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Clinical and molecular genetic assessment of a chorea-acanthocytosis pedigree

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Abstract

Background: Chorea-acanthocytosis (ChAc) is an autosomal recessive hereditary disease characterized by neurodegeneration in the striatum and acanthocytosis that is caused by mutations in the *VPS13A* gene. There are only few reports that studied clinical status of the obligate carriers of ChAc. Clinical courses with follow-up neuroradiological and neuropsychological evaluations in individuals with ChAc have been rarely reported.
Methods: We followed an index patient with ChAc and evaluated the clinical features of the pedigree members. Genetic analyses of *VPS13A* and genes responsible for other neuroacanthocytotic and neurodegenerative diseases were performed.
Conclusions: The index patient was homozygous for a 3889C>T nonsense mutation in the *VPS13A* gene and presented with a typical ChAc phenotype. Neuropsychological evaluation with brain imaging in the patient over 3 years revealed atrophy and a decrease in blood flow at the basal ganglia and frontal lobe, and impairment in cognitive function reflecting frontal lobe dysfunction in progressive manners. Four out of five heterozygous mutation carriers in the pedigree showed signs or symptoms potentially attributable to a heterozygous *VPS13A* mutation.

Keywords: Chorea-acanthocytosis; *VPS13A* gene (ChAc); Signs or symptoms potentially attributable to a heterozygous *VPS13A* mutation; Heterozygous mutation carriers; Frontosubcortical dementia; Neurodegeneration

1. Introduction

Chorea-acanthocytosis (ChAc) is a rare hereditary neurodegenerative disease characterized by adult-onset progressive involuntary choreic movements and erythrocyte acanthocytosis. The main neuropathological feature of ChAc is degeneration of the striatum [1]. Other clinical symptoms, including psychiatric features, epilepsy, peripheral neuropathy, myopathy, and oral self-mutilation, are often found. Several prior case studies on ChAc have reported neuroimaging results, clinical neuropsychiatric symptoms, and neuropathological findings at autopsy [1,2], but no study has followed the clinical course with neuroradiological and neuropsychological evaluations for more than 1 year. Serial neuroradiological and neuropsychological studies of a patient with ChAc who was homozygous for mutations of the causative gene are shown in the present report.

VPS13A, the gene responsible for ChAc, is located on chromