

# AP4 deficiency

## A novel form of neurodegeneration with brain iron accumulation?

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## Abstract

### Objective

To describe the clinico-radiological phenotype of 3 patients harboring a homozygous novel *AP4M1* pathogenic mutation.

### Methods

The 3 patients from an inbred family who exhibited early-onset developmental delay, tetraparesis, juvenile motor function deterioration, and intellectual deficiency were investigated by magnetic brain imaging using T1-weighted, T2-weighted, T2\*-weighted, fluid-attenuated inversion recovery, susceptibility weighted imaging (SWI) sequences. Whole-exome sequencing was performed on the 3 patients.

### Results

In the 3 patients, brain imaging identified the same pattern of bilateral SWI hypointensity of the globus pallidus, concordant with iron accumulation. A novel homozygous nonsense mutation was identified in *AP4M1*, segregating with the disease and leading to truncation of half of the *adap* domain of the protein.

### Conclusions

Our results suggest that *AP4M1* represents a new candidate gene that should be considered in the neurodegeneration with brain iron accumulation (NBIA) spectrum of disorders and highlight the intersections between hereditary spastic paraplegia and NBIA clinical presentations.

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## Glossary

**HSP** = hereditary spastic paraplegia; **NBIA** = neurodegeneration with brain iron accumulation; **SWI** = susceptibility weighted imaging; **WES** = whole-exome sequencing.

Hereditary spastic paraplegias (HSPs) are a heterogeneous group of neurodegenerative diseases clinically characterized by progressive lower extremity weakness and spasticity, which may be isolated (pure HSP) or combined with other neurologic or nonneurological signs (complex HSP).<sup>1,2</sup> More than 70 genes have been implicated, emphasizing diverse molecular pathogenic mechanisms.<sup>3</sup> In this respect, recessive mutations in genes encoding the different subunits of adaptor protein complex-4, (*AP4B1*, *AP4M1*, *AP4E1*, and *AP4S1*) have been identified in patients with complex HSP (*SPG 47*, *50*, *51*, and *52* respectively).<sup>4–8</sup> The AP4-deficiency syndrome is characterized by progressive spasticity, microcephaly, intellectual deficiency, dysmorphic traits, and growth retardation,<sup>4–8</sup> while epilepsy and peripheral neuropathy might be associated.<sup>4,9</sup> Brain imaging phenotypes reported up to now are characterized by cerebral atrophy, asymmetric enlargement of lateral ventricles, white matter loss, and thin corpus callosum splenium.<sup>8–10</sup> Thin and globoid hippocampal cortex<sup>9</sup> and tortuosity of intraextracranial large vessels were also reported.<sup>4</sup>

Neurodegeneration with brain iron accumulation (NBIA), which is characterized by dystonia, parkinsonism, spasticity, and brain iron accumulation on MRI, represents another inherited group of neurodegenerative disorders, due to mutations in 10 genes, with molecular overlaps with HSP.<sup>11,12</sup>

Here, we report 3 patients from the same kindred who harbor a homozygous *AP4M1* mutation. They exhibit the typical clinico-radiological phenotype of AP4-deficiency syndrome, but surprisingly associated with bilateral pallidal iron accumulation on brain imaging, thus establishing a link between AP4-related complex HSP and NBIA disorders.

## Methods

### Standard protocol approvals, registrations, and patient consents

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethical committee. Written informed consent was obtained from the patients' legal representatives.

### Whole-exome sequencing and brain imaging

Whole-exome sequencing (WES) was performed on the DNA from the 3 affected patients by Aros Ltd. Homozygous mutations common to the 3 patients were filtered progressively for their frequency (<1%), alteration of the open reading frame (frameshift, splicing, missense, and nonsense mutations), and ultimately for their localization in the

homozygous regions common to the 3 patients. Sanger sequencing allowed for their confirmation and segregation study in the family.

CT was performed on a 64-section CT scanner (Discovery750 HD; GE Health care, Milwaukee, WI). MRIs were acquired on a 1.5-T system (AVENTO; Siemens medical solutions, Erlangen, Germany) as follows: axial slices T2-weighted, T2\*-weighted, fluid-attenuated inversion recovery, susceptibility weighted imaging (SWI) sequences, and sagittal slices T1-weighted sequences.

