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## Dominant Form of Vanishing White Matter–like Leukoencephalopathy

Pierre Labauge, MD, PhD,<sup>1</sup> Anne Fogli, PhD,<sup>2</sup> Giovanni Castelnovo, MD,<sup>1</sup> Alice Le Bayon, MD,<sup>1</sup> Laetitia Horzinski, MSc,<sup>2</sup> François Nicoli, MD, PhD,<sup>3–5</sup> Patrick Cozzone, PhD,<sup>3,4</sup> Michel Pagès, MD,<sup>1</sup> Caroline Briere, MD,<sup>1</sup> Christiane Marty-Double, MD,<sup>1</sup> Olivier Delhaume, MD,<sup>1</sup> Antoinette Gelot, MD, PhD,<sup>6</sup> Odile Boespflug-Tanguy, MD, PhD,<sup>2</sup> and Diana Rodriguez, MD, PhD<sup>6,7</sup>

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**Leukoencephalopathy with vanishing white matter syndrome (childhood ataxia with central nervous system hypomyelination/vanishing white matter disease) is an autosomal recessive disorder characterized by the occurrence of acute episodes of deterioration after minor head trauma or infection, and symmetrical demyelination on magnetic resonance with cavitation aspects. Mutations in each of the five subunits of eIF2B have been identified. We report in an affected man and his mother an adult-onset form of childhood ataxia with central nervous system hypomyelination/vanishing white matter disease–like disorder with no mutations in the *EIF2B* genes and normal guanine nucleotide exchange factor eIF2B activity, suggesting a new dominant inheritance of this syndrome that may involve other genes.**

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Childhood ataxia with central nervous system hypomyelination/vanishing white matter disease (CACH/VWM) is an autosomal recessive disorder, defined according to clinical and nuclear magnetic resonance criteria (magnetic resonance imaging [MRI] and magnetic resonance spectroscopy [MRS]).<sup>1,2</sup> Initially described in young children, a wide clinical *spectrum* has been reported from congenital forms with rapid death

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From the <sup>1</sup>Service de Neurologie, CHU Montpellier-Nîmes, Hôpital Caremeau, Nîmes; <sup>2</sup>INSERM UMR 384, Faculté de Médecine, Clermont Ferrand; <sup>3</sup>Centre de Résonance Magnétique Biologique et Médicale, Unité Mixte de Recherche-Centre National de Recherche Scientifique, Marseille; <sup>4</sup>Faculté de Médecine, Université de la Méditerranée, Hôpital de la Timone, Marseille; <sup>5</sup>Service d'Urgences Neuro-vasculaires, CHU Timone, Marseille; <sup>6</sup>Service de Neuropédiatrie, Hôpital Armand Trousseau, Paris; and <sup>7</sup>INSERM U546, Faculté de Médecine Pitié Salpêtrière, Paris, France.

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Address correspondence to Dr Labauge, Service de Neurologie, CHU Montpellier-Nîmes, Hôpital Caremeau, 2 Avenue du Pr Debré, 30029 Nîmes cedex 4, France. E-mail: labauge@yahoo.fr

to adult-onset forms with slow mental decline, progressive ataxia, and spasticity.<sup>3-6</sup> Disease progression can be exacerbated by rapid deterioration during febrile illnesses or after head trauma. MRI abnormalities of the cerebral white matter are diffuse and symmetric with a signal intensity close to the cerebrospinal fluid (CSF). Over time, increasing amounts of white matter vanish and are replaced with CSF.<sup>2</sup> Neuropathological findings are a cavitating orthochromatic leukodystrophy with rarity of myelin breakdown and relative sparing of axons. Diffuse vacuolation results in a spongiform to a cavitated appearance of the white matter.<sup>1,6-8</sup> Oligodendrocytes are increased in number with “foamy” cytoplasm, and astrocytes are scarce but reactive, sometimes atypical.<sup>6-9</sup> Mutations in the five eucaryotic initiation factor 2B genes (*EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5*), encoding the subunits EIF2B  $\alpha$  to  $\epsilon$ , have been found in more than 95% of patients with CACH/VWM criteria.<sup>3,10,11</sup> We report adult-onset forms of CACH/VWM in an affected man and his mother, suggesting a new dominant inheritance of this syndrome.

