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LETTER TO THE EDITOR

A novel mutation in the *CSF1R* gene causes hereditary diffuse leukoencephalopathy with axonal spheroids

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Dear Editor,

Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS; OMIM 221820) is a rare autosomal dominant disease that is neuropathologically characterized by the widespread loss of myelin sheaths and axons and the presence of axonal spheroids, gliosis and lipid-laden, pigmented macrophages [1]. HDLS is caused by mutations in the *colony-stimulating factor 1 receptor* (*CSF1R*) gene on chromosome 5q34 [2, 3]. Typical clinical manifestations include a variable combination of personality and behavioral changes, cognitive impairment, unsteady gait, parkinsonism, and seizures. Onset commonly occurs in the fourth to fifth decade of life [4]. Brain magnetic resonance imaging (MRI) shows nonspecific leukoencephalopathy, mainly involving the subcortical white matter of the frontal and parietal lobes, with concomitantly progressive cortical atrophy [5]. In this study, we report a novel heterozygous frameshift mutation, c.2645delC (p.P882PfsX70), in an exon of the *CSF1R* gene in a Chinese family (Fig. 1). This case provides further evidence for the phenotypic heterogeneity of HDLS.

In January 2017, a 24-year-old Chinese man with no significant past medical history presented with constant numbness of the limbs on his right side. Four months later, the numbness worsened and his left lower limb became weak, leading to an obviously abnormal gait. He was admitted to West China Hospital, and brain MRI indicated patchy lesions with low T1 and high T2 signals in the bilateral periventricular regions and corpus callosum. A hyperintense signal was observed on the fluid attenuated inversion recovery (FLAIR) sequence without Gd-enhancement, suggesting demyelinating lesions of cerebral white matter (Fig. 2). A positron emission tomography with fluorodeoxyglucose (FDG–PET) scan demonstrated reduced glucose metabolism in the cortex of the left frontal and parietal lobes as well as in the thalamus and putamen. A bilateral periventricular hypodense shadow was observed without increased FDG metabolism. The cerebrospinal fluid (CSF) was almost normal. Oligoclonal band (OB), aquaporin-4 (AQP4), myelin oligodendrocyte glycoprotein (MOG), and neuronal cell surface antibodies including NMDAR, AMPAR1/2, LGI1, CASPR2, GABAR, and GAD65 were negative in his serum and CSF. Tests for anti-nuclear antibodies (ANA), anti-DNA antibodies, anti-extractable nuclear antigen (ENA) antibodies, and anti-neutrophil cytoplasmic antibodies (ANCA) were normal. Tandem mass spectrometry (TMS) of his blood and urine was also normal, as were the neuronal antibody spectrum in his serum and the level of very long chain fatty acids in his blood. He was treated with intravenous methylprednisolone pulse therapy (1000 mg/day for 5 days), but his symptoms did not improve much. After discharge, his symptoms worsened further: he suffered weakness of all four limbs, which led to progressive spastic quadriplegia and dysarthria, and declined cognition, involving memory, calculation, and visuospatial reactions. In August 2017, the patient was confined to a wheelchair. Three months later, he was unable to stand or raise his hands and experienced dysphagia, dysarthria, and urinary incontinence. In January 2018, he had a generalized tonic-clonic seizure that lasted for approximately 10 min. After the seizure, the patient fell into a coma and regained consciousness 3 days later. In March 2018, another seizure occurred. According to the clinical manifestations and radiological findings, the case was compatible with a clinical diagnosis of HDLS. Six months after the

