CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Extension of the Clinicoradiologic Spectrum of Newly Described End-Truncating *LAMB1* Variations

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Neurol Genet 2023;9:e200069. doi:10.1212/NXG.0000000000200069

Abstract

Objectives

To refine the clinical spectrum of a very recently identified phenotype associated with *LAMB1* end-truncating pathogenic variations.

Methods

Detailed clinical, neuropsychological, and MRI investigation of 6 patients from 2 unrelated families segregating end-truncating *LAMB1* variations.

Results

All patients harbored *a LAMB1* end-truncating pathogenic variation. The specific association of a hippocampal type episodic memory dysfunction and a diffuse leukoencephalopathy was observed in all 4 patients aged older than 50 years, slightly worsening over time in 2 patients with several years of follow-up. Additional unspecific neurologic symptoms are reported, such as episodes of numbness, language troubles, or faintness in these 4 patients and the 2 younger ones.

Discussion

The association of an extensive leukoencephalopathy with an episodic memory dysfunction of the hippocampal type is strongly suggestive of a *LAMB1* end-truncating variation in adults older than 50 years. Early cognitive complaints and imaging abnormalities might exist decades before. Additional transient manifestations can be observed, and this association should lead to *LAMB1* screening to avoid unnecessary invasive investigations.

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NG.

Recently, 3 patients were described showing a very unusual combination of an episodic memory dysfunction of the hippocampal type starting in their 60s, associated with extensive and confluent white matter (WM) hypersignals. This condition was caused by highly specific premature termination codon (PTC) variations all located at the end of the *LAMB1* gene, a major extracellular matrix coding gene. This type of PTC variant escapes nonsense-mediated RNA decay (NMD) and leads to the production of an end-truncated LAMB1 protein.[1]

In this study, we describe a large family including 5 affected members and 1 unrelated proband with an end-truncating *LAMB1* pathogenic variation, which allowed us to extend the clinical spectrum of this newly identified condition.

Materials and Methods

Participants

Three siblings and the 2 daughters of one of them (Family F1) and 1 additional unrelated proband (F2-1) were included (Figure 1A). All patients provided written informed consent for participation in genetic studies, in accordance with ethical recommendations in France for genetic disorders (eAppendix 1, links.lww.com/NXG/A595).

Molecular Screening

Genomic DNA was extracted from peripheral blood leukocytes according to standard protocols. Targeted next-generation sequencing of 8 genes known to be involved in monogenic cerebral small vessel diseases (*NOTCH3, COL4A1, COL4A2, HTRA1, APP, GLA, TREX1, LAMB1*) was performed for 3 affected members of family F1 (F1-5, F1-7, and F1-10) and for the F2 proband (methodology detailed in eAppendix 1, links.lww.com/NXG/A595). Sanger sequencing was used to screen patients F1-3 and F1-11 and to confirm the variation in patients F1-5, F1-7, and F1-10 (primers available on request). In addition to cerebral small vessel diseases genes screening, targeted next-generation sequencing of 153 genes known to be involved in leukodystrophies was performed for patients F1-7 and F1-10 as described in reference 2.

Data Availability

Data are not publicly available and may be obtained on reasonable request by sending an email to Guillaume Mathey (g.mathey@chru-nancy.fr) for clinical data or to Hélène Morel (helene.morel2@aphp.fr) for molecular data.

