

Adult-onset leukoencephalopathy with homozygous *LAMB1* missense mutation

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LAMB1 encodes laminin subunit beta 1, a constituent of the extracellular matrix glycoprotein of basement membranes.¹ Mutations of *LAMB1* have been reported in patients with congenital or infantile- to childhood-onset leukoencephalopathy and severe developmental retardation.^{2,3} We report an adulthood-onset case with mild leukoencephalopathy and a novel homozygous *LAMB1* missense mutation. Our findings expand the clinical spectrum of *LAMB1*-related disorder.

Case report

A 37-year-old woman with headache, memory loss, and gait disturbance was referred to our department. She was born to consanguineous parents (figure 1A), and her elder sister was asymptomatic. She had been healthy until age 22 years, when migraine developed. Brain MRI showed a cerebral white matter lesion at age 30 years. She developed gait disturbance at age 31 years. She had been aware of memory loss, executive dysfunction, and menstrual irregularity since age 35 years. On neurologic examination, hyperreflexia of jaw jerk and legs and lower limb spasticity were observed. The Wechsler Adult Intelligence Scale–Third Edition indicated a full-scale IQ of 69, suggesting borderline intelligence. Blood test findings were negative/normal for syphilis, HIV, autoantibodies, lactate, pyruvate, and very-long-chain fatty acids. Measurement of enzyme activity did not suggest gangliosidosis, metachromatic leukodystrophy, or Krabbe disease. Ophthalmologic evaluation revealed mild flexion of retinal vessels (figure 1B), but neither optic atrophy nor subcapsular lens opacification. Brain MRI showed diffuse T2 hyperintensity of cerebral white matter, but neither cortical dysgenesis nor cystic lesions were observed (figure 1, C–D). Neurologic examination and brain MRI of her father showed no abnormalities, whereas her mother did not consent to neurologic examination or brain MRI. These suggested autosomal recessive inheritance. We focused exome sequencing analysis on the 115 genes retrieved from Online Mendelian Inheritance in Man (OMIM)⁴ using the terms: “leukoencephalopathy”, “leukodystrophy”, and “small vessel” and identified 2 potent biallelic pathogenic mutations in *LAMB1* (c.1378T>C, p.Cys460Arg) on chromosome 7 and *ARSE* (c.220G>A, p.Val74Met) on chromosome X. Careful reading of the OMIM text of *ARSE* revealed that not *ARSE* (arylsulfatase E) but *ARSA* (arylsulfatase A) was related to leukodystrophy. Therefore, we focused on *LAMB1* and validated the mutation by Sanger sequencing. The parents had heterozygous mutations (figure 1E). *LAMB1* p.Cys460Arg was absent in the nucleotide variation databases (gnomAD and 4.7KJPN)⁴ and predicted to be pathogenic by multiple software programs (SIFT, PolyPhen-2, Mutation Taster, PROVEAN, and CADD).⁴ These findings suggest that *LAMB1* was a causative gene for leukoencephalopathy in this patient.

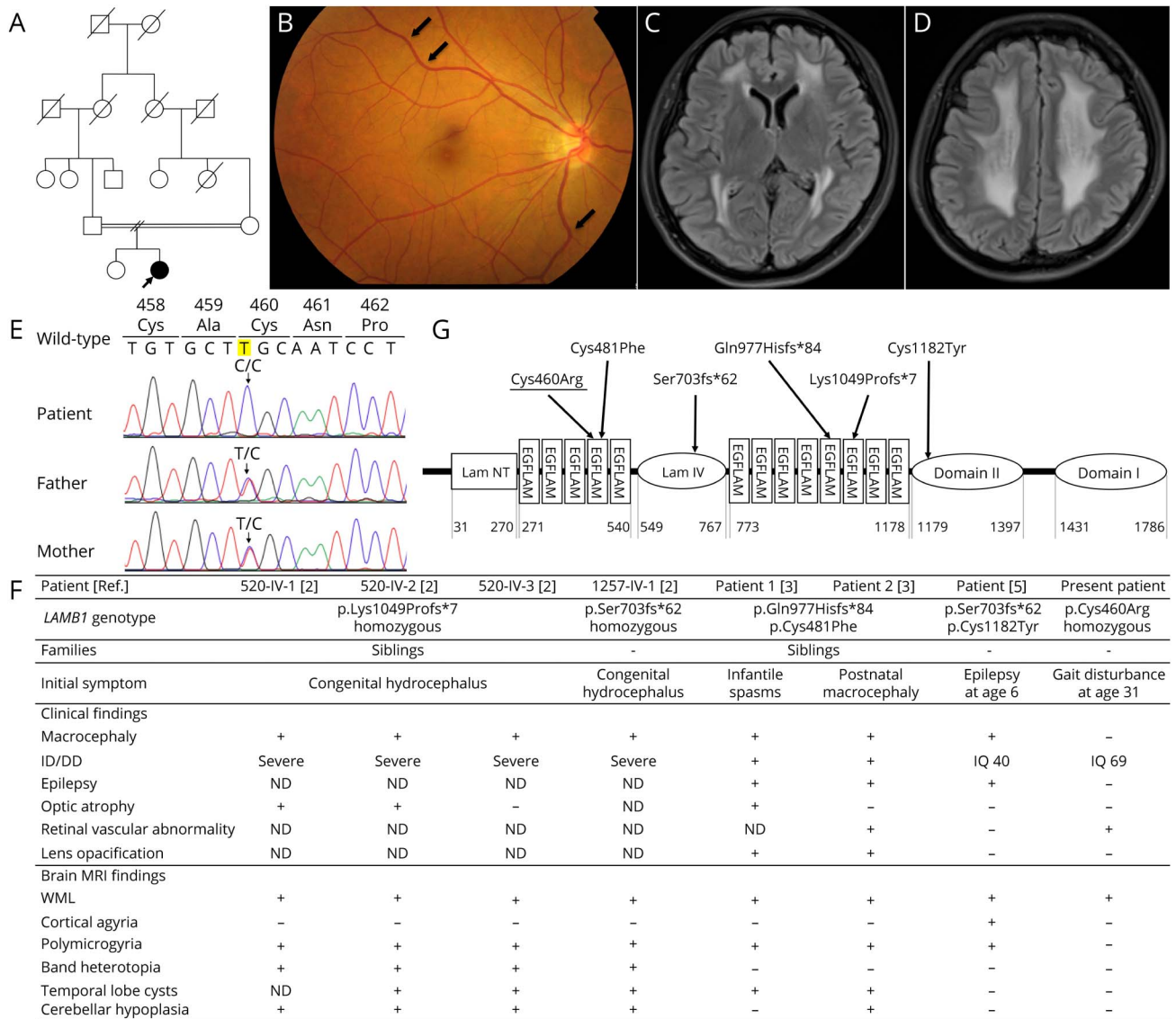
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Figure 1 Clinical, radiologic, and genetic findings of the patient