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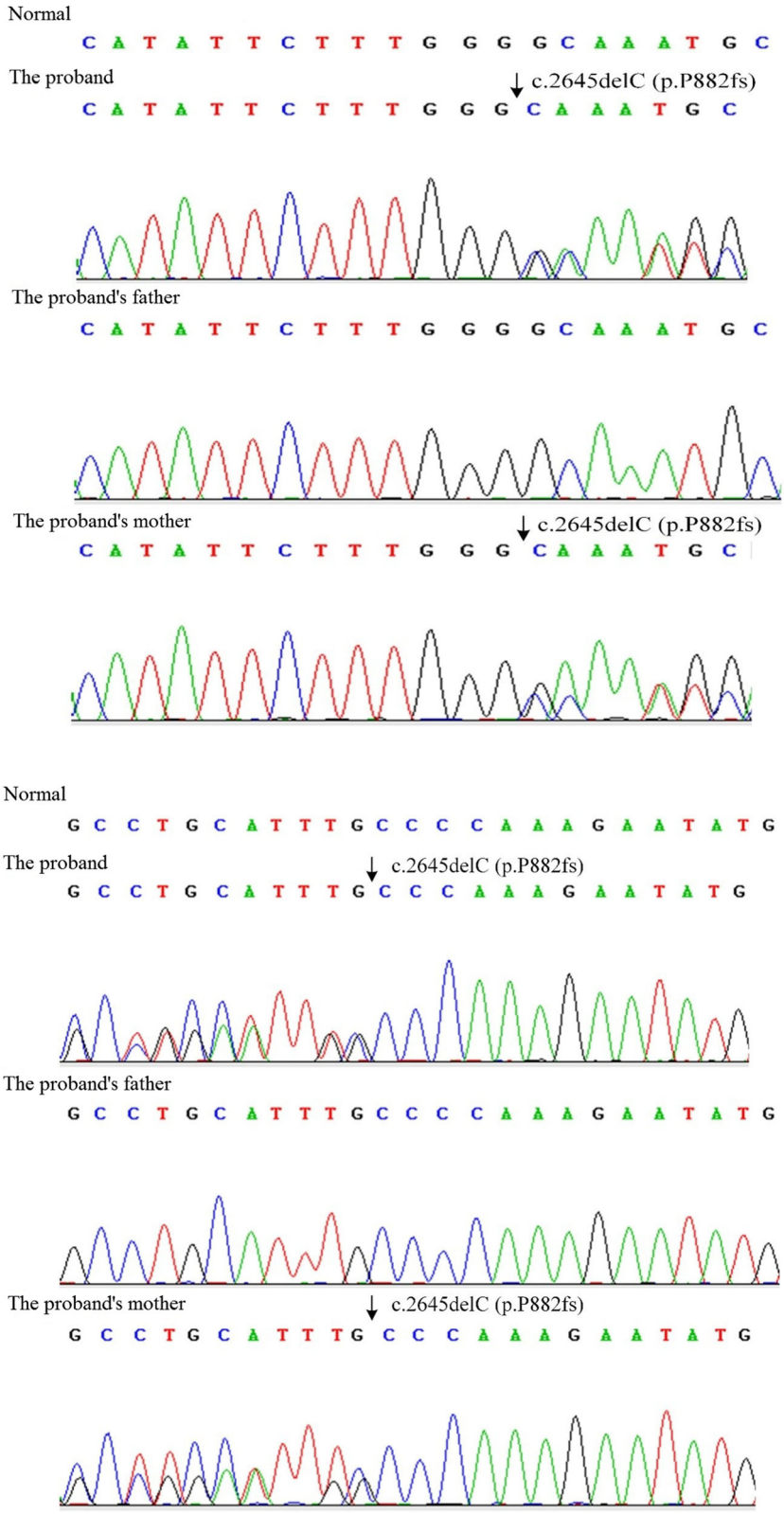

Fig. 1 Sequencing chromatogram of part of exon 20 showing the mutation in *CSF1R* (indicated by an arrow). Direct DNA sequencing revealed one pathogenic mutation—a heterozygous C deletion at nucleotide 2645 (counting from the start codon) of exon 20 in *CSF1R*, which causes a frameshift mutation

diagnosis, he progressively suffered from aphasia, aphagia, severe muscle atrophy and complete spastic quadriparesis with articular contractures. He was finally bedridden and unable to speak. Both parents are symptom free, and physical examination of the nervous system and a brain MRI of his mother were normal (Fig. 3).