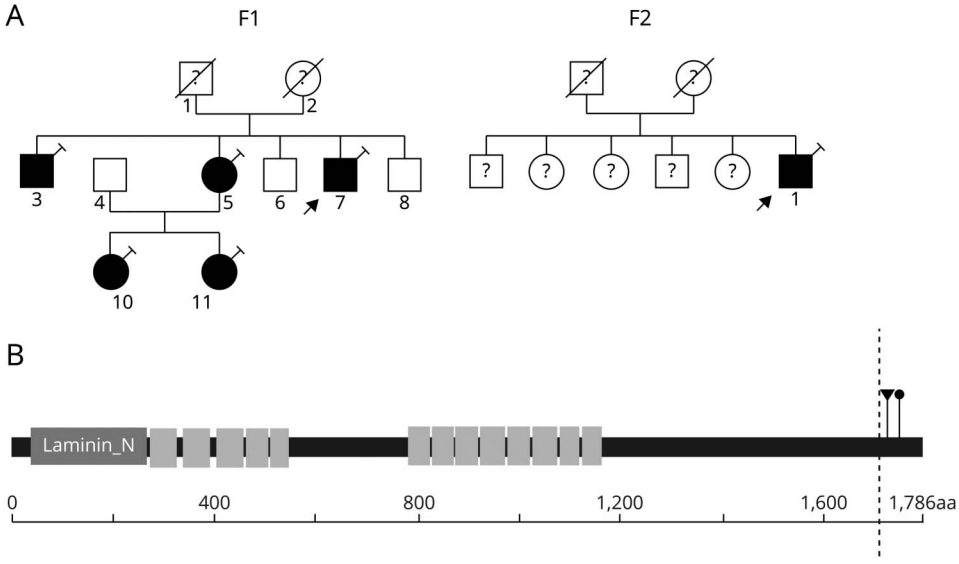
Results

Genealogical trees of family F1 and proband F2-1 are provided in Figure 1 (panel A). Patient F1-7, aged 61 years, the proband of family F1, is a man who experienced short episodes of faintness without loss of consciousness from his 50s. He complained of occasional tingling of superior limbs and memory disturbance. Cognitive tests in his 60s were consistent with an early amnestic syndrome of the hippocampal type (ASHT). Six years later, he felt a rapid worsening of his cognitive complaint confirmed by cognitive tests, still in accordance with ASHT (Table) Neurologic examination remained unremarkable.

Patient F1-5, aged 71 years, is the sister of patient F1-7. She was diagnosed with depression with psychotic features in her 70s, treated with neuroleptics onward. Her 2 daughters reported that she had cognitive difficulties that she was unaware of. At this time, her neurologic examination showed a mild stiffness of her right upper limb. Cognitive tests revealed an ASHT (Table).

Patient F1-3, aged 74 years, a brother of patients F1-7 and F1-5, developed a mild intentional tremor of his left hand associated

Figure 1 Genealogical Trees of F1 and F2 Families and Location of the 2 Mutations Identified in *LAMB1*



(A) Genealogical trees of F1 and F2 families. Square = male; circle = female; diagonal black line = deceased individual; black filled symbol = clinically and MRI-proven affected individual; open symbol = clinically healthy individuals based on family history but no MRI performed; open symbol with a question mark = unknown clinical status; arrow symbol = proband. (B) Schematic representation of LAMB1 protein and location of pathogenic variations identified in F1 (dot) and F2 (triangle). Dark gray box = laminin N-terminal domain; light gray boxes = laminin EGF domains; dashed vertical line = NMD boundary (~c.5166/p.1722); triangle = pathogenic variation identified if F2 (p.(Lys1708IlefsTer23)), dot = pathogenic variation identified if F1 (p.(Asn1750LysfsTer4)).

Table Patients Neuropsychological Scores[a]

Patient	F1-3	F1-5	F1-7	F1-7	F1-10	F1-11	F2-1
Evaluation number	1	1	1	2	1	1	1
Age range at evaluation (y)	70–80	70–80	60–70	60-70 (+6 y)	40–50	30–40	50–60
Global cognitive functioning							
Mini-mental state examination (30)	28	24	28	NA	NA	NA	25
Executive functions							
Frontal assessment battery (18)	NA	15	NA	NA	NA	NA	13
Trail making test part a (s)	NA	42	30	25	37	24	43
Trail making test part B (s)	NA	140	56	94	91	45	100
Trail making test part B-A (s)	NA	98	26	69	54	21	57
Letter P fluency task 2 min	NA	16	15	18	22	20	12
Verbal episodic memory							
Memory free and cued recall test							
Encoding (16)	NA	15	14	13	NA	NA	16
Free recall (48)	NA	15	24	21	NA	NA	6
Total recall (48)	NA	29	40	37	NA	NA	16
Delayed free recall (16)	NA	5	8	5	NA	NA	2
Delayed total recall (16)	NA	9	14	13	NA	NA	9
Intrusions	NA	NA	1	2	NA	NA	18
RI 48 task							
Immediate (48)	NA	NA	NA	NA	NA	48	NA
Delayed (48)	NA	NA	NA	NA	NA	48	NA
Buschke selective reminding test							
Free recall (15)	NA	NA	NA	NA	11,4	NA	NA
Learning index (%)	NA	NA	NA	NA	62,28	NA	NA
Delayed recall (15)	NA	NA	NA	NA	14	NA	NA
Language							
Oral confrontation naming							
40 items (40)	NA	NA	NA	NA	NA	40	40
80 items (80)	NA	73	74	76	76	NA	NA
Semantic fluency (animals) 2 min	NA	14	23	23	30	33	32