## Results

### Clinical data

The clinical features of the 3 patients originating from a large consanguineous Moroccan family (figure 1A) are described in table. Psychomotor retardation with spasticity of the 4 limbs was noticed early in life. Clinical examination from the first year showed spastic tetraplegia, with pyramidal tract signs and equinovarus. Patients IV-2 and IV-5 sat unaided at 7 months; patient IV-2 was able to crawl at 2 years but never managed to walk; her sister IV-5 could walk short distances with unsteady spastic gait from the age of 5 years. Patient IV-7 sat unaided at 11 months of age and walked at 3 years, with a broad-based unsteady gait. The patients exhibited stable severe mental deficiency, without behavioral disturbance. Motor achievements progressively deteriorated at adolescence, with loss of the highest motor skills, but without additional cognitive decline; from that time, bradykinesia, hypomimic, drooling, and athetoid movements of the hands were also noticed. Patients IV-5 and IV-7 displayed short stature. Dysmorphic features (figure 2, Aa, Ba, Ca) were also present. The 3 patients needed assistance to most common daily living activities.

The following investigations were normal: electromyoneurography recording, cardiac ultrasound scan, visual and auditory evoked potentials, fundus examination, karyotype analysis on lymphocytes (cases IV-2, IV-5 and IV-7), *PANK2* and *PLA2G6* Sanger sequencing (patient IV-7), and analyses of mitochondrial enzymatic activities on a muscle sample (patient IV-2).

### Genetic results

Comparison of WES results performed for patients IV-2, IV-5, and IV-7 revealed 3 homozygous regions, 1 on chromosome 7 (5.7 Mb) and 2 on chromosome 9 (2.25 and 1.31 Mb). A total of 14,753 exonic variants were common to the 3 patients, and by progressively filtering them, we identified 4,974

**Table** Clinical features of 3 *AP4M1* individuals

Patient	Patient IV-2	Patient IV-5	Patient IV-7
Sex/age at last examination	F/25 y	F/16 y	F/23 y
Perinatal parameter	Normal	Normal	Low birth weight
Seizures	No	1 febrile seizure during the second year of life	1 febrile seizure at 20 m
Age at acquisition of unaided sitting	7 m	7 m	11 m
Highest motor achievements	Able to crawl at 2 y	Unsteady spastic gait at 5 y	Independent broad-based unsteady gait at 3 y
Motor deterioration/age	Unable to crawl at 13 y	Assisted gait from 12 y	Assisted gait from 15 y
Spasticity and pyramidal tract signs	Yes	Yes	Yes
Equinovarus	Yes	Yes	Yes
Bradykinesia and athetoid movements of the hands	From adolescence	From adolescence	From adolescence
Language	Short sentences	Short sentences	Less than 10 words
Behavior	Shy and introverted form adolescence	Normal	Smiley
Intellectual deficiency	Severe	Moderate	Severe
Growth parameter at last follow-up	Normal	Short stature	Short stature
	Height 160 cm, weight 68 kg	Height 150 cm, weight 55 kg	Height 143 cm, weight 44 kg
Microcephaly	No	No	Yes
Head circumference	53 cm	52 cm	48.5 cm
Dysmorphism	Yes	Yes	Yes

m = month; y = year.

homozygous variants, among which 2,546 were non-synonymous, frameshift, splicing, or stop variants. Further filtering for damaging variants with a frequency lower than 1% identified 3 mutations in the *AP4M1*, *HRNR*, and *NPIPL3* genes, but only the 1 in *AP4M1* was located in chromosome 7, in 1 of the 3 homozygous regions.

This c.916C>T mutation (rs369459721) is leading to a premature stop codon (p.R306X), truncating the last 147 residues of the protein (figure 1, B and C). It has a global allelic frequency of  $2.4 \times 10^{-5}$  in the ExAC and a frequency of  $3.0 \times 10^{-5}$  in Non-Finnish European and  $9.3 \times 10^{-5}$  in African, while it was not encountered in the rest of the world.

Analysis of the homozygous variants located in the 10 known NBIA genes revealed 2 common variants, located in *CP* (rs701753) and *PANK* (rs3737084), but they were not damaging, had a frequency higher than 1%, and were located away from the 3 homozygous regions.

