Dear Editor,

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive disease characterized by iron deposition in the basal ganglia, primarily in the globus pallidus and substantia nigra. Common clinical manifestations include dystonia, parkinsonism, spasticity, neuropsychiatric disorders and retinal degeneration. PKAN is included in the spectrum of disorders related to neurodegeneration with brain iron accumulation (NBIA), which includes eleven diseases.

We present a patient with a phenotypic syndrome known as HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration), without hypoprebetalipoproteinemia in our case, with a new allelic variant in the \( PANK2 \) gene, consisting of a deletion of eight nucleotides (c.502-512delAGCGCGTC) in exon 1, which has not been described previously. To the best of our knowledge, no other mutations in exon 1 of the \( PANK2 \) gene have been reported in patients with HARP syndrome.

A 5-year-old boy presented with delay in motor skills. His parents were nonconsanguineous, and he had one healthy sibling. His perinatal and family history were normal. He showed generalized dystonia and hypomimicry, spasticity and speech difficulty but no cognitive problems. Kidney and hepatic function, serum copper, ceruloplasmin and lipids were normal. Conventional EEG revealed a generalized slowing pattern. A cerebrospinal fluid study was normal. Magnetic resonance imaging (MRI) demonstrated subtle linear bilateral hypointense lesions in the globus pallidus on T2-weighted sequences with a blooming artifact on susceptibility weighted imaging (Supplementary Figure 1 in the online-only Data Supplement). This picture was not clearly recognizable as a characteristic “eye-of-the-tiger” sign.

Ocular fundoscopy was compatible with retinitis pigmentosa, and a peripheral blood smear exhibited 6% acanthocytes (Supplementary Figure 2 in the online-only Data Supplement). Nutritional status was normal, and we excluded other possible conditions that could cause acanthocytosis. \( PANK2 \) gene (20p13) sequencing performed in 2018 revealed two compound heterozygous variants. The first was a frameshift mutation consisting of a deletion of eight nucleotides in exon 1 of the gene (c.502-512delAGCGCGTC). This change produces the replacement of serine for glycine at codon 169, which generates a stop signal nine amino acids later (p.Ser169GlyfsTer9). This variant had not been previously reported (HGMD, NCBI, ClinVAR). Nonetheless, predictor genetic databases classified this mutation as likely pathogenic, taking into account that it is a frameshift mutation with an impact on \( PANK2 \) gene function.

Given that HARP syndrome is inherited in an autosomal recessive manner, the phenotype of our patient can be explained by two pathogenic mutations in \( PANK2 \). Other variants in exon 1 of the \( PANK2 \) gene have been described previously as causative of PKAN; however, there are no cases of exon 1 mutations described in HARP syndrome (Table 1).1-6

The other variant found was a missense mutation in exon 6, causing a glycine to arginine change in position 521 of the protein (p.Gly521Arg; c.1561G>A). This mutation had been pre-

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**Table 1. Reported cases of HARP syndrome**

| References       | Cases (n) | Age of onset | Initial symptoms                                                                 | Clinical                             | Genetics                                                                                              | Magnetic resonance imaging                                                                 |
|------------------|-----------|--------------|----------------------------------------------------------------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Higgins et al.3, Ching et al.1 | 1         | 3 years      | Lower extremities spasticity                                                      | HBLP, acanthocytosis, retinitis pigmentosa, and pallidal degeneration | Homozygous mutation: \texttt{PANK2}: c.1111 A>T                                                                 | Marked signal decrease in the pallidal nuclei on T2-weighted images                           |
| Houlden et al.2  | 1         | 18 years     | -                                                                                | HBLP, acanthocytosis, retinitis pigmentosa, and pallidal degeneration | Compound heterozygous mutation: \texttt{PANK2}: c.980 T>C \texttt{PANK2}: IVS4–1 G>T                                 | Bilateral high signal intensity surrounded by a region of low signal intensity in the medial globus pallidus |
| Orrell et al.4   | 1         | 16 years     | Intermittent dysphagia. Poor night vision in early childhood                      | HBLP, acanthocytosis, retinitis pigmentosa, and pallidal degeneration | -                                                                                                      | Hypointense signal in the globus pallidus on T2-weighted with an enclosed high-signal region |
| Our patient*     | 1         | 5 years      | Psychomotor delay without cognitive affection, dystonia and spasticity           | Acanthocytosis, retinitis pigmentosa and pallidal degeneration | Compound heterozygous mutation: \texttt{PANK2}: c.502-512delAGCGCGTC \texttt{PANK2}: c.1561G>A                  | Symmetrical hypointensity signal in globus pallidus on T2-weighted and FLAIR sequences. Hypointense signal of bilateral globus pallidus. on susceptibility weighted imaging sequences |
| Orrell et al.6*  | 2         | -18 months   | -N/A                                                                             | Acanthocytosis, retinitis pigmentosa and pallidal degeneration | -                                                                                                      | -Reduced signal in the globus pallidus bilaterally with an internal increased signal region. Low signal in the globus pallidus bilaterally |
|                   |           | -19 months   | -Lower extremities dystonia and clumsiness of hands                              | -                                     | -                                                                                                      |                                                                                             |
| Higgins et al.3* | 6         | -16 months   | -22 months                                                                        | Acanthocytosis, retinitis pigmentosa and pallidal degeneration | -                                                                                                      | -N/A                                                                                       |
| Malandrini et al.5* | 2       | -2 years     | Delay in reaching motor milestones and frequent falls                            | Acanthocytosis, retinitis pigmentosa and pallidal degeneration | -                                                                                                      | -CT scan at 5 years-old: normal. Bilateral hypointensity of the globus pallidus on T2-weighted sequences, mostly on the right side, with a small central punctate area of increased signal |
| Kazek et al.6*   | 1         | 3 years      | Pyramidal signs                                                                   | Retinitis pigmentosa, pallidal degeneration | Compound heterozygous mutation: \texttt{PANK2}: Leu315His \texttt{PANK2}: Gly411Arg                           | “Eye of the tiger” sign                                                                       |

