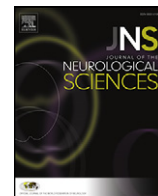




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Short communication

A novel A781V mutation in the CSF1R gene causes hereditary diffuse leucoencephalopathy with axonal spheroids<sup>☆</sup>Rebekah Ahmed<sup>a</sup>, Rita Guerreiro<sup>b</sup>, Jonathan D. Rohrer<sup>a</sup>, Gamze Guven<sup>c</sup>, Martin N. Rossor<sup>a</sup>, John Hardy<sup>a</sup>, Nick C. Fox<sup>a,\*</sup><sup>a</sup> Dementia Research Centre, Department of Neurodegenerative Disease, University College London, Institute of Neurology, Queen Square, London WC1N 3BG, UK<sup>b</sup> Reta Lila Weston Institute and Department of Molecular Neuroscience, UCL, Institute of Neurology, Queen Square, London, UK<sup>c</sup> Institute for Experimental Medicine, Genetics Department, Istanbul University, Istanbul, Turkey

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## ABSTRACT

We report a family with a novel CSF1R mutation causing hereditary diffuse leucoencephalopathy with axonal spheroids. Family members presented with neuropsychiatric and behavioural symptoms, with subsequent development of motor symptoms and gait disturbance. MRI brain showed extensive white matter change with a frontal predominance and associated atrophy in two members of the family. Genetic testing revealed a novel mutation c.2342C > T (p.A781V) in the CSF1R gene in two brothers of the family. This report highlights the difficulties in diagnosing HDLS and discusses the indications for testing for mutations in the CSF1R gene.

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## 1. Introduction

Mutations in the colony stimulating factor 1 receptor gene (CSF1R) have recently been shown to cause hereditary diffuse leucoencephalopathy with axonal spheroids (HDLS) [1]. Typically, patients present with personality change and neuropsychiatric symptoms, followed by cognitive decline and motor impairment particularly affecting gait [2]. There is phenotypic heterogeneity and patients have been diagnosed in life with a variety of different neurological diagnoses including Alzheimer's disease, frontotemporal dementia, atypical parkinsonism, multiple sclerosis and small vessel cerebrovascular disease. [1,2] We report a novel mutation in the CSF1R gene in a family with an autosomal dominant dementia with prominent behavioural cognitive symptoms.

## 2. Case report

DRC155 is a family from the UK with an autosomal dominant history of dementia (Fig. 1 – family tree). Five of seven siblings were

affected. Both parents were said to be cognitively normal prior to their deaths at age 61 years and 71 years, however their young age of death may have concealed a diagnosis of dementia.

## 2.1. Sibling 1.5

This gentleman presented at the age of 54-years-old with a six year history of depression and anxiety. He had been working as a piano maker and over the previous few years had increasing difficulties with his work. Over a similar time period his mobility had become worse and he felt slow and unsteady whilst walking. More recently he developed problems with episodic memory over the previous year and difficulty speaking over the last six months. His wife felt that there had been a recent change in his personality with apathy, irritability and socially inappropriate behaviour. On examination he scored 26/30 on MMSE and was noted to be bradyphrenic. Cranial nerve territory examination was normal but in the limbs he had increased tone throughout with brisk reflexes, although normal power. His gait was broad-based and slow. Neuropsychometry revealed severely impaired executive function with some impairment of verbal recognition memory as well. MRI brain (Fig. 2) showed white matter change and atrophy which was widespread but with a frontal predominance. There was also involvement of the corpus callosum with associated atrophy.

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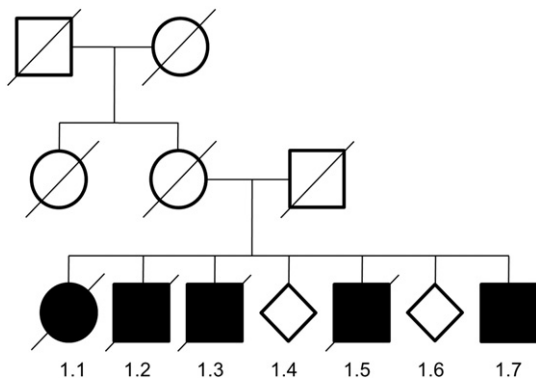


Fig. 1. Family pedigree. Black colour indicates affected by dementia.

### 2.2. Sibling 1.7

This patient the brother of 1.5 was assessed at the age of 67 years with difficulty walking and slowing of movements. Cognitively his family had not noticed any deficits, but on neurophysiological examination he had reduced executive function and problems with visuo-constructional skills, suggesting moderate cognitive impairment affecting the anterior regions. On neurological examination he had increased tone throughout and clonus affecting the left ankle, power and reflexes were normal. On gait examination he was felt to be slowed and dragging his left foot. MRI of the brain showed global atrophy and enlarged ventricles with extensive white matter change affecting the parietal and frontal lobes, there was thinning of the corpus callosum more marked posteriorly.