## Case Report

### Index Case

A 42-year-old man was the single child from unrelated parents. His motor, as well as psychological and cognitive, development was completely normal. At 35 years old, he presented with an upper respiratory tract infection with fever, quickly followed by excessive somnolence and mental confusion, apathy, vomiting, and left-sided hemiparesis, requiring mechanical ventilation. Routine blood tests and CSF analysis were normal. Electroencephalogram showed generalized slowing

activity. Brain computed tomography scan demonstrated an extensive hypodensity of the cerebral white matter. Extensive metabolic workup was normal, including leukocytes lysosomal enzymes activities, very long chain fatty acids, and histoenzymological examination of a muscle biopsy with analysis of respiratory chain enzyme complexes. No mutation was found in the *NOTCH3* gene, the mutations of which cause cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The patient progressively recovered normal strength and conscience in 2 weeks. Nine months after this initial acute episode, neuropsychological examination found only a mild decrease in verbal fluency (Mini-Mental State Examination score: 25/30). After banal viral infections, three similar acute episodes occurred at aged 36, 39, and 40 years, respectively. After the fourth episode, progressive neurological deterioration was observed. At aged 41 years, cerebellar ataxia, spastic quadriparesis, and pseudobulbar syndrome were present. Neuropsychological examination found reduced concentration and decrease of verbal fluency (Mini-Mental State Examination score: 21/30).

The first MRI performed during the last acute episode, at aged 40 years (Fig 1), showed diffuse and severe abnormalities of hemispheric cerebral, cerebellar, and brainstem white matter with a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted images, mild dilated ventricles, without any mass effect or abnormal contrast enhancement. On proton density images, deep hemispheric white matter had a low signal intensity, close to the CSF signal, suggesting cavitating white matter degeneration. On a second brain MRI, at aged 41 years, corticosubcortical at-

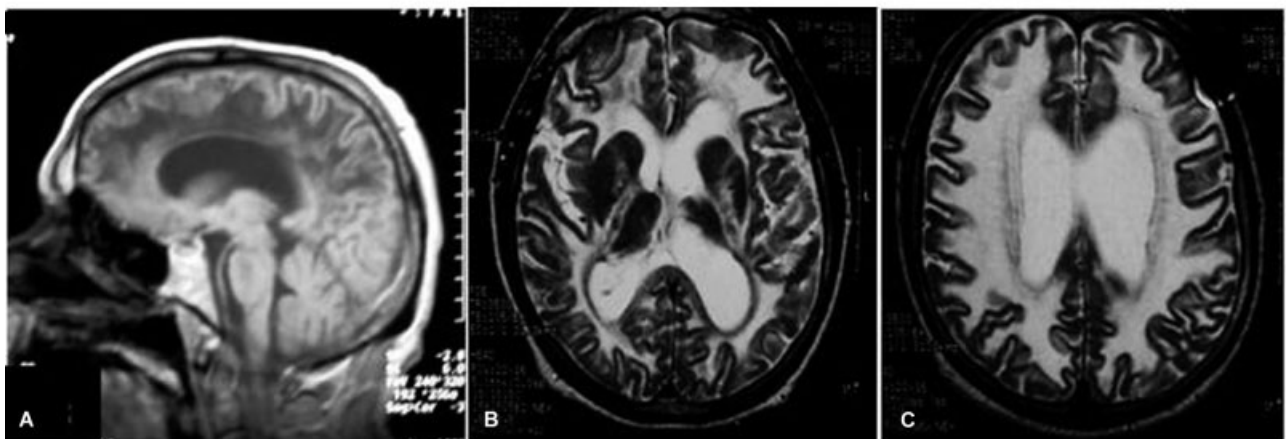


Fig 1. Index patient's magnetic resonance imaging (MRI) at age 40 years. MRI shows diffuse white matter abnormalities. Hemispheric cerebral white matter signal is hypointense on T1-weighted images (A), seen as hyperintense on T2-weighted images (B, C). Note the corpus callosum was thin but relatively spared (A) and the internal capsule was partially affected with a double line of signal abnormality in the posterior limb on the T2 sequences (B).