*cases without complete phenotype of HARP syndrome. HARP: hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration, HBLP: hypoprebetalipoproteinemia, CT: computed tomography, FLAIR: fluid attenuation inversion recovery, N/A: not available.
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Supplementary Materials
The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.19071.

Conflicts of Interest
The authors have no financial conflicts of interest.

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None.

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REFERENCES
1. Ching KH, Westaway SK, Gitschier J, Higgins JJ, Hayflick SJ. HARP syndrome is allelic with pantothenate kinase-associated neurodegeneration. Neurology 2002;58:1673-1674.
2. Houlden H, Lincoln S, Farrer M, Clenden PG, Hardy J, Orrell RW. Compound heterozygous PANK2 mutations confirm HARP and Hallervord-Spatz syndromes are allelic. Neurology 2003;61:1423-1426.
3. Higgins JJ, Patterson MC, Papadopoulos NM, Brady RO, Penteche PG, Barton NW. Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP syndrome). Neurology 1992;42:194-198.
4. Orrell RW, Amrolia PJ, Heald A, Cleland PG, Owen JS, Morgan-Hughes JA, et al. Acanthocytosis, retinitis pigmentosa, and pallidal degeneration: a report of three patients, including the second reported case with hypoprebetalipoproteinemia (HARP syndrome). Neurology 1995;45(3 Pt 1):487-492.
5. Malandrini A, Cesaretti S, Mulini M, Palmieri S, Fabrizi GM, Villanova M, et al. Acanthocytosis, retinitis pigmentosa, pallidal degeneration: a report of two cases without serum lipid abnormalities. J Neurol Sci 1996;140:129-131.
6. Kazez B, Jamroz E, Gencik M, Jezea Stanek A, Marszel E, Wójcieszynska-Stanek K. A novel PANK2 gene mutation: clinical and molecular characteristics of patients short communication. J Child Neurol 2007;22:1256-1259.
7. Chérot E, Keren B, Dubourg C, Carré W, Fradin M, Lavillaureix A, et al. Using medical exome sequencing to identify the causes of neurodevelopmental disorders: experience of 2 clinical units and 216 patients. Clin Genet 2018;93:567-576.
**Supplementary Figure 1.** Magnetic resonance imaging was performed at 5 years old boy. A: T2-weighted turbo spin-echo symmetrical hypointensity signal in the globus pallidus. B: Fluid attenuation inversion recovery (FLAIR) bilateral hypointensity signal in the globus pallidus. C–E: Susceptibility weighted imaging sequences show hypointense signals of the bilateral globus pallidus.
Supplementary Figure 2. Additional tests performed in our patient. A: Right eye ocular fundus shows retinitis pigmentosa. B: Optical coherence tomography (OCT) of cystic macular lesions. C: Blood examination of acanthocytes (hematoxylin and eosin stain, ×400).
**Supplementary Figure 3.** Visual description of allelic variant in our patient. From top to bottom: PANK2 gene cytogenetic location in 20p13 chromosome; graphic description of PANK2 gene exons and location of patient variants; family pedigree.