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A novel *CSF1R* missense mutation in a Chinese family with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia: A case report

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Abstract

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare autosomal dominant disorder caused by mutations in the colony-stimulating factor 1 receptor (*CSF1R*) gene. We report a case of a 41-year-old man with rapid decline in cognition within 7 months of onset. Magnetic resonance imaging showed periventricular confluent white matter changes and atrophy of the corpus callosum. Clinical exome sequencing showed a mutation (c.2390T>G) in exon 18 of the *CSF1R* gene. In conclusion, the differential diagnosis of adult-onset leukodystrophy is extensive. Neuroimaging and genetic analysis greatly aid in the differential diagnosis of leukoencephalopathy.

Keywords: Leukoencephalopathy, genetic diseases, cognitive impairment, *CSF1R,* mutation

INTRODUCTION

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is an adult onset leukodystrophy, causally related to mutations in the *CSF1R* gene. As of October 2021, a total of 114 mutation sites has been reported globally.[1] The disease onset typically occurs in the fourth or fifth decade and is followed within a few years by a progressive cognitive decline, motor impairment and other clinical presentations, such as sensory disturbance and epilepsy.[2] Here we present a Chinese family harboring a rare, novel, heterozygous, missense mutation (c.2390T>G) in exon 18 of the *CSF1R* gene by whole exome sequencing (WES).

CASE REPORT

The proband, a 41-year-old Chinese man who was referred to our hospital with a 7-month history of progressive memory loss and personality changes. He has completed high school education. His symptoms started in the form of memory disturbances, forgetting what he had for supper and important occasions like his son's birthday. By next 5 months, the patient had impaired attention and was unable to manage his work. For the last 3 months, he became withdrawn and were unwilling to pursue his hobbies. There were no other complaints at the time. On the neurological examination, he had a significant memory impairment and decreased attention with a mini-mental state examination (MMSE) score of 19/30 and a Montreal cognitive assessment scale (MoCA) score of 17/30. He scored 17/(7-51) in the Hamilton Depression (HAMD) scale which showed mild depression. Cranial nerve examination, motor, sensory examination were normal. Further investigation with laboratory studies of serum electrolytes, cell blood count, hepatic function were normal. Syphilis serology and HIV tests were negative. Cerebrospinal fluid analyses of antibodies specific for demyelinating diseases of the central nervous system and autoimmune encephalitis were absent. Brain T2 fluid-attenuated inversion recovery (Flair) and diffusion-weighted imaging (DWI) MRI showed multiple, patchy and hyperintense lesions in the periventricular areas, corpus callosum, and deep white matter regions of the frontal and parietal lobes. DWI images showed a persistent hyperintensities over 4 months (Figure 1).

The patient's DNA was extracted from peripheral blood for genetic analysis. A heterozygous missense variant NM 005211:c.2390T>G in the *CSF1R* gene was identified, confirming a diagnosis of ALSP (Figure 2). This mutation was not reported previously and has not been indexed in dbSNP, the Human Gene Mutation Database (HGMD) or the ClinVar database. The mutation leads to an amino acid substitution of phenylalanine (F) to cysteine (C) at codon

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position 797 (p.F797C), while phenylalanine at 797 position is highly conserved among vertebrates from Zebrafish to humans. The variant was absent in the general population (gnomAD https://gnomad.broadinstitute.org/). Based on the evaluation score created by Polyphen2(score at 1.00), SIFT (score at 0.00), CADD (score at 29.9) and M-CAP (score at 0.875), c.2390T>G was predicted to have disease-damaging effects. However, the variant did not meet ACMG criteria for pathogenicity and was therefore considered a variant of uncertain significance (one piece of moderate evidence). The patient's elder brother shared the same mutation in *CSF1R*. The pedigree of this ALSP family is shown in Figure 3.

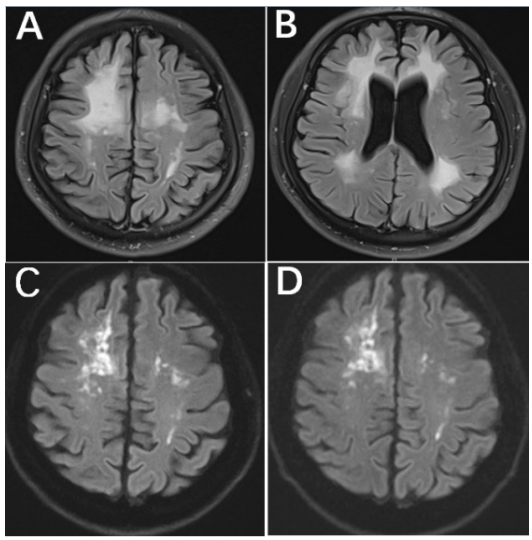

Figure 1. (A). Confluent multiple, patchy white matter lesions in the frontal and parietal lobes on FLAIR. (B). Symmetrical and hyperintense lesions in the periventricular areas on FLAIR. (C). DWI hyperintensities in frontal and parietal lobes in June, 2021. (D). DWI hyperintensitiesin October, 2021.