(A) Family tree of the patient (arrow). (B) Fundus image of the right eye shows mild flexion of retinal vessels (arrow). (C and D) Brain MRI at age 40 years. FLAIR axial images show diffuse hyperintensity of white matter. (E) Sanger sequencing of genomic DNA demonstrates that the patient has homozygous C/C, whereas each parent has heterozygous T/C at c.1378T (highlighted in wild-type sequence). (F) Clinical and MRI findings of patients with *LAMB1* mutations. ID/DD = intellectual disability/developmental delay; ND = not described; WML = white matter lesions on MRI. (G) Summary of the *LAMB1* protein structure and location of mutations. Our case is underlined. EGFLAM = laminin epidermal growth factor-like domain; FLAIR = fluid-attenuated inversion recovery; Lam NT = laminin N-terminal; LAM IV = laminin IV type B.

Discussion

We report a patient with adult-onset leukoencephalopathy and a homozygous *LAMB1* missense mutation. The clinical phenotype included mild intellectual disability and spastic gait. Periventricular rim on brain MRI and retinal vessel abnormalities were features not reported in other adult-onset leukoencephalopathies (table e-1, figure e-1, links.lww.com/NXG/A265).

LAMB1 mutation was originally reported to cause autosomal recessive cobblestone brain malformation, presenting with congenital hydrocephalus, severe developmental delay, and an increased head circumference.² Subsequently, the phenotype of

LAMB1-related disorders was extended to include progressive leukoencephalopathy with seizures, ocular abnormalities, and porencephalic lesions.³ Recently, a patient with a relatively milder phenotype, including childhood-onset epilepsy, macrocephaly, and intellectual development arrest, was reported.⁵ Retinal vascular abnormality was reported in a patient with *LAMB1* compound hetero mutation, similar to our patient,³ which might be a key finding to suspect *LAMB1*-related basement membrane pathologies.

Comparison of previous cases and the present patient with biallelic *LAMB1* mutations indicated genotype-phenotype correlations. Homozygous frameshift mutations (p.Lys1049Profs*7

and p.Ser703fs*62) were identified in the most severe congenital-onset patients (figure 1F).² Compound heterozygous mutations including 1 missense mutation (p.Gln977Hisfs*84/p.Cys481Phe and p.Ser703fs*62/p.Cys1182Tyr) were identified in less severe patients with postnatal to childhood onsets.^{3,5} Our patient with homozygous missense mutations showed a much milder phenotype. Taken together, the effect of missense mutations on the phenotype may be milder compared with that of frameshift mutations.

Localization of 5 mutations previously reported and that identified by us in LAMB1 protein is shown (figure 1G). Frameshift mutations are considered to result in truncating protein, suggesting loss-of-function effects. The effect of p.Cys480Phe and p.Cys460Arg may be conformational change because each EGF-like repeat contains 8 cysteine residues participating in 4 pairs of disulfide bonds that determine appropriate protein conformation.¹ Similarly, in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, cysteine-related missense mutations in a certain EGF-like repeat were confirmed as pathogenic.^{6,7} Further molecular analysis will clarify the effects of LAMB1 missense mutations.

In conclusion, our findings expand the clinical spectrum of LAMB1-related disorder. LAMB1 gene mutation should be considered in the setting of adult-onset autosomal recessive leukoencephalopathy with retinal vascular abnormality.

Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

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