rophy and white matter abnormalities progressed, with a complete involvement of internal capsules, corpus callosum, middle cerebellar peduncles, and pontine tegmentum on T2-weighted images and CSF-like aspect of the subcortical white matter on fluid-attenuated inversion recovery (Fig 2A). Within these white matter lesions, the isotropic apparent diffusion coefficient was increased (see Figs 2B, C). Mean apparent diffusion coefficient values measured in the parietooccipital white matter was  $1.58 \pm 0.012 \times 10^{-9} \text{m}^2/\text{sec}^{-1}$  (healthy control subjects:  $0.89 \pm 0.07 \times 10^{-9} \text{m}^2/\text{sec}^{-1}$ ). Single-voxel ( $20 \times 20 \times 15 \text{mm}^3$ ) brain MRS (1.5-Tesla system, with point resolve spectroscopy (PRESS): TR, 135 milliseconds; stimulation echo acquisition mode (STEAM) sequences: TR, 30 milliseconds) showed a marked decrease of all usually detected brain metabolites (*N*-acetylaspartate, choline, creatine/phosphocreatine, myoinositol) in the centrum semiovale white matter contrasting with the normal profile observed in the medial parietal and occipital cortex. The signal-to-noise ratio in the white matter lesions

was 1.88-fold less than the mean signal-to-noise ratio measured in the white matter of healthy control subjects. A slight lactate signal was observed in the centrum semiovale white matter on PRESS spectra. No significant glucose signal and lipid accumulation was found on STEAM spectra (data not shown).

No mutation was found by direct sequencing of the coding, splicing sites and promotor regions of the five *EIF2B* genes, as described previously.<sup>3,5</sup> Moreover, the eIF2B guanine nucleotide exchange factor activity measured on lymphoblastoid cell lines, as reported previously,<sup>12</sup> was normal ( $107 \pm 15\%$ ) compared with age- and sex-matched control subjects.

#### *Mother's History*

The index case' mother had presented a 3-month history of progressive ataxia when she fell down with a minor head trauma at aged 38 years. She died at arrival in the neurosurgical department, and a brain autopsy was performed immediately. No abnormalities were noted on external inspection of the brain. Coronal sec-

