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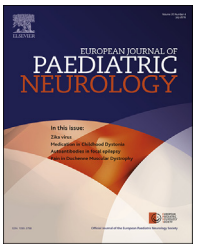

A brother and sister with intellectual disability and characteristic neuroimaging findings

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ABSTRACT

Leukoencephalopathy with brain calcifications and cysts (LCC) is a genetic white matter disorder, which involves the brain small blood vessels. In the absence of extra-neurological symptoms, LCC has a pathognomonic radiological phenotype. Recently, biallelic mutations in the SNORD118 gene, which is a non-protein coding gene, were discovered to cause LCC. We present here two siblings with developmental delay and a typical MRI pattern, who were diagnosed with LCC. The mutations in the SNORD118 gene were initially missed with whole exome sequencing (WES), but recognition of the MRI patterns of both children raised the suspicion of LCC and led to a genetically proven diagnosis after re-evaluation of the WES data.

1. Introduction

Leukodystrophies are genetic white matter disorders, caused by a variety of disease mechanisms among which disorders of brain small blood vessels. One of these disorders is leukoencephalopathy with brain calcifications and cysts (LCC), also known as Labrune syndrome.[1] Clinical symptoms of LCC may appear at any age and presenting symptoms may vary substantially, consisting of e.g. headache, seizures, hemiparesis, ataxia or changed behaviour. LCC is a form of leukodystrophy with recognizable radiological and pathological findings.[1,2] MRI reveals extensive signal abnormalities of the periventricular and deep cerebral white matter, and supratentorial and cerebellar cysts can be present. CT images are characterized by progressive calcifications in the basal ganglia and cerebellar nuclei, and the supratentorial white matter.[1] The most prominent neuropathological feature is angiomatous-like rearrangements of the microvessels, with degenerative secondary features; perivascular foci of calcifications, hyaline deposits, and formation of Rosenthal fibers.[1] The available therapy is currently only symptomatic.

Very recently it was shown that bi-allelic mutations of the *SNORD118* gene on chromosome 17p13.1 cause LCC.[3] Here we report a brother and a sister with intellectual disability, who were radiologically diagnosed as patients with LCC (Fig. 1), and subsequently proven to harbour two compound heterozygous *SNORD118* mutations.

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2. Case study

Patient 1, a boy, was born at 33 weeks and 3 days of gestation with normal birth weight and APGAR scores. He was the first child of non-consanguineous parents. At the age of 11 months, he was referred to our outpatient clinic with epileptic seizures and developmental delay. With medication (valproate) he became seizure free, and the treatment was successfully stopped at 4 years. He could roll over and sit independently at 18 months, and walk without support when he was almost 5 years old. He spoke his first words when he was over 4 years old. At the time of this report, he is 10 years old. His height and head circumference are growing at −2 standard deviation (SD). He has a moderate intellectual disability, with a slightly dysmorphic facial appearance

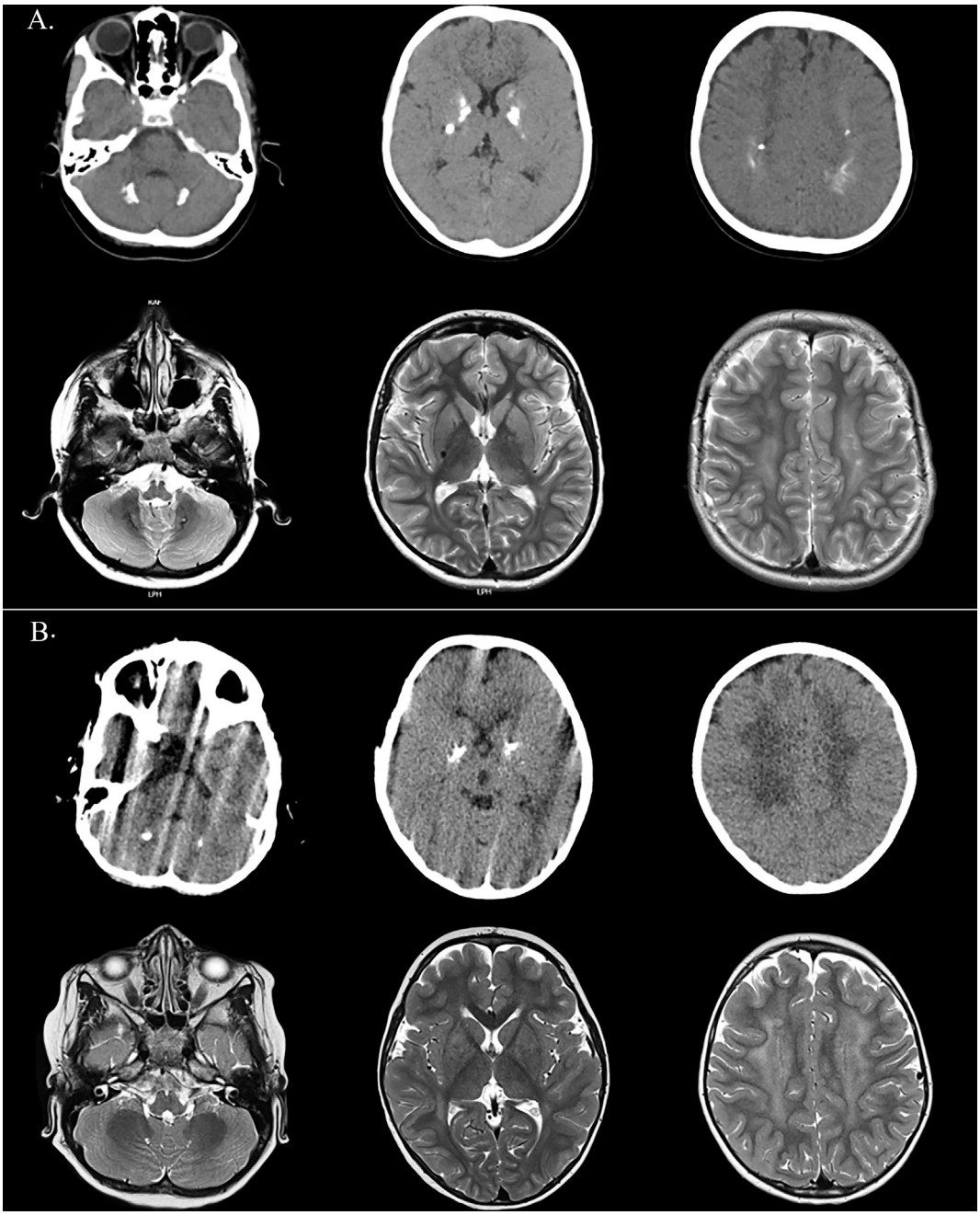

Fig. 1 – Neuroimages. A. Patient 1, T2-weighted MR images (lower panel, A1) and CT (upper panel, A2), at 9 years. MRI shows bilateral, mildly and inhomogeneously increased signal in the periventricular and deep cerebral white matter; very low signals are present in the dentate nucleus on both sides and a single focus in right dorsal putamen. CT clearly shows calcification of the dentate nucleus, globus pallidus and some areas in the cerebral white matter. B. Patient 2, T2-weighted MR images (lower panel, B1) and CT (upper panel, B2), at 4 years. MRI shows bilateral, mildly and inhomogeneously increased signal in the periventricular and deep cerebral white matter; no areas with very low signal are present. CT clearly shows calcifications of the bilateral dentate nucleus and globus pallidus.

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