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Citation	eNeurologicalSci (2015), 1(1): 7-9
Issue Date	2015-03
URL	http://hdl.handle.net/2433/203174
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Type	Journal Article
Textversion	publisher



A novel A792D mutation in the *CSF1R* gene causes hereditary diffuse leukoencephalopathy with axonal spheroids characterized by slow progression



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ARTICLE INFO

Article history:

Received 22 July 2015

Accepted 22 July 2015

Available online 13 August 2015

Keywords:

Hereditary diffuse leukoencephalopathy with spheroids

HDLS

CSF1R

White matter disease

Autosomal dominant

Adult-onset cognitive impairment

A792D

ABSTRACT

Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is an autosomal dominant white matter disease that causes adult-onset cognitive impairment. The clinical manifestations are a variable combination of personality and behavioral changes, cognitive decline, parkinsonism, spasticity, and epilepsy. In 2012, mutations in the gene encoding colony stimulating factor 1 receptor (*CSF1R*) were identified as the cause of HDLS. As the numbers of reported mutations are limited, the understanding of whole pathogenesis needs accumulation of disease-causing mutations with detailed clinical descriptions. We describe a Japanese family with autosomal dominant adult-onset cognitive impairment and characteristic white matter lesions. Genetic testing revealed a novel p.A792D mutation in the tyrosine kinase domain of *CSF1R* in two affected family members. The symptom profile of the present cases mostly matched the previously reported cases, with the notable exceptions of late-onset and long disease duration.

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1. Introduction

Hereditary diffuse leukoencephalopathy with spheroids (HDLS) was first described by Axelsson et al. in 1984 [1]. It is an autosomal dominant white matter disease with high penetrance that causes adult-onset cognitive impairment. The clinical manifestations are a variable combination of personality and behavioral changes, cognitive decline, depression, parkinsonism, spasticity, and epilepsy. Cognitive decline and parkinsonism are particularly common symptoms. The histopathological hallmarks of HDLS are widespread leukoencephalopathy with numerous neuroaxonal spheroids in the affected white matter, accumulation of pigmented microglia, and gliosis. Pigmented microglia poorly express *CSF1R* and are distributed diffusely throughout the white matter in the early disease stage, preceding axonal degeneration and myelin loss [2].

In 2012, mutations in the gene encoding colony stimulating factor 1 receptor (*CSF1R*) were identified as the cause of HDLS [3]. Then, *CSF1R* mutations linked two previously separate disease entities, HDLS and pigmented orthochromatic leukodystrophy, as a single disease [4]. The *CSF1R* mutations disturb autophosphorylation of tyrosine residues in the cytoplasmic tyrosine kinase domain of *CSF1R* and result in the

partial loss of its function, which is important for microglial proliferation and differentiation in the brain [5]. Recently, it was suggested that haploinsufficiency of *CSF1R* is sufficient to cause HDLS [6].

Several features on computed tomography (CT) or magnetic resonance imaging (MRI) have been described in cases of genetically confirmed HDLS [7–9]. Subcortical calcifications on CT and restricted diffusion on MRI have been reported as relatively specific findings [6, 9]. These characteristic findings of neuroimaging in addition to clinical features help to distinguish HDLS from other white matter diseases.

We describe a Japanese family with autosomal dominant early-onset dementia. Genetic testing revealed a novel p.A792D mutation in *CSF1R*. The proband and other affected members initially exhibited personality changes and executive dysfunction, which are characteristic for HDLS, but the disease tended to be late-onset with a disease course of long duration [2].

2. Case report

A 43-year-old man presented with a two-year history of cognitive decline. He had a family history compatible with autosomal-dominant early-onset dementia (Fig. 1). He had stopped participating in his favorite sport and had become apathetic two years ago. He was an office worker but had made mistakes in calculations and could not arrange long-term plans. His colleagues did not notice personality changes, but

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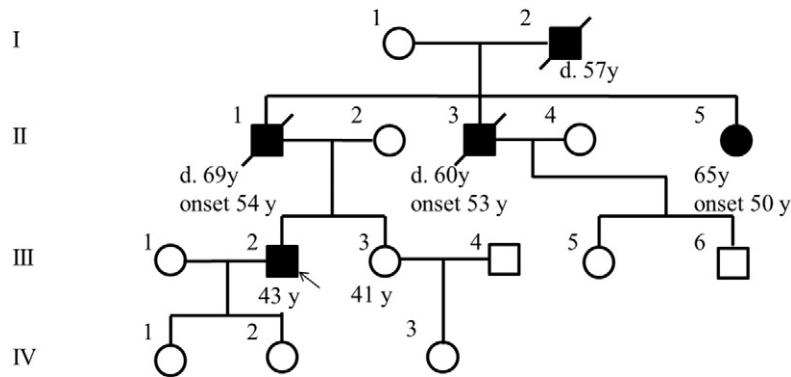


Fig. 1. Family pedigree. Filled symbols indicate individuals affected by cognitive decline. An arrow indicates the proband. The age of onset in patient I-2 is unknown.