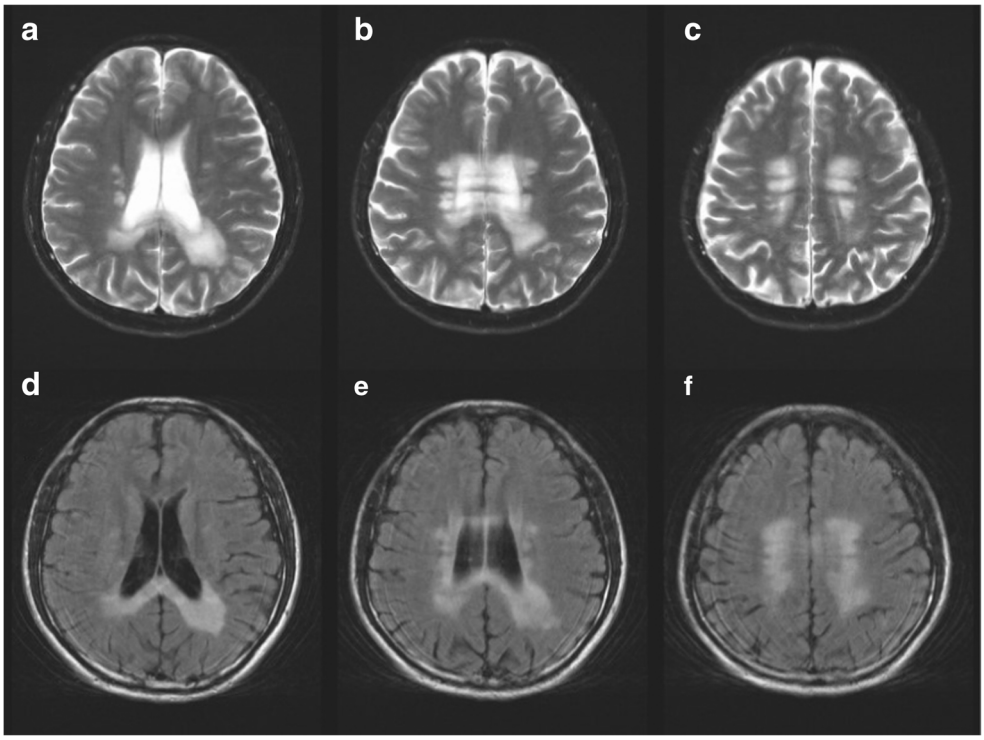

Fig. 2 Brain MRI of the proband indicating bilateral periventricular demyelinating lesions of the cerebral white matter

Genomic deoxyribonucleic acid (gDNA) was isolated from peripheral blood leukocytes using a DNA Isolation Kit (Bioteke, AU1802). Exons 1 to 22 and the exon-intron boundaries of the *CSF1R* gene were amplified by polymerase chain reaction (PCR). Sanger sequencing was performed to validate the mutation identified in the patient, and the PCR product was sequenced using ABI 3730XL and BigDye Terminator v3.1 Cycle Sequencing Kit (Applied biosystems, Forester City, CA, USA). The DNA sequences were analyzed using Chromas software and then compared with the reference