### Brain imaging

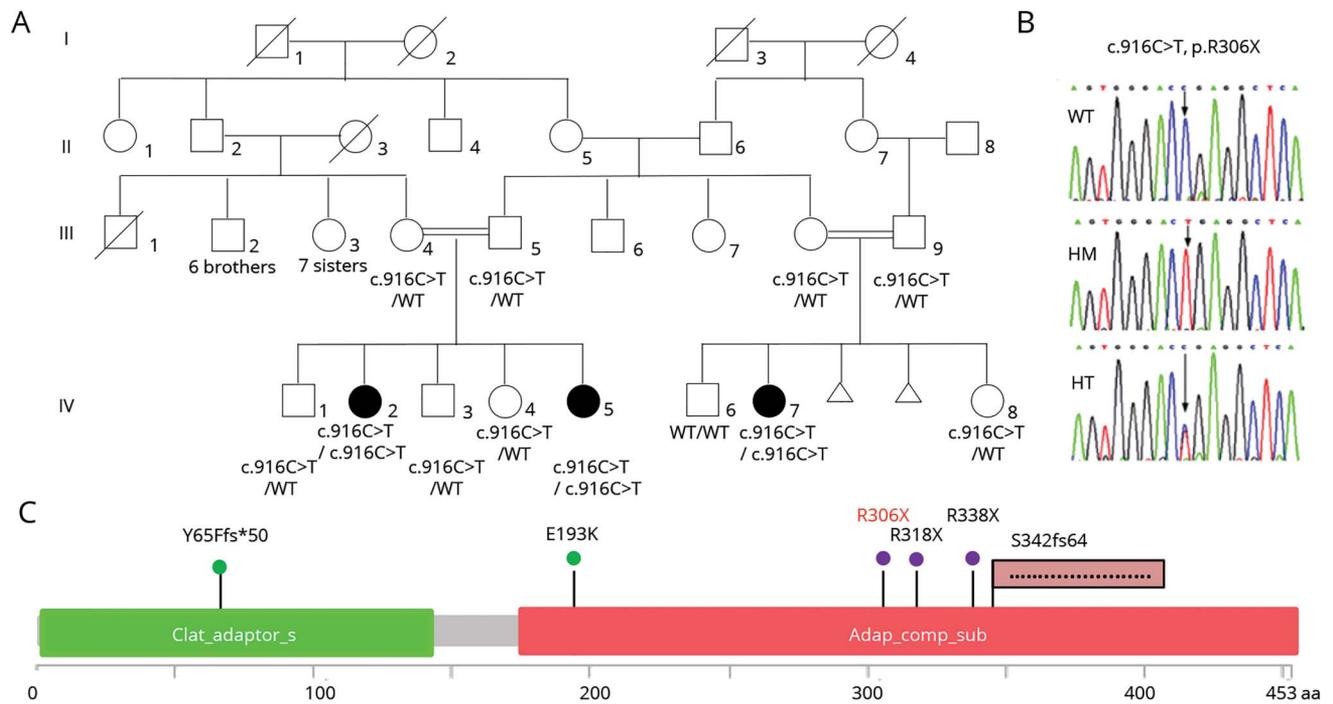
Brain MRI of the 3 patients showed global cerebral atrophy, white matter loss, asymmetric ventriculomegaly (figure 2, B, E, and H), and thinning of the splenium of the corpus

callosum (data not shown J). T1 sequences showed an iso-intense pattern of the globus pallidus (data not shown). T2 sequences revealed symmetric mild hypointensity of the globus pallidus, which was significantly accentuated on SWI sequences (figure 2, Ab, Ac, Bb, Bc, Cb, Cc, D). Patient IV-7's CT was normal (data not shown).

## Discussion

We identified a homozygous nonsense mutation in *AP4M1* in 3 women from the same inbred family by WES. This R306X mutation deletes the last 147 residues of the protein, truncating half of the *adap* domain, an effect similar to that reported in 2 other families who harbored a stop codon truncating the *AP4M1* protein at positions 318 and 338.<sup>9</sup> Until now, only 5 different *AP4M1* mutations have been reported in 7 families with a common clinical presentation<sup>4,5,9,13-15</sup> (figure 1C). The 3 patients from our study share the same clinical phenotype with variable severity, consisting in early-onset developmental delay, tetraparesis, juvenile motor function deterioration, intellectual deficiency, athetoid upper limb movements, bradykinesia, and mild dysmorphism, which fits with the previously described *AP4*-deficiency syndrome. Even if the bilateral pallidal

