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Short communication

A novel A781V mutation in the CSF1R gene causes hereditary diffuse leucoencephalopathy with axonal spheroids ☆

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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.

1. Introduction

Mutations in the colony stimulating factor 1 receptor gene (*CSF1R*) have recently been shown to cause hereditary diffuse leukoencephalopathy 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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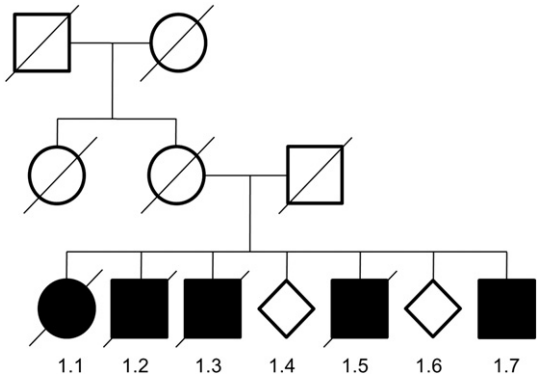

Fig. 1. Family pedigree. Black colour indicates affected by dementia.

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

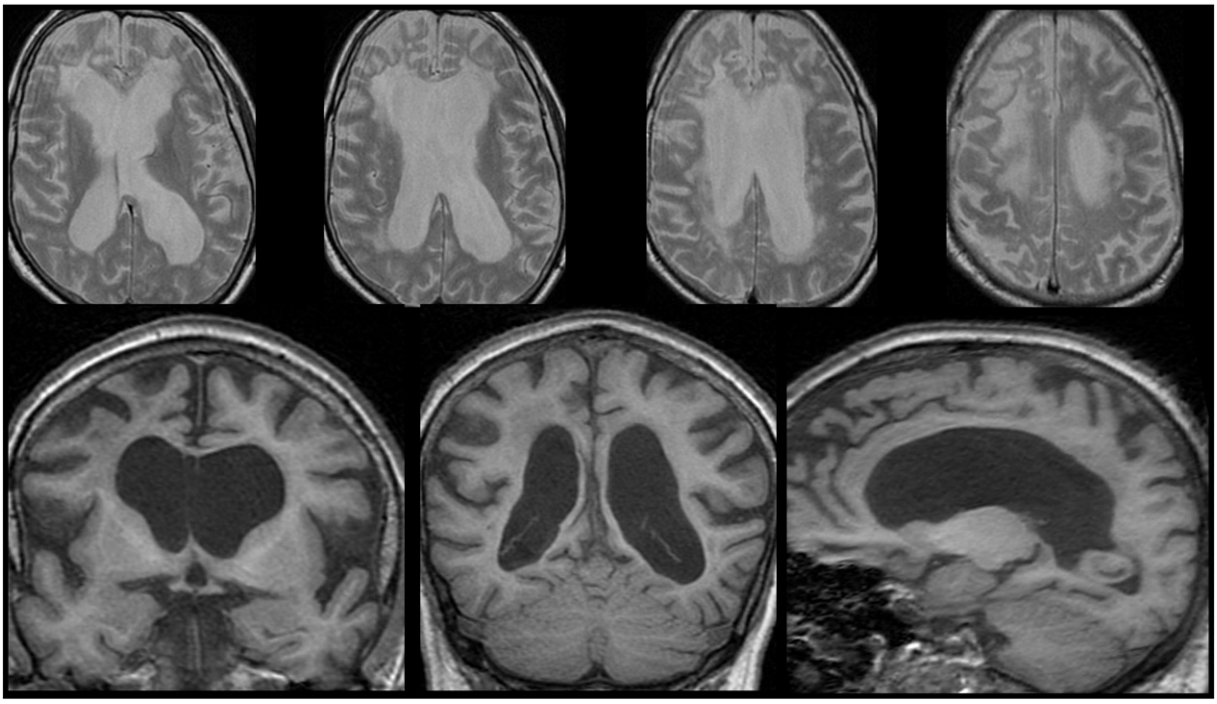

Fig. 2. MR imaging of 1.5 showing widespread white matter change with a frontal predominance. There is associated atrophy and thinning of the corpus callosum.

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Analyzer (Applied Biosystems). Sequence traces were analyzed using Sequencher (version 4.2 Gene Codes Corporation) and variants were named based on sequences with accession numbers NM_005211.3 and NP_005202.2. A novel c.2342C > T (p.A781V) mutation was found in exon 18. In silico analysis of pathogenicity using PROVEAN (Protein Variation Effect Analyzer) v.1.1 [3] and PolyPhen-2 (Polymorphism Phenotyping v2) [4] tools predicted *CSF1R* p.A781V mutation to be pathogenic (PROVEAN: deleterious with score of −3.332 and PolyPhen: probably damaging with a score of 1.0).

4. Discussion

28 different mutations have now been described in the *CSF1R* gene causing an autosomal dominant disorder with neuropsychiatric and behavioural symptoms followed by cognitive and motor impairment [1,2,5–9]. The family that we report is consistent with previous descriptions with a predominantly behavioural syndrome at presentation. Imaging features in patients with *CSF1R* gene mutations are usually T2 hyperintense foci in the periventricular deep and subcortical frontal and bifrontal cerebral white matter that may be asymmetric, with involvement of the corpus callosum and corticospinal tracts [10]. This is similar to what was found in the three members of the reported family that were scanned at our institution, including atrophy that was predominantly frontal and in the corpus callosum.

Although complete segregation analysis was not possible, as DNA was available for only two affected siblings, several facts lead us to conclude that this mutation is most likely pathogenic: 1) it has not been reported in the large-scale genome and exome sequencing databases (dbSNP132, 1000 Genomes Project, March 2012 release and the NHLBI Exome Sequencing Project); 2) it is predicted by different prediction tools (PROVEAN and PolyPhen-2) to be damaging to the protein; and 3) the residue mutated is highly conserved between species (see Fig. 3) and it is located in the tyrosine kinase domain of the CSF1R gene, where all pathogenic mutations previously identified have been described (Fig. 4).

This report highlights the difficulty in diagnosing HDLS antemortem. Prior to genetic testing in the current family two of the siblings were given a diagnosis of Alzheimer's disease and one of frontal lobe degeneration. Testing for the *CSF1R* gene mutation now provides a definitive diagnosis and we recommend testing for this in patients with a typical history, particularly when behavioural and cognitive symptoms are predominant with associated gait problems, and white matter changes that have a frontal predominance and involvement of the corpus callosum.

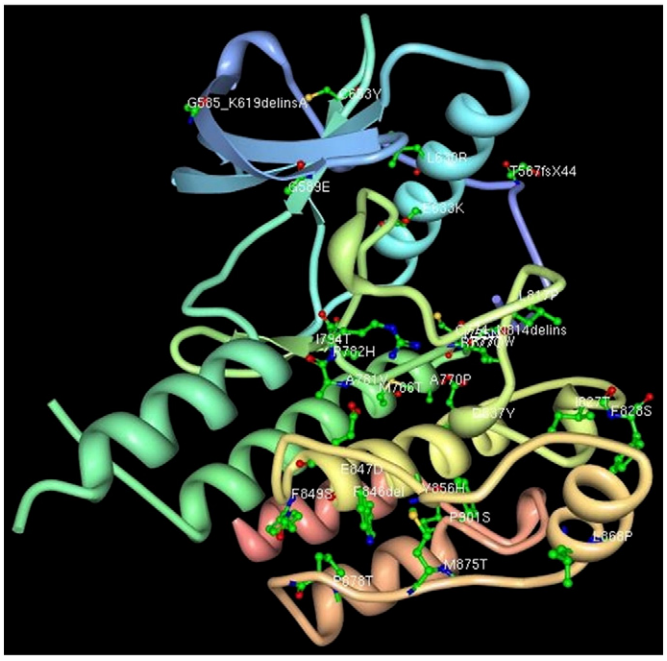

Fig. 4. Distribution of all the mutations described so far in the three-dimensional structure of the tyrosine kinase domain of the CSF1R protein, including the mutation here identified (p.A781V). Protein representation made using the Protein Workshop [11].

Author contribution

Rebekah Ahmed, Jonathan Rohrer, Martin Rossor, and Nick Fox — patient review and manuscript preparation.

Rita Guerreiro, Gamze Guven, John Hardy: genetic testing, sequencing of mutation, manuscript preparation.