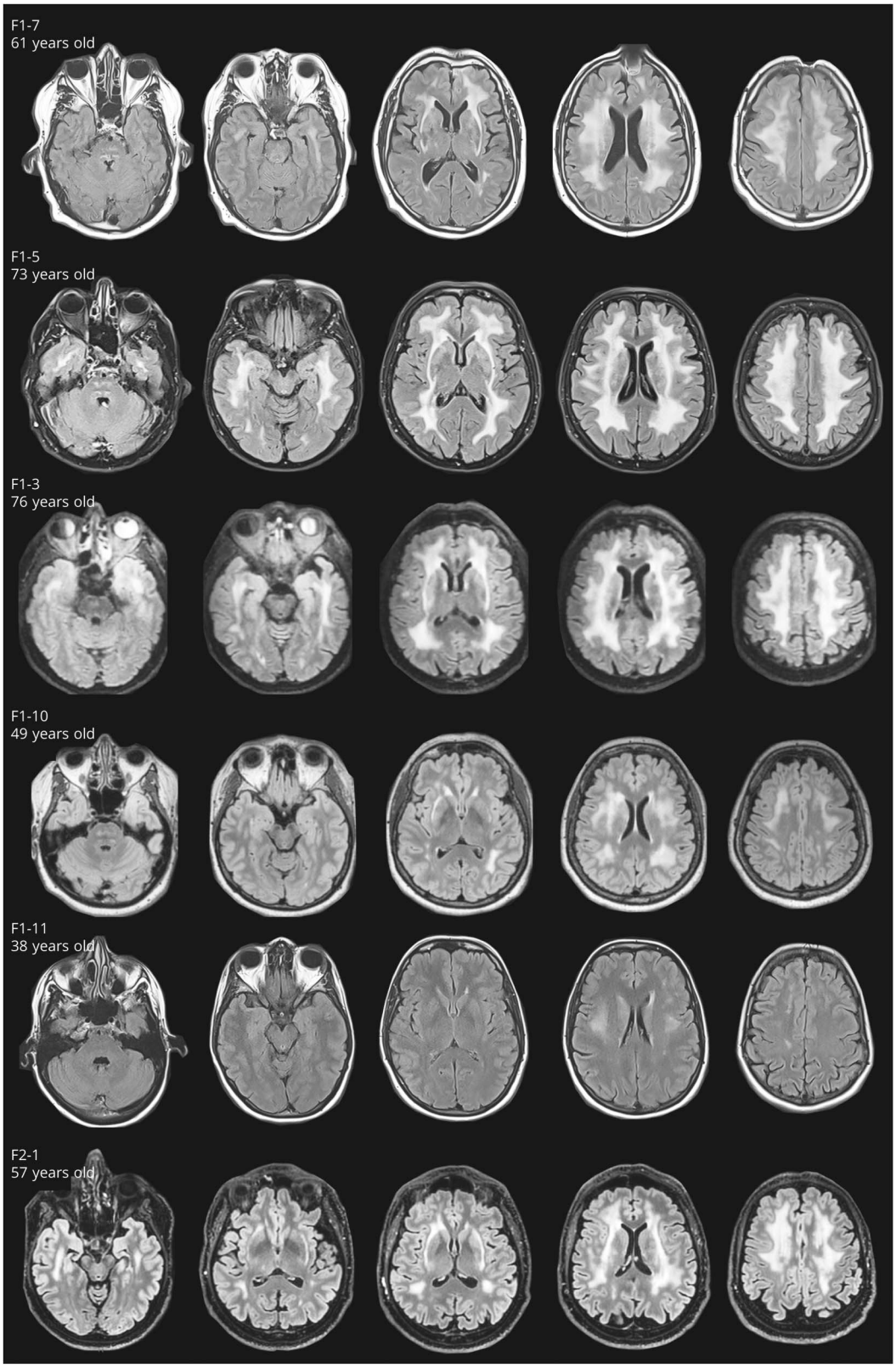
[a] The maximum score for each test and subtest is indicated in parentheses.

with memory complaint in his 70s. His mini-mental state examination revealed 2 errors in delayed recall of the 3 words (28/30).

Patient F1-10, aged 48 years, is the daughter of patient F1-5. She complained of episodes of faintness without loss of consciousness, starting in her 40s, attacks of paraphasia, numbness of the right half body, and imbalance. These episodes lasted for several weeks. She also complained of attentional and "word finding" problems. The neurologic examination has always been normal, even during "attacks." Cognitive tests in her 40s revealed very mild executive difficulties (Table) without episodic memory impairment.

Patient F1-11, aged 38 years, is the second daughter of patient F1-5. She complained of anterograde memory defects and

Figure 2 Selected Brain MRI Data (Axial Fluid-Attenuated Inversion Recovery Sequences) of Symptomatic Patients



Fluid-Attenuated Inversion Recovery sequence images showing diffuse white matter hyperintensities in all patients. Hyperintensities affect deep white matter, especially the external capsule (except for the youngest patient) and the *centrum semiovale*. Gyral white matter is also affected in part, although juxtacortical white matter remains spared. No infarcts, lacunar infarcts, microbleed, or hemorrhage was noticed.

"word finding" problems. Cognitive tests in her 40s were normal (Table).

Patient F2-1, aged 57 years, was a man, unrelated to family F1. From his 50s, his relatives noticed a progressive decline in anterograde memory, leading to severe apathy. Cognitive tests revealed an ASHT and a mild dysexecutive syndrome (Table).