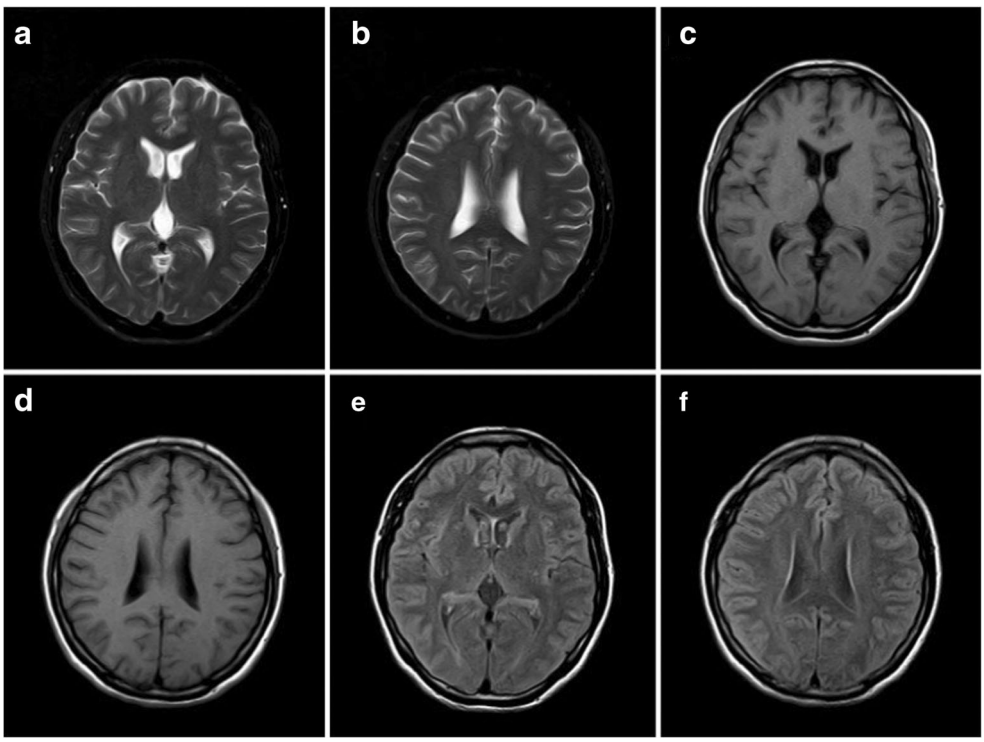

Fig. 3 Brain MRI of the proband's mother, which was normal

sequence of *CSF1R* gene (NCBI Reference Sequence: NG_012303.1). The disease-causing mutation was predicted by Mutation Taster.

Direct sequence analysis of the PCR-amplified DNA revealed a novel heterozygous mutation in exon 20 of the *CSF1R* gene: c.2645delC (p. P882PfsX70). This mutation is predicted to cause a base C deletion at nucleotide 2645, the deletion causes a frameshift leading to a premature termination codon after 70 amino acids. The mutation causes the change of the part of the tyrosine kinase domain (TKD), thus disrupting the function of CSF1R.

CSF1R is a tyrosine kinase receptor that is highly expressed on cells of the mononuclear phagocyte lineage, including microglia in the CNS. It regulates the proliferation, differentiation and survival of these cells [6]. CSF1R is activated by cytokine colony-stimulating factor-1 (CSF1) and interleukin-34. Mutant CSF1R on the cell surface can bind CSF1, which induces receptor dimerization and results in the autophosphorylation of tyrosine residues in its kinase domain. CSF1R consists of a single-pass transmembrane domain, an extracellular ligand-binding domain and an intracellular TKD, which is involved in downstream signaling [7].

In this case, the novel frameshift mutation is located in the highly evolutionarily conserved TKD (exons 12 to 22), where all HDLS-related mutations to date have been identified [3]. The patient exhibited typical symptoms of HDLS, such as cognitive and memory decline, dysarthria, seizures, and spastic quadriplegia. He experienced rapid disease progression. In addition, the brain MRI indicated obvious demyelinating lesions of the cerebral white matter, consistent with HDLS. Therefore, this novel mutation is most likely pathogenic.

The severity of the pathogenic effects of this mutation can be different due to variable penetrance, which may explain why the mother, as a carrier, does not have the disease. This phenomenon indicates a dominant mode of transmission with intrafamilial phenotypic variability or incomplete penetrance. Karle et al. previously reported one family in which incomplete penetrance could be observed: the index patient was severely affected since the age of 28 whereas his father carrying the same *CSF1R* mutation (c.2629C.T, p.Q877X) was still unaffected at age 69. It cannot be excluded that the unaffected individuals will develop symptoms at an older age considering that the latest reported disease onset is at age 78. These findings provided the evidences of incomplete penetrance in HDLS [8].

Early genetic diagnoses in affected individuals will help guide early diagnosis and appropriate treatment of this disease to determine the genetic risk of other family members and to provide reproductive counseling. Further studies will be necessary to better understand the pathophysiological role of *CSF1R* mutations and the detailed molecular mechanism that leads to HDLS.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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