**Figure 1** Identification of a novel *AP4M1* mutation



(A) Pedigree showing the segregation of the *AP4M1* c.916C>T (p.R306X) mutation in the family; black symbols indicate affected patients. (B) Electrophoregrams showing the wild-type (top), the homozygous mutated (middle), and heterozygous (bottom) sequence of *AP4M1*. (C) Localization of *AP4M1* mutations in the protein: the structure of the *AP4M1* protein (domain and amino acid positions) is described with all the pathogenic missense mutations<sup>5,14</sup> (green), nonsense mutation<sup>9,15</sup> (violet), frameshift<sup>4,13</sup> (pink flag) mutations reported to date (in black), and in the present cases (in red). HM = homozygous; HT = heterozygous; WT = wild type.

hyposignal is mild on T2 sequences and could be interpreted as physiologic iron accumulation at this age, the substantial hyposignal on SWI is totally unusual in patients of the same age. These findings, correlated with the absence of hypersignal on T1-weighted imaging or CT hyperdensities in the patients, are strongly suggestive of brain iron overload.

Iron deposits have not been previously reported in patients with AP4-deficiency syndrome. Nevertheless, magnetic susceptibility sequences, which can confirm the presence of iron, have not been performed in most of the reported cases; therefore, this feature might have been underdiagnosed. A search for homozygous mutations common to the 3 patients in the 10 published NBIA genes revealed 2 variants located in *PANK* and *CP*, but their frequency and the absence of pathogenicity were somehow incompatible with their involvement as modifier mutations switching HSP clinical presentation to NBIA.

Of interest, a patient with *AP4E1* mutations, whose brain MRI showed bilateral T2-hypointensity of the globus pallidus, has already been described.<sup>8</sup> This peculiar finding, although not discussed in the article, strongly suggests iron accumulation in this *AP4E1* patient, as in our 3 *AP4M1* patients.

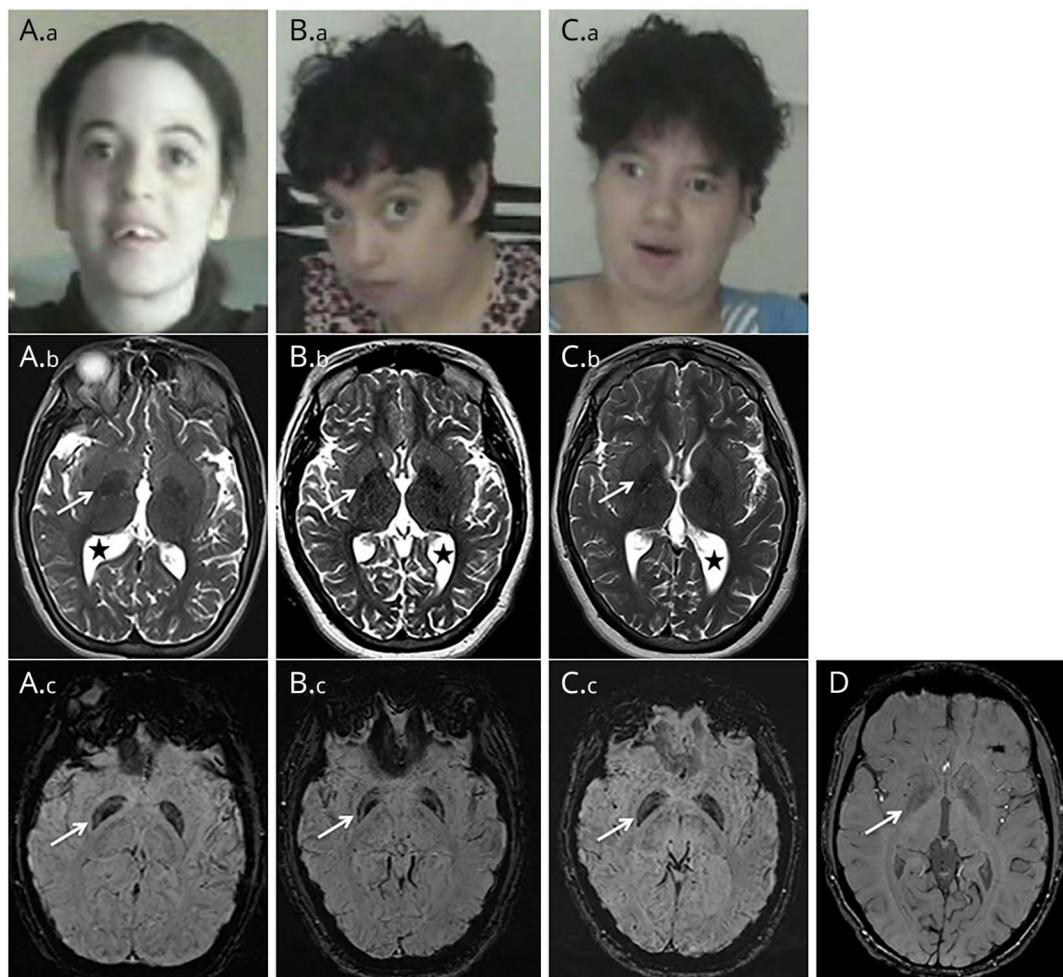
The pathophysiology of HSP involves many cellular pathways as cellular transport, nucleotide metabolism, and synapse and axon developments, providing a causative link