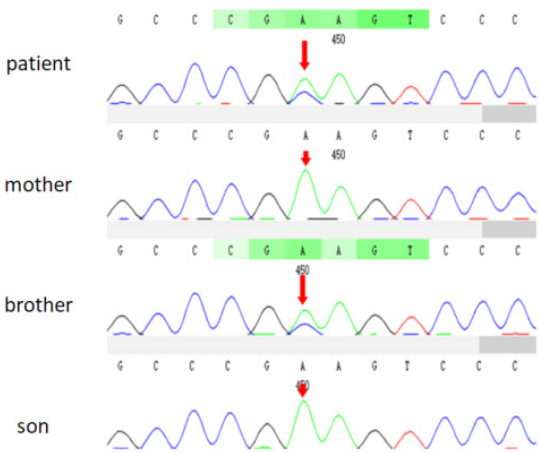

Figure 2. Sanger sequencing confirmed that the patient and his brother harbored c.2390T>G mutation.

DISCUSSION

In this study we report a patient with a novel missense mutation (c.2390T>G) in exon 18 of the *CSF1R* gene. *CSF1R* is mainly expressed in microglia and participates in the development and maintenance of microglia.[2] The *CSF1R* gene includes 22 exons that encode cellular membrane proteins. The normal function of *CSF1R* is essential for proliferation, survival and differentiation of microglia in the central nervous system.[3] Functional studies suggested that the mutations in *CSF1R* affect the tyrosine kinase activity of the protein, most likely altering the phosphorylation of downstream target.[4] This patient was eventually diagnosed with ALSP based on the clinical features and detection of *CSF1R* mutation (c.2390T>G). It is predicted to be pathogenic by Mutation Taster because the mutation site is highly conserved in a wide variety of species. It is classified as a variant of undetermined significance according to the ACMG guidelines.

The average onset age of ALSP is 43 years. Median life expectancy is 6 years. Clinically ALSP often start with neuropsychiatric symptoms, including behavioral changes and cognitive declines, followed by or concurrent with motor and gait disturbances.[5] In this case, age of onset, cognitive decline, personality change are all

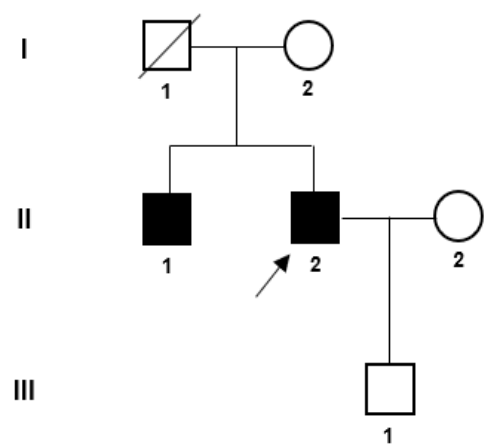

Figure 3. Family pedigree: black squares indicate affected individuals, the arrow indicates the proband.

typical symptoms of ALSP. The gene carriers in the family were found to have different phenotypes. The patient's elder brother shared the same mutation in *CSF1R* but remains clinically asymptomatic currently. The proband's father had died in an accident at the age of 20 years old. Since ALSP is an autosomal dominant disease, we speculate the (c.2390T>G) mutation was inherited from the proband's father. Due to the broad age of onset and various clinical phenotypes, it is uncertain whether patient's brother will develop symptoms with advancing age. Unfortunately, neuroimaging of the patient's brother were unavailable since he had refused to perform brain MRI or CT. We will pay close attention during his brother's clinical follow-up to improve our understanding of the disease.

Typical imaging manifestations of ALSP involved periventricular, deep white matter lesions of the frontoparietal lobe and corpus callosum. Persistent high signal on DWI due to intramyelinic edema is another main feature of ALSP.[6] In our patient, the persistence of hyperintensities on DWI lasted at least 4 months, which are characteristic brain MRI findings of ALSP. In addition, spotty calcification on the brain CT scans has also been suggested as a characteristic finding in patients with ALSP.[3] However, calcification was not shown on the patient's brain CT.

Although there is no cure for patients with ALSP, microglial replacement therapy has become a topical research area. Nowadays hematopoietic stem cell transplantation (HSCT), a type of microglia replacement, was proved to help normalize *CSF1R* protein expression and activate the inhibited *CSF1R* pathways.[7] ALSP patients can achieve disease control 6-30 months after undergoing transplantation.[3] Currently, the patient's family is searching for a suitable unrelated hematopoietic stem cell donor. More cases should be included inclinical investigations to prove the effects of HSCT on the heterogeneity of *CSF1R* mutations.

In conclusion, our findings identify a novel missense mutation, c.2390T>G, in exon 18 of the *CSF1R* gene within a Chinese family with ALSP and broaden the genetic spectrum of *CSF1R*-associated ALSP. Further research will be necessary to confirm genotype-phenotype correlations in ALSP.

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DISCLOSURE

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Conflicts of interest: None

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