he became irritable with his family and sometimes spoke too loudly. He was unaware of the problems. On neurological examination, he was polite, and his appearance was clean. His Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) scores were 28/30 and 10/18, respectively; difficulties in orientation to time, digit span, and word fluency were detected by these tests. Although aphasia, agnosia, or apraxia was not detected, difficulty with abstract thinking was observed to some extent. Visuospatial impairment was not apparent, and the patient was able to copy the Rey–Osterrieth Complex Figure; however, each part of the figure was inefficiently copied. The patient showed few motor symptoms. Dysarthria, dysphasia, weakness, spasticity, rigidity, bradykinesia, gait disturbance, or involuntary movement was not observed. Brain MRI revealed hyperintensity in the frontal-lobe-dominant deep white matter and corpus callosum by FLAIR and also marked atrophy (Fig. 2a). The white matter lesion partially showed spotty diffusional limitation. The parietal and occipital lobes were relatively preserved. Brain CT revealed refined calcifications in the basal ganglia and deep white matter, especially along the bilateral frontal horns of the lateral ventricle (Fig. 2b). ^{18}F -fluorodeoxyglucose positron emission tomography (FDG–PET) revealed hypometabolism throughout the entire cerebral cortex, except for the motor area (Fig. 2c).

The father of the proband (II.1) presented literal paraphasia (towel to scissor) as the first symptom in his fifties. He voluntarily went to hospital and diagnosed as Pick disease at the age of 54. He had become apathic, had difficulty to work. His family were suffering from his wandering after 8 years. At the age of 65, he had difficulty in going to a toilet and in eating, and died at the age of 69. The patient of II.4 presented cognitive decline at the age of 53. He had become irritable, annoyed his family with wandering about and died at the age of 60. The patient of II.5 presented behavioral change around fifties, when she drove in the opposite direction of an expressway. She has become bedridden and hospitalized in a care hospital. The clinical course of patients I.2 is unknown, because all his children were affected. Unfortunately, neuroimaging date of them has been lost.

3. Gene analysis

Because the patient had a family history of adult-onset cognitive impairment suggestive of autosomal dominant inheritance and the characteristic brain MRI for HDLS, we sequenced the *CSF1R* gene by using the Sanger method. Genomic DNA was extracted from peripheral blood leukocytes after informed consent and approval by IRB for research ethics. The genetic analysis demonstrated a novel heterozygous c.2375C>A, p.Ala792Asp mutation in exon 18 of *CSF1R*. The substituted amino acid is located within the tyrosine kinase domain of *CSF1R*. Protein sequence alignment was performed with ClustalW, demonstrating that the amino acid is conserved through the process of evolution in vertebrates except for *Xenopus tropicalis*. The same mutation was also revealed in the aunt of the proband, the only other patient from whom DNA was available in this family at the time of the study (Fig. 3). The

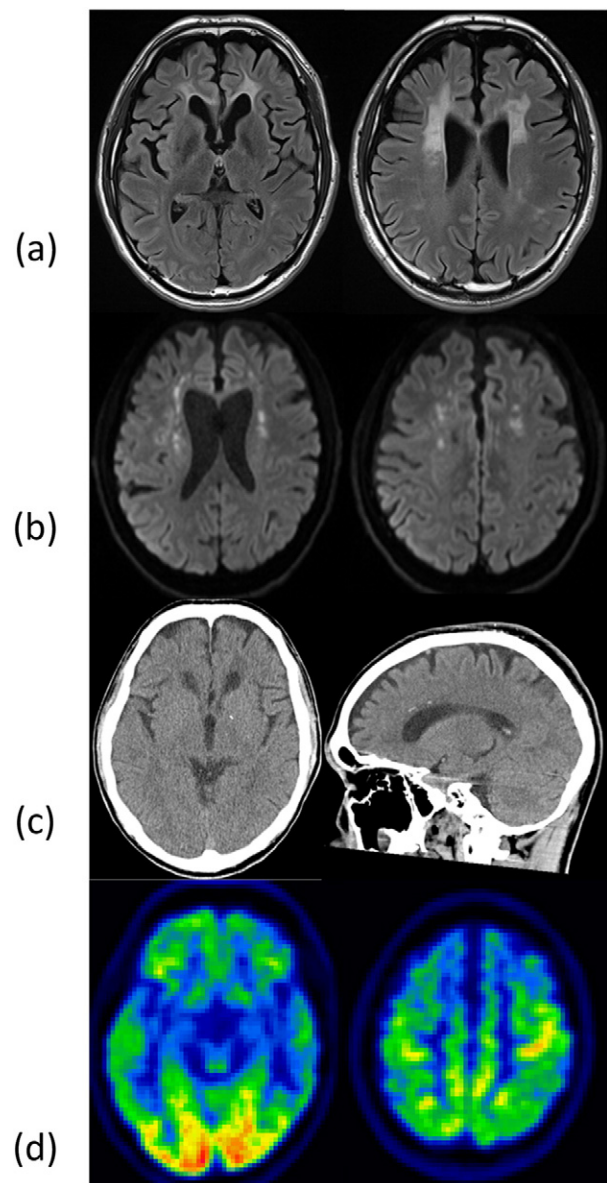


Fig. 2. Neuroimaging studies of the patient (III-2). (a) Brain MRI of the patient at the age of 43 years old (two years after onset) showed hyperintensity in the frontal-lobe-dominant deep white matter and corpus callosum by FLAIR and also showed marked atrophy. Diffusion weighted imaging showed hyperintensity in the basal ganglia and deep white matter of the frontal lobe. (b) Brain CT of 43 years old showed refined calcifications in the basal ganglia and deep white matter. (c) FDG–PET of 43 years old showed hypometabolism throughout the whole cerebral cortex, except for the motor area.

