PANK2 gene mutation. *Mov Disord.* 2009;24(6):940-1.