between HSP and other neurodegenerative diseases.<sup>3,16</sup> Overlaps between HSP and NBIA are well known, as already reported for cases with mutations in *FA2H* and *C19orf12* genes (SPG 35 and 43, respectively).<sup>11,17</sup> The AP-4 complex is a heterotetramer ubiquitously expressed in the CNS early in the embryologic and postnatal development and is implicated in vesicle formation, post-Golgi protein trafficking, and sorting processes.<sup>18</sup> Eventually, AP-4 dysfunction might affect autophagy by disrupting the early steps of endosomal formation, a process shared with Kufor-Rabeb disease and beta-propeller protein-associated neurodegeneration, 2 forms of NBIA related to *ATP13A2* and *WDR45* genes, respectively.<sup>11,12</sup>

Moreover, NBIA disorders are probably underdiagnosed, and the evolution of technologies and practices in radiology leads to the identification of many new candidate genes through the incorporation of susceptibility weighted sequences more frequently in the brain imaging protocols.<sup>19</sup> Our study has limitations, especially because of the small sample size.

Nevertheless, according to our findings in *AP4M1* mutated patients, we recommend that brain MRI with susceptibility weighted sequences be included in the brain imaging protocol for patients with suspected HSP and AP4-deficiency syndrome to collect a larger group of patients, and we propose

**Figure 2** Facial appearance and brain imaging



(A) Patient IV-2, 25 years. (B) Patient IV-5, 16 years. (C) Patient IV-7, 23 years. (D) Control, 20 years. (A.a, B.a, and C.a) Photographs showing dysmorphism, with bulbous nose, broad nasal bridge, coarse features, and wide-open mouth. (A.b, B.b, and C.b) Axial T2-weighted sequence showing asymmetric ventriculomegaly (black stars) and mild hypointense aspect of the globus pallidus (arrows). Diffuse brain atrophy and loss of white matter without signal abnormality, particularly in occipito parietal areas, are also observed. (A.c, B.c, C.c, and D) Axial susceptibility weighted imaging sequence showing bilateral intense hypointense signal of the globus pallidus, significantly predominant in their medial part (arrows, A.c, B.c, and C.c) compared with the control (D).

that mutations in *AP4* genes be considered and screened in a subset of patients with NBIA spectrum disorders.

### Author contributions

Design or conceptualization of the study: Agathe Roubertie, Christian P. Hamel, and Guy Lenaers. Analysis or interpretation of the data: Charles-Joris Roux, Nicolas Leboucq, Gael Manes, Majida Charif, Bernard Echenne, Cyril Goizet, Claire Guissart, Pierre Meyer, Cecilia Marelli, François Rivier, Lydie Burglen, and Rita Horvath. Drafting or revising the manuscript for intellectual content: Agathe Roubertie, Charles-Joris Roux, Cyril Goizet, and Guy Lenaers.

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### Disclosure

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R. Horvath report no disclosures. C.P. Hamel is deceased; disclosures are not included for this author. G. Lenaers reports no disclosures. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/NG](http://Neurology.org/NG).

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