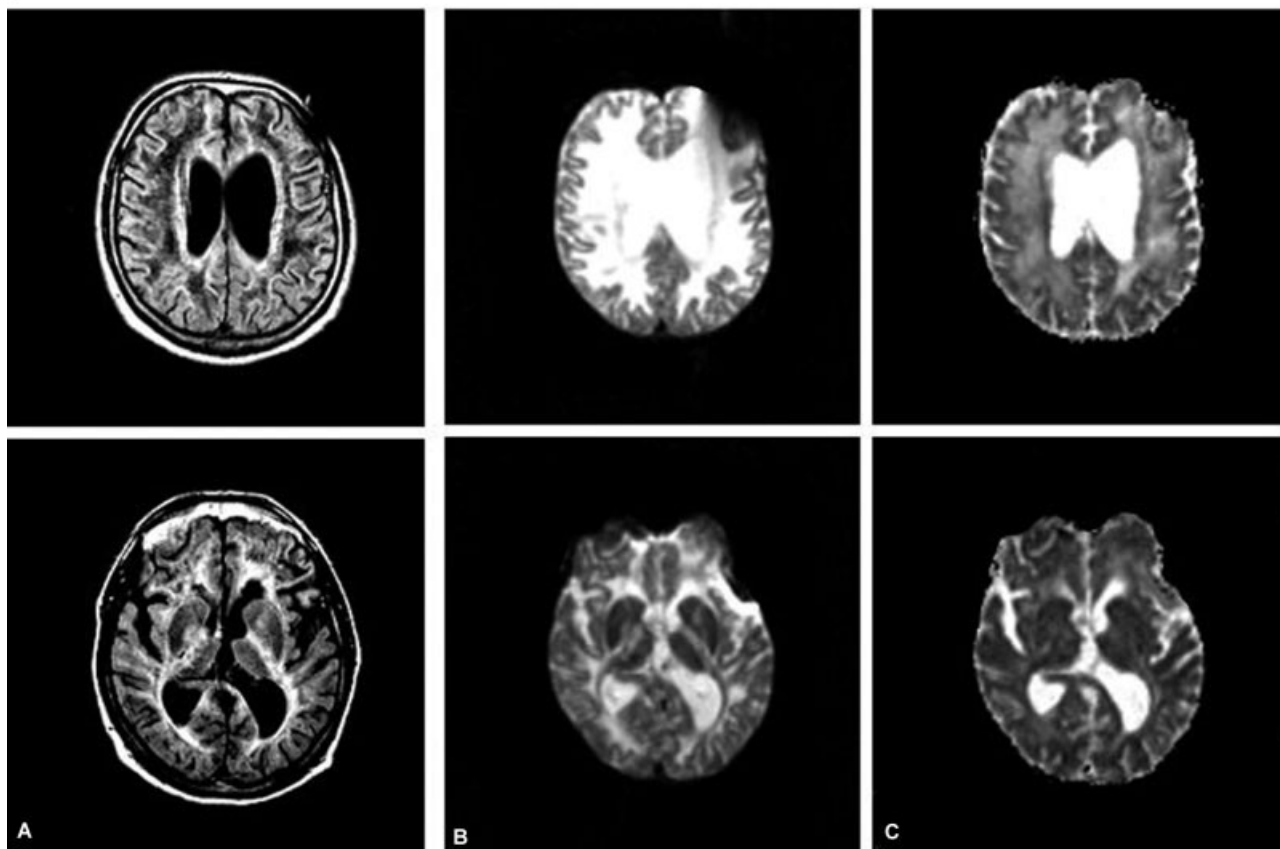
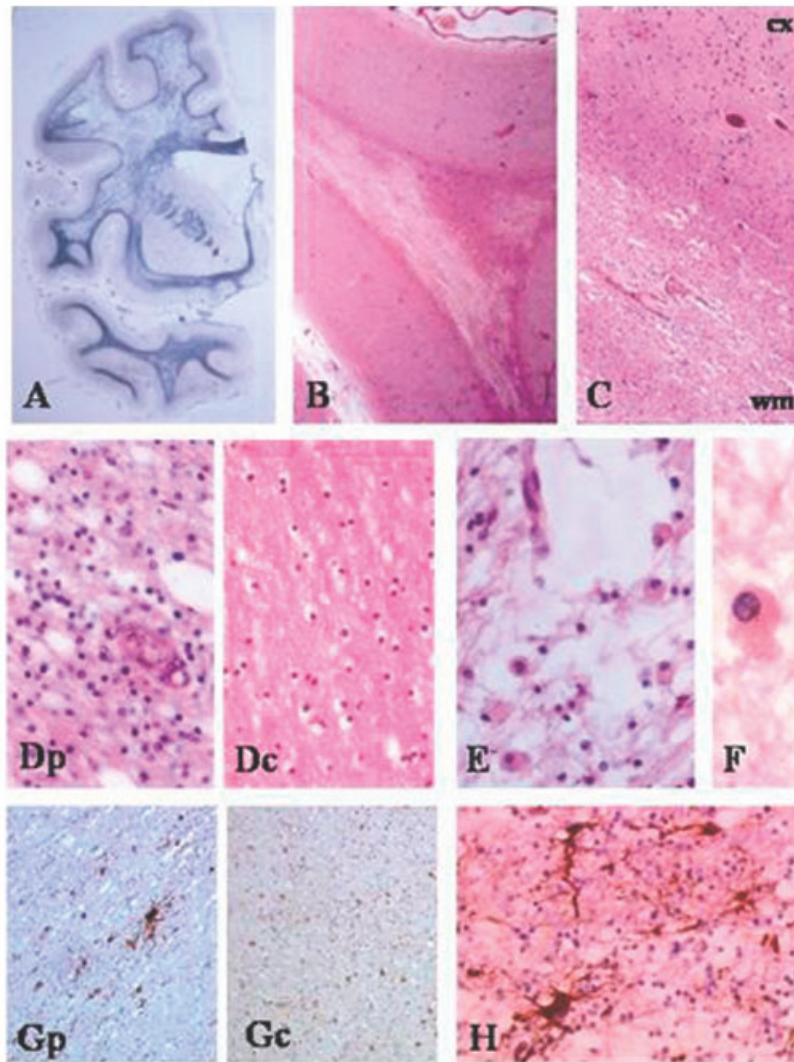


Fig 2. Index patient's magnetic resonance imaging (MRI) at age 41 years. Fluid-attenuated inversion recovery (FLAIR) images (A) (TR, 8,000 milliseconds; inversion time, 180 milliseconds; TE, 110 milliseconds) in the frontoparietal white matter show a diffuse hypointense signal of the subcortical region, suggesting a cavitation process contrasting with the abnormal hyperintense signal of the periventricular regions (A, top), which are also found in the temporal white matter lesions (A, bottom). Diffusion-weighted imaging (DWI; single-shot echo planar imaging sequence,  $b = 0, 500, 1,000 \text{sec}/\text{mm}^2$  applied in the x, y, z directions) demonstrates extensive hyperintense white matter lesions on  $b_0$  images (B) associated with an increase in apparent diffusion coefficient in these lesions (C).



