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LETTER TO THE EDITOR

A New Allelic Variant in the *PANK2* Gene in a Patient with Incomplete HARP Syndrome

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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: *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: *PANK2*: c.980 T>C *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	Intermitent 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 affectation, dystonia and spasticity	Acanthocytosis, retinitis pigmentosa and pallidal degeneration	Compound heterozygous mutation: *PANK2*: c.502-512delAGCGCGTC *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.[4]*	2	-N/A -18 months	-N/A -Lower extremities dystonia and clumsiness of hands	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
Higgins et al.[3]*	6	-22 months -N/A -N/A -N/A -19 months -16 months	-	Acanthocytosis, retinitis pigmentosa and pallidal degeneration	-	-N/A -Increased iron uptake in basal ganglia -Increased iron uptake in basal ganglia -Increased iron uptake in basal ganglia -CT: dilated ventricles, widened sulci and folia -CT: hyperdense zones in the pallidal nuclei
Malandrini et al.[5]*	2	-2 years -Early childhood	-Delay in reaching motor milestones and frequent falls -Delay in reaching motor milestones and frequent falls, difficulty to speech and walking	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: *PANK2*: Leu315His *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.

viously described as a pathogenic variant.[7] Segregation analysis revealed that each of the parents was heterozygous for one of the two variants (Supplementary Figure 3 in the online-only Data Supplement). Neither of them was symptomatic.

Our patient had a rapidly progressive evolution with severe dystonia despite treatment with oral and intrathecal baclofen, clonazepam, trihexyphenidyl and vitamin B5 (pantothenic acid). Percutaneous endoscopic gastrostomy was performed to improve nutritional intake. He is currently being treated with phospho-pantothenic replacement therapy, with no relevant results to report due to the short duration of treatment to date.

PKAN (NBIA1) is the most common type of NBIA and has a wide phenotypic spectrum. To date, 176 pathogenic mutations in the *PANK* gene have been reported. The estimated incidence of PKAN is 3/1,000,000. In the classic form, symptoms appear before 6 years old and are rapidly progressive. HARP syndrome is an allelic variant of this entity[1,2] with an autosomal recessive inheritance. It is characterized by iron accumulation in the basal ganglia, acanthocytosis, retinitis pigmentosa and hypolipoproteinemia. As in other forms of NBIA, iron storage in the basal ganglia creates the typical "eye-of-the-tiger" sign on MRI. Nevertheless, this radiological finding could be missing in early stages of the disease. HARP syndrome was initially described by Higgins et al. in 1992.[3] They reported a case of a young woman with generalized dystonia since childhood associated with retinitis pigmentosa, acanthocytosis and hypolipoproteinemia. In the same decade, Orrell et al.[4] reported a similar patient. *PANK* gene mutations were found in both cases, and HARP syndrome was described as a variant of PKAN disease.

In our case, apolipoprotein B deficiency was not present. This fact has been reported previously.[4,5] To the best of our knowledge, the genetics of cases without hypolipoproteinemia have not been studied comprehensively. The newly found variant c.502-512delAGCGCGTC in our patient may be an important report of incomplete HARP syndrome (Table 1).[1-6] A limitation of our case is that no functional studies have been carried out with this new allelic variant.

To date, there is no curative treatment, and palliative therapy offers poor results. The present case report adds a probably pathogenic variant to those previously described in HARP syndrome. Better knowledge of the genetics and pathophysiology, including the role of iron accumulation in specific brain areas and cellular oxidation, may help lead to a new approach and effective therapy in the future for patients with PKAN.

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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Author Contributions

Conceptualization: Myriam Ley Martos, María Jesús Salado Reyes, Carmen Gutiérrez Moro, Lorena Estepa Pedregosa, and Manuel Lubián Gutiérrez. Data curation: Lorena Estepa Pedregosa and Manuel Lubián Gutiérrez. Formal analysis: Myriam Ley Martos, María Jesús Salado Reyes, Carmen Gutiérrez Moro, Lorena Estepa Pedregosa, and Manuel Lubián Gutiérrez. Investigation: Myriam Ley Martos, María Jesús Salado Reyes, Carmen Gutiérrez Moro, Lorena Estepa Pedregosa, and Manuel Lubián Gutiérrez. Methodology: Lorena Estepa Pedregosa and Manuel Lubián Gutiérrez. Project administration: Myriam Ley Martos. Resources: Rosario Marín Iglesias. Software: Rosario Marín Iglesias and Manuel Lubián Gutiérrez. Supervision: Myriam Ley Martos. Validation: Myriam Ley Martos, María Jesús Salado Reyes, Carmen Gutiérrez Moro, Lorena Estepa Pedregosa, and Manuel Lubián Gutiérrez. Visualization: Myriam Ley Martos, María Jesús Salado Reyes, Carmen Gutiérrez Moro, Lorena Estepa Pedregosa, and Manuel Lubián Gutiérrez. Writing—original draft: Lorena Estepa Pedregosa and Manuel Lubián Gutiérrez. Writing—review & editing: Manuel Lubián Gutiérrez. Approval of final manuscript: all authors.