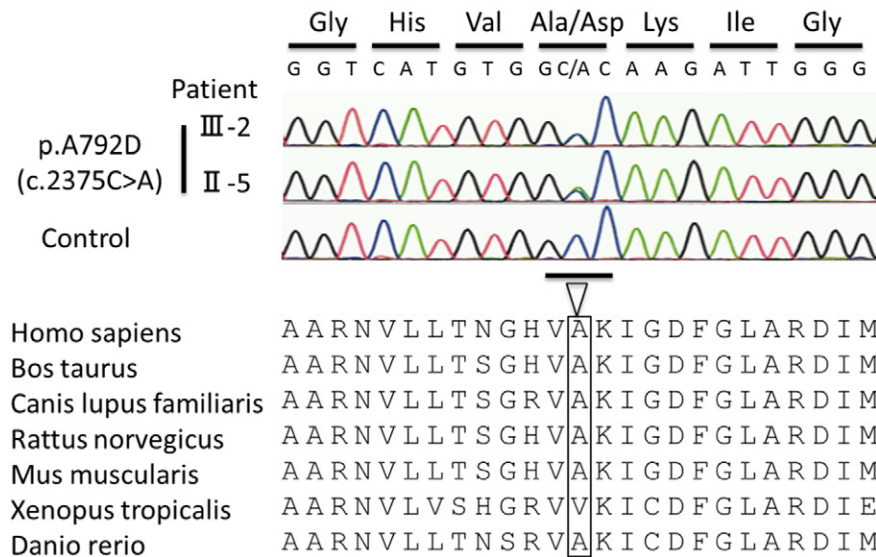


Fig. 3. Gene analysis of *CSF1R*. A heterozygous *c.2375C>A* (p.A792D) mutation in exon 18 of *CSF1R* was identified in two affected patients (III-2 and II-5) in the pedigree. Protein sequence alignment demonstrated that the substituted amino acid is conserved in vertebrates except for *Xenopus tropicalis*.

two unaffected members (the cousins of II-5) did not carry this mutation. This mutation was not registered in dbSNP142, the 1000 Genomes project, or the Human Genetic Variation Browser, which includes genetic variations determined by exome sequencing of 1208 Japanese individuals. The effect of the novel missense mutation was evaluated by *in silico* analysis. Polyphen-2 analysis with the HumVar-trained model showed that the A792D substitution was probably damaging to the protein structure. In Mutation Taster, A792D was predicted to be a disease-causing mutation (probability >0.999).

4. Discussion

We identified a novel missense mutation in the *CSF1R* gene in a Japanese family with leukoencephalopathy presenting as adult-onset cognitive impairment. The mutation was located within the tyrosine kinase domain, which is the location of all pathological mutations. The two affected members in the family for which DNA was available carried the mutation, and the mutation had not been reported in the large-scale genome and exome sequencing databases. *In silico* analyses of pathogenicity predicted that this mutation would be pathogenic. Although complete segregation analysis was not performed, these facts strongly suggest that the mutation causes HDLS.

We showed the clinical features of the proband (III-2) and the pedigree. The proband exhibited cognitive impairment with apathy, executive dysfunction, and mild personality changes as the first and only symptoms; there were few pyramidal or extrapyramidal signs. Consistent with these symptoms, the white matter involvement was mainly in the anterior part of the frontal lobe with less involvement in the parietal lobe. The calcification observed in the basal ganglia and deep white matter of the frontal lobe is characteristic of HDLS and a useful sign for differentiating HDLS from numerous leukoencephalopathies. As the calcification of HDLS is refined, thin-slice CT is needed for detection. The pathogenic significance of the calcification remains unknown.

In this family, the age at disease onset ranged from 43 to 54 years old with a disease duration of 6 to 29 years. The initial symptom was cognitive impairment in all of the cases. Konno et al. presented a review of 73 reported cases of HDLS from 54 kindreds [10]. Mean age at onset was 45 years old (range, 18–78 years), and mean duration was 6 years

(range, 2–29 years). Cognitive impairment was the most common initial symptom shown in 64.3% (36 out of 56) of cases. So far, it has not been revealed how the type of mutation influences the clinical phenotype, while it has been suggested that haploinsufficiency of *CSF1R* is sufficient to cause HDLS. The symptom profile of the present cases mostly matched the cases in the review, but interestingly tended to be late-onset (51 years old on average) with long disease duration (>12 years on average). Further accumulation of HDLS cases might reveal the phenotype–genotype correlations.

Conflicts of interest

The authors declare no conflict of interests.

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