tions showed a grayish, gelatinous, and precavitary aspect of the hemispheric white matter, involving also internal and external capsules and part of the corpus callosum. The U-fibers and part of optic radiations were unaffected. Lateral ventricles were mildly dilated. Cortex, brainstem, and cerebellum appeared normal. Death was related to the occurrence of a posttraumatic subarachnoid hemorrhage. We retrospectively reviewed histology slides accessible from the frontal and occipital lobes, hippocampus, brainstem, and thalami. On microscopic examination, the cerebral cortex and thalami

appeared normal. Abnormality of white matter was diffused but predominated in hemispheric deeper areas (Figs 3A, B). Myelin stains showed a severe depletion of myelin sheaths, with spongiform changes and precavitary appearance in the most affected areas. Axons were relatively preserved, except in the precavitary lesions where axonal loss was evident. In areas with relative myelin preservation (U-fibers and perivascular areas), an hypercellularity was observed in comparison with a control brain (see Fig 3C, Dp vs Dc). This increased cellularity is caused by the presence of a homogeneous



*Fig 3. Neuropathological features of the index patient's mother. Hemispheric white matter appears diffusely affected, with a relative preservation of subcortical (A, B) and corpus callosum myelin (A). The subcortical white matter is vacuolated (C, Dp), these vacuoles increasing in the deeper region of the white matter (WM; E). In relatively preserved WM areas, a hypercellularity is observed in the patient's brain (Dp) in comparison with an age-matched female control brain (Dc). This increased cellularity is composed of a homogeneous cell population with a small, dark, round nucleus characteristic of oligodendrocytes. Most of these oligodendrocyte-like cells display an unusual abundant cytoplasm (E, F). The glial fibrillary acidic protein (GFAP) immunostaining is increased in the patient's white matter (Gp) compared with control subject (Gc). However, GFAP increase is not related to a high density of astrocytes, but rather to their highly reactive features: astrocytes appear large with a rigid shape and thick, blunted processes (H). (A) Woelcke staining of a macroscopic frontal section; hematoxylin and eosin staining: original magnification  $\times 16$  (B),  $\times 10$  (C),  $\times 40$  (Dc, Dp, E),  $\times 100$  (F); GFAP immunostaining: original magnification  $\times 20$  (Gp, Gc),  $\times 40$  (H). Cx = cortex.*

cell population displaying morphological features of oligodendrocytes. Most of these oligodendrocyte-like cells displayed an increased cytoplasm that was foamy in severely affected areas (see Figs 3E, F). In contrast, astrocytes, recognized by glial fibrillary acidic protein immunostaining, were scarce and displayed highly reactive features in affected compared with control brain (see Fig 3H, Gp vs Gc). Inflammatory lymphocytic infiltrates were absent. A few macrophages with abundant cytoplasm were seen.

## Discussion

The most striking features of our index case are acute episodes of deterioration after minor infections and the vanishing pattern of white matter on MRI. These two features are the hallmarks of CACH/VWM.<sup>1,2</sup> Moreover, proton MRS showed a marked decrease in concentration of brain metabolites (*N*-acetylaspartate, choline, creatine/phosphocreatine, myoinositol) in white matter lesions, providing *in vivo* evidence of vanishing white matter degeneration, with a progressive replacement by CSF, as described previously.<sup>1,2,11,13,14</sup> In our index case, the increased apparent diffusion coefficient, measured in hypointense white matter lesions detected on fluid-attenuated inversion recovery images, reinforces the hypothesis of a cavitating white matter degeneration. The index case's mother suddenly died after a head trauma after a short history of cerebellar ataxia. Neuropathology demonstrated an extensive loss of brain myelin without "plaques" and with a relative axonal preservation, excluding inflammatory demyelination and suggesting leukodystrophic changes. Increased severity of the white matter spongiosis involving the deeper layers resulted in cavitated lesions. Preservation of oligodendrocytes with abundant "foamy" cytoplasm contrasting with scarcity of astrocytes is considered to be the most specific neuropathological hallmark of the disease.<sup>5-9</sup>

Pigmented orthochromatic leukodystrophy (POLD) has also been neuropathologically defined as a cavitated degeneration of the white matter with increased numbers of oligodendrocytes but associated with glial/microglial cytoplasmic pigment inclusions.<sup>15,16</sup> However, these inclusions sometimes are not found in affected relatives of patients with POLD.<sup>17</sup> The nonrecessive inheritance and the clinical course of our family could be consistent with POLD,<sup>16,17</sup> even if acute neurological episodes are rare in POLD. In addition, POLD is sometimes associated with ovarian failure,<sup>18</sup> as in CACH/VWM.<sup>19,20</sup> These similarities shared by CACH/VWM and POLD have been evoked previously.<sup>3,7</sup>