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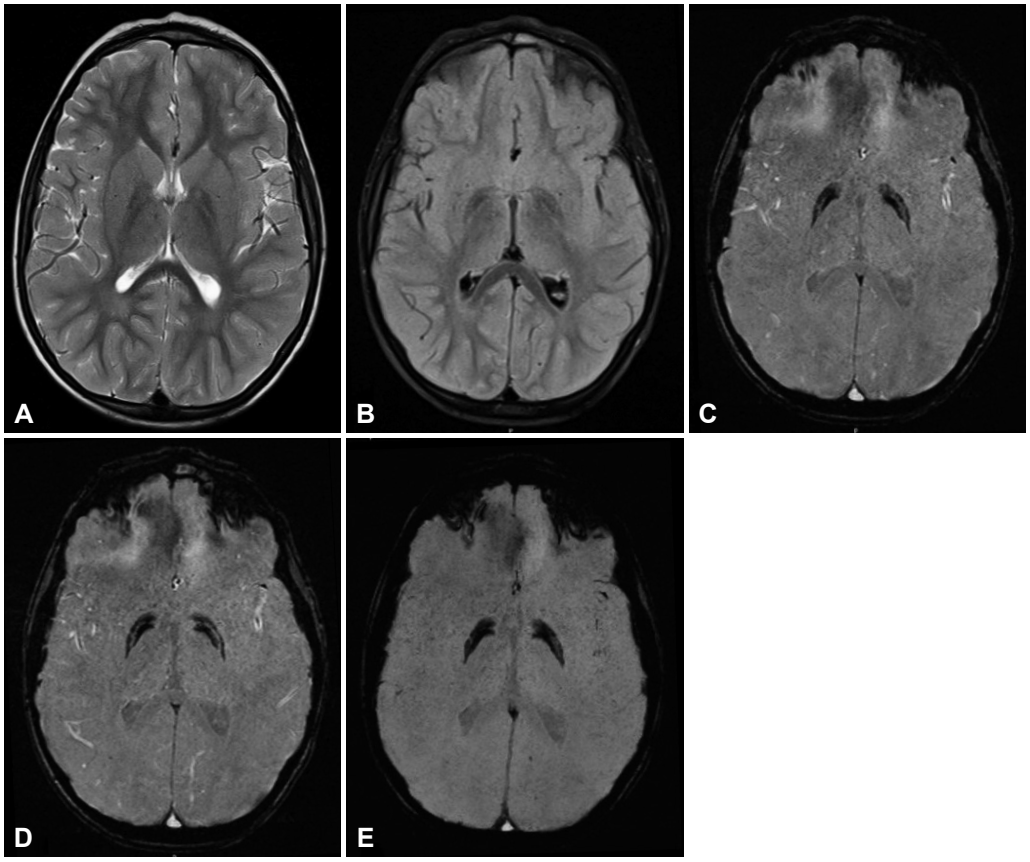
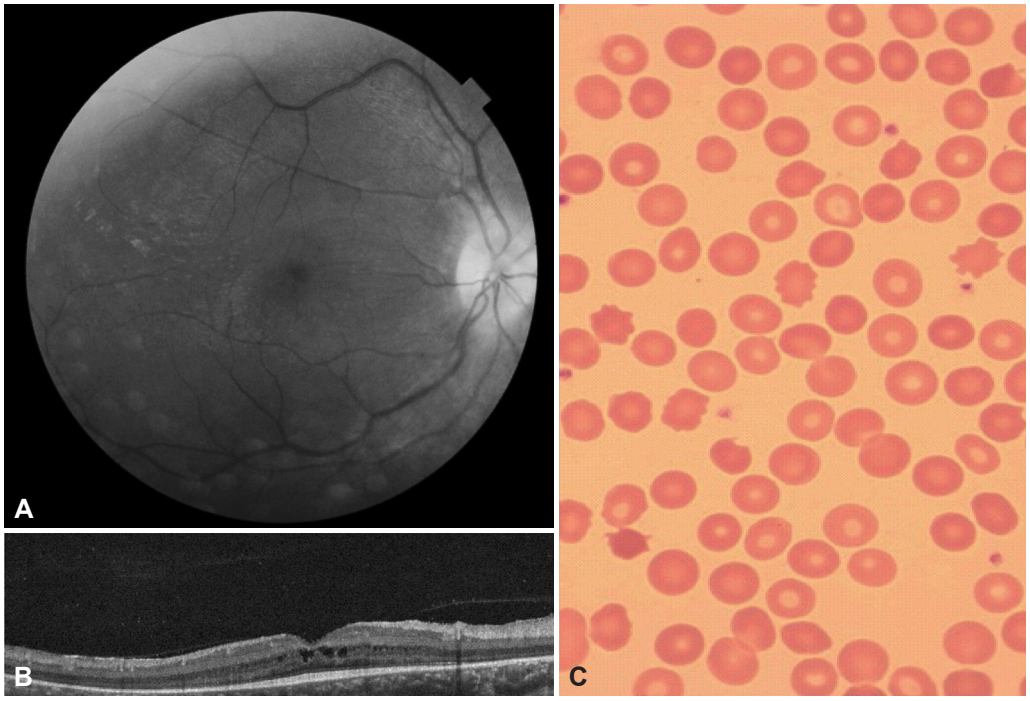
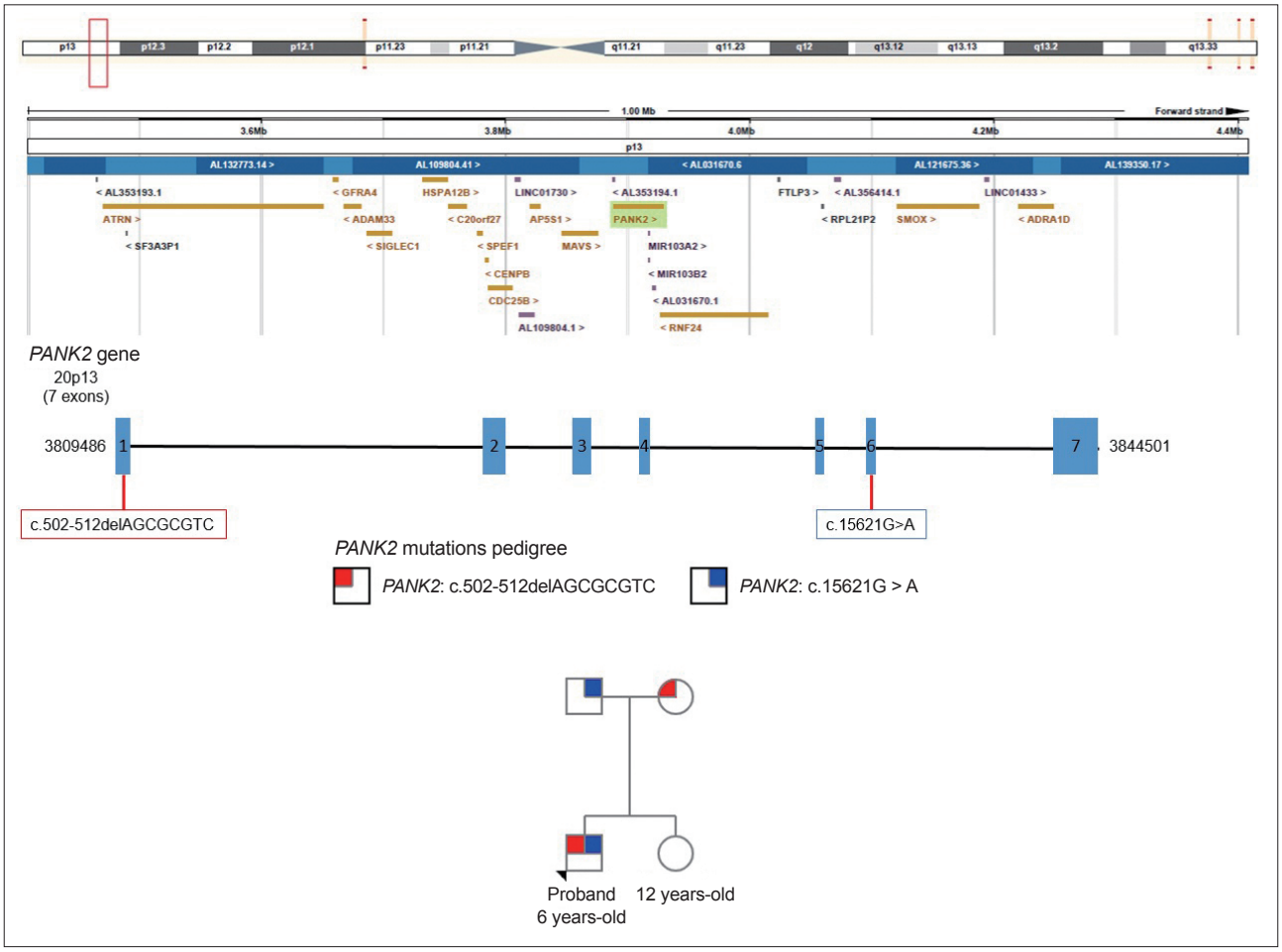


Supplementary Figure 1. Magnetic resonance imaging was performed at 5 years old boy. A: T2-weighted turbo spin-echo symmetrical hypointensity signal in the globus pallidus. B: Fluid attenuation inversion recovery (FLAIR) bilateral hypointensity signal in the globus pallidus. C–E: Susceptibility weighted imaging sequences showes hypointense signals of the bilateral globus pallidus.



Supplementary Figure 2. Additional tests performed in our patient. A: Right eye ocular fundus showes 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 chromosme; graphic description of *PANK2* gene exons and location of patient variants; family pedigree.