The 6 patients all remained fully independent in their daily living at any time of their medical follow-up. Many other neurologic (spinal cord MRI and CSF analysis with amyloid and tau markers notably), visual, and cardiovascular investigations were performed and were all normal. No therapeutic intervention was warranted.

Neuroimaging Data

T2 hypersignals in the supratentorial WM were observed in all patients (Figure 2), limited to *centrum semiovale* in the 2 youngest patients, whereas they were extensive and confluent in the 4 oldest ones. Pontine T2 hypersignals were visible in most patients. Neither focal nor generalized atrophy of the grey or the white matter, nor microbleeds, hemorrhage, or ischemic lesions were found (except 1 right thalamic lacune in patient F2-1). On T1 imaging, T2 hyperintensities appeared hypointense, without gadolinium enhancement.

Molecular Data

Targeted next-generation sequencing performed on patients F1-5, F1-7, and F1-10 identified a pathogenic variation in the last exon of *LAMB1* (Figure 1, panel B). This variation (NM_002291.3:c.5250_5253del) led to a frameshift and a PTC escaping NMD, p.(Asn1750LysfsTer4). A pathogenic variation (NM_002291.3:c.5123_5124delinsT) leading to a PTC predicted to escape NMD, p.(Lys1708IlefsTer23), was identified in patient F2-1.

Discussion

We report herein the detailed clinical, neuropsychological, and neuroimaging features of 6 patients harboring heterozygous *LAMB1* premature stop codons escaping NMD.

The 4 patients older than 50 years presented with an ASHT with mild executive dysfunction. The consequences of these troubles in daily life remained moderate, leading to a diagnosis of mild cognitive impairment without dementia, even after a 6-year follow-up in 1 patient. This cognitive profile is similar to the ones detected in 3 other probands harboring similar *LAMB1* variations and reported in reference 1. Significant cognitive complaints were also present in the 2 family F1 younger patients, despite normal tests or some slightly abnormal executive scores, suggesting a possible early onset of cognitive disorders, before the age of 50. Intriguingly, 4 of our patients, including 1 before the age of 40, presented with attacks of unspecific neurologic symptoms such as episodes of numbness, tremor, or tingling. These "low-noise" symptoms could suggest an ischemic origin, but neurologic examinations as well as brain MRI at the time of symptoms failed to find any specific deficit or vascular lesion.[1]

All patients shared extensive T2 hypersignals in the brain WM, very similar to the ones described in the original publication.[1] This leukoencephalopathy was already detectable in the youngest patients in their 30s and 40s.

Little is known on the exact nature of the leukoencephalopathy associated with *LAMB1* mutations. A leukoencephalopathy has been associated with another laminopathy caused by *LAMA2* mutations, mainly responsible for a muscular dystrophy. However, this phenotype is not associated, to the best of our knowledge, with memory defects.[3,4] In our *LAMB1*-mutated patients, the hypersignals may be secondary to water leakage through the blood-brain barrier or oligodendrocyte alterations suggestive of demyelination as seen in leukodystrophies.[5] The lesions seen in our patients share many characteristics with leukodystrophies.[6] However, this MRI pattern is also consistent with the ones observed in vascular leukoencephalopathies such as *COL4A1/COL4A2* angiopathies or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, despite the absence of lacunes and microbleeds.[7,8] Of note, pontine lesions were present in our patients, even at a young age, which might be a remarkable point in the radiologic characterization of this phenotype.[9]

To conclude, the specificity of this clinical and MRI phenotype is so strong that it should lead to the testing of *LAMB1*. This will avoid both clinical wandering and long-lasting and expensive tests, and the "favorable" clinical course of the disease might reassure patients diagnosed with the variation.

Acknowledgment

The authors thank the patients for their participation in this study. The authors are greatly indebted to Florence Marchelli for her excellent figure editing.

Study Funding

This research was supported by the National Research Agency, France (ANR-16-RHUS-004).

Disclosure

H. Morel reports no disclosures relevant to the manuscript; L. Bailly reports no disclosures relevant to the manuscript; C. Urbanczyk reports no disclosures relevant to the manuscript; D. Hervé reports no disclosures relevant to the manuscript; S. Berroir reports no disclosures relevant to the manuscript; R. Le Bouc reports no disclosures relevant to the manuscript; R. Levy reports no disclosures relevant to the manuscript; M. Meyer reports no disclosures relevant to the manuscript; C. Aloui reports no disclosures relevant to the manuscript; E. Tournier-Lasserve reports no disclosures relevant to the manuscript; G. Mathey reports no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NG.

Publication History

Received by *Neurology: Genetics* January 25, 2023. Accepted in final form February 14, 2023. Submitted and externally peer reviewed. The handling editor was Editor Stefan M. Pulst, MD, Dr med, FAAN.

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