Inheritance of CACH/VWM syndrome has always been described as recessive. Mutations in the five subunits of EIF2B are involved in this disease.<sup>3-5,10,11</sup> The major role of EIF2B is to convert protein synthesis ini-

tiation factor 2 (EIF2) from an inactive guanosine diphosphate-bound form to an active EIF2/guanosine triphosphate complex. EIF2B mutations recently were shown to decrease this guanine nucleotide exchange factor activity.<sup>12</sup> An abnormal regulation of translation under different stress conditions could explain the acute and transient deterioration of CACH/VWM patients after minor viral infections or head trauma. As clinical, MRI, MRS, and neuropathological criteria for CACH/VWM were observed in our family, extensive research of mutations in the five *EIF2B* genes and determination of guanine nucleotide exchange factor eIF2B activity were performed and were negative. Absence of *EIF2B* genes mutations have already been reported in sporadic cases of CACH/VWM,<sup>4,10,11</sup> suggesting protein heterogeneity. Clinical and neuropathological criteria of CACH/VWM syndrome in the proband mother, excluding recessive inheritance, are consistent with a maternal or autosomal dominant transmission. In this new dominant form of CACH/VWM-like leukoencephalopathy, other genes involved in the eIF2 stress regulation cascade represent candidate genes.

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## A Novel *AβPP* Mutation Exclusively Associated with Cerebral Amyloid Angiopathy

Laura Obici, MD,<sup>1</sup> Andrea Demarchi, MD,<sup>2</sup> Giulia de Rosa, MD,<sup>3</sup> Vittorio Bellotti, MD,<sup>1,4</sup> Sabrina Marciano, BSc,<sup>1</sup> Simona Donadei, BSc,<sup>1</sup> Eloisa Arbustini, MD,<sup>5</sup> Giovanni Palladini, MD,<sup>1</sup> Marta Diegoli, PhD,<sup>5,6</sup> Egidio Genovese, MD,<sup>7</sup> Giancarlo Ferrari, MD,<sup>3</sup> Sergio Coverlizza, MD,<sup>2</sup> and Giampaolo Merlini, MD<sup>1,4</sup>

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**Mutations in *AβPP* cause deposition of Aβ amyloid fibrils in brain parenchyma and cerebral vessels, resulting in Alzheimer's disease (AD) and/or cerebral amyloid angiopathy (CAA). We report a novel mutation (L705V) within the Aβ sequence of *AβPP* in a family with autosomal dominant, recurrent intracerebral hemorrhages. Pathological examination disclosed severe CAA, without parenchymal amyloid plaques or neurofibrillary tangles. This variant highlights the vascular tropism of mutated Aβ, resulting in CAA instead of the pathological hallmarks of AD.**

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The cerebrovascular deposition of amyloid fibrils, particularly in leptomeningeal and cortical arteries and arterioles, is a well-recognized cause of intracerebral hemorrhagic stroke, ischemic lesions, and dementia.<sup>1</sup> The amyloid β-peptide (Aβ), released by proteolysis from the amyloid β precursor protein (AβPP), is the amyloid fibril subunit in most forms of cerebral amyloid angiopathy (CAA), such as sporadic, age-related CAA and CAA associated with Alzheimer's disease (AD).<sup>1,2</sup> Aβ-related CAA also includes autosomal dominant disorders (MIM 104760) caused by mutations within the Aβ region of *AβPP*.<sup>2,3</sup> These mutations cluster at codons 692–694, corresponding to residues 21–23 of

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From the <sup>1</sup>Amyloid Center, Biotechnology Research Laboratories, IRCCS Policlinico San Matteo, Pavia; <sup>2</sup>Department of Pathology, Ospedale San Giovanni Bosco, Torino; <sup>3</sup>Division of Neurology, ASL Ivrea, Ivrea; <sup>4</sup>Department of Biochemistry, University of Pavia, Pavia; <sup>5</sup>Transplant Research Area, IRCCS Policlinico San Matteo, Pavia; <sup>6</sup>Department of Pathology, University of Pavia, Pavia; and <sup>7</sup>Service of Neuroradiology, Clinica Eporediese, Ivrea, Italy.

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Address correspondence to Dr Merlini, Amyloid Center–Biotechnology Research Laboratories, IRCCS–Policlinico San Matteo, Viale Golgi, 19-27100 Pavia, Italy. E-mail: gmerlini@smatteo.pv.it