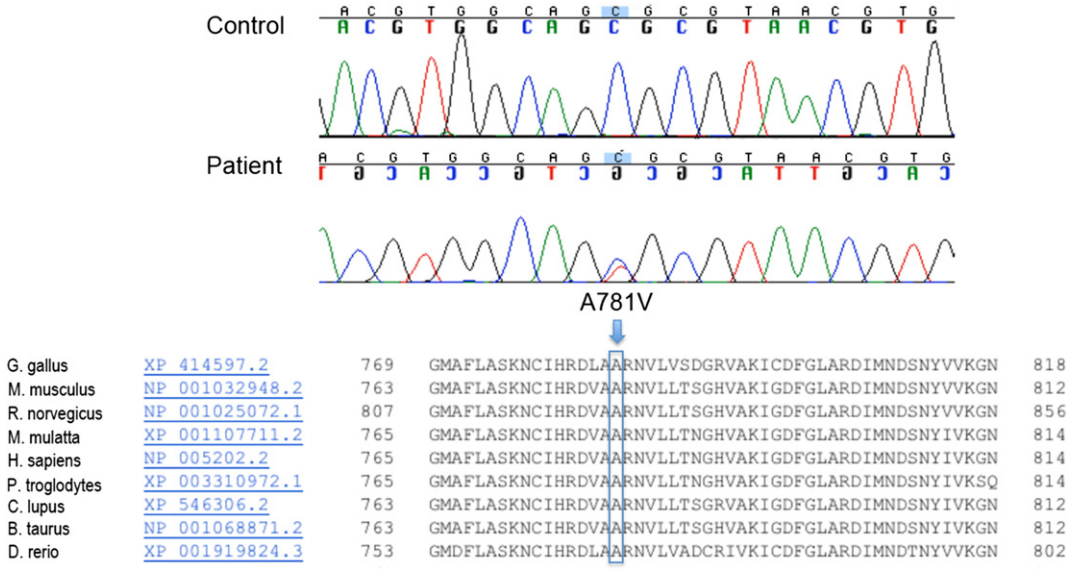

Fig. 3. Molecular analysis of *CSF1R*. A novel heterozygous mutation (c.2342C > T, p.A781V) was found in exon 18 of *CSF1R*. cDNA and protein references used were NM_005211.3 starting at the translation initiation codon and NP_005202.2, respectively. Protein sequence alignment around the mutation site (A781) is shown for different CSF1R orthologues: this residue of the CSF1R protein is highly conserved between species.

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Disclosure

The authors report no conflicts of interest or competing interests.

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References

[1] Rademakers R, Baker M, Nicholson AM, Rutherford NJ, Finch N, Soto-Ortolaza A, et al. Mutations in the colony stimulating factor 1 receptor (CSF1R) gene cause hereditary diffuse leukoencephalopathy with spheroids. Nat Genet 2012;44:200–5.

[2] Sundal C, Lash J, Aasly J, Øygarden S, Roeber S, Kretzschman H, et al. Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS): a misdiagnosed disease entity. J Neurol Sci 2012;314:130–7.

[3] Choi Y, Sims GE, Murphy S, Miller JR, Chan AP. Predicting the functional effect of amino acid substitutions and indels. PLoS One 2012;7:e46688.

[4] Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. Nat Methods 2010;7:248–9.

[5] Sundal C, Wszolek Z. CSF1R related hereditary diffuse leukoencephalopathy with spheroids. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [2012 Aug 30].

[6] Kinoshita M, Yoshida K, Oyanagi K, Hashimoto T, Ikeda S. Hereditary diffuse leukoencephalopathy with axonal spheroids caused by R782H mutation in CSF1R: case report. J Neurol Sci 2012;318:115–8.

[7] Mitsui J, Matsukawa T, Ishiura H, Higasa K, Yoshimura J, Saito TL, et al. CSF1R mutations identified in three families with autosomal dominantly inherited leukoencephalopathy. Am J Med Genet B Neuropsychiatr Genet 2012;159B:951–7.

[8] Kleinfeld K, Mobley B, Hedera P, Wegner A, Sriram S, Pawate S. Adult-onset leukoencephalopathy with neuroaxonal spheroids and pigmented glia: report of five cases and a new mutation. J Neurol 2013;260:558–71.

[9] Guerreiro R, Kara E, Le Ber I, Bras J, Rohrer JD, Taipa R, et al. Genetic analysis of inherited leukodystrophies: genotype phenotype correlations in the CSF1R gene. JAMA Neurol May 6 2013:1–9 [Epub ahead of print].

[10] Sundal C, Van Gerpen JA, Nicholson AM. MRI characteristics and scoring in HDLS due to CSF1R gene mutations. Neurology 2012;79:566–74.

[11] Moreland JL, Gramada A, Buzko OV, Zhang Q. Bourne PE.“ The molecular biology toolkit (MBT): a modular platform for developing molecular visualization applications”. BMC Bioinformatics 2005;6:21.

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