### 2.3. Sibling 1.3

The brother of 1.5 had been assessed at the age of 58 with a 2 year history of behavioural change which was predominantly apathy with self-neglect. He also had a gait disorder which started around the same time as the behavioural change. On examination he was noted to be bradyphrenic; cranial nerve examination was normal. He had

increased tone throughout the limbs, but normal power and reflexes. His gait was broad based and slow. CT imaging was reported as showing generalised cerebral atrophy of central and cortical grey matter, with widespread white matter low density, both in the white matter and around the bodies of the lateral ventricles. An FDG-PET scan showed a reduction in cerebral glucose uptake, with an anterior–posterior gradient with hypometabolism more marked in the frontal lobes. He was given a provisional diagnosis of a frontal lobe dementing illness.

### 2.4. Sibling 1.2

Another brother had been diagnosed with a young onset dementia, most likely Alzheimer's disease, although no other information was available. He had an age of onset of 32-years-old and had died four years later at the age of 36.

### 2.5. Sibling 1.1

The eldest of the siblings also had a young onset dementia and was given a diagnosis of Alzheimer's disease and had died at age 60. No further information was available.

## 3. Genetic analysis

A blood sample was available from patients 1.5 and 1.7 for genetic analysis. ExonPrimer was used to generate primers for amplification of *CSF1R* exons 1 to 22 plus exon–intron boundaries (primer sequences available on request). These exons were PCR amplified using Roche FastStart PCR Master Mix polymerase (Roche Diagnostics Corp., IN) or Roche FastStart PCR Master Mix polymerase plus Dimethyl sulfoxide (DMSO) (Qiagen, CA, USA), 15 ng of genomic DNA and the respective forward and reverse primers. The PCR amplification products were cleaned and approximately 15 ng of each PCR product was used as template per sequencing reaction containing 5× Reaction Buffer, BigDye® (Applied Biosystems) and the forward or reverse primer that was used for amplification of the original product. Sequencing reactions were cleaned and sequencing was performed on an ABI 3730 DNA

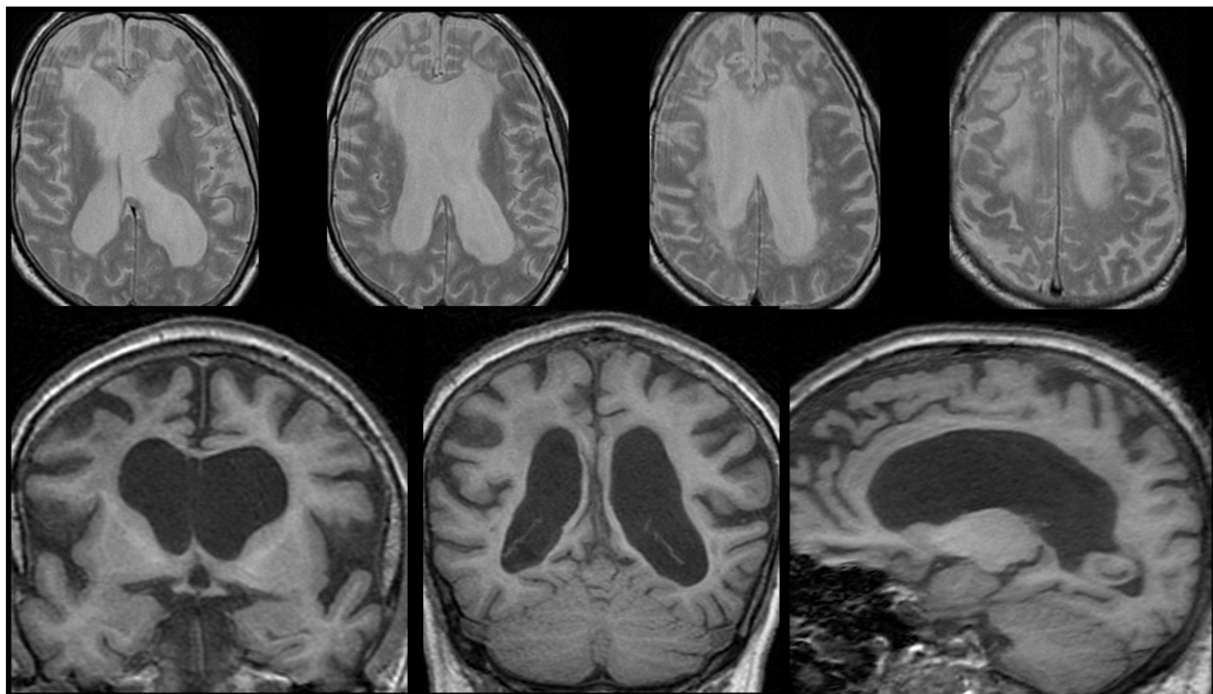


Fig. 2. MR imaging of 1.5 showing widespread white matter change with a frontal predominance. There is associated atrophy and thinning of the corpus callosum.



## Disclosure

The authors report no conflicts of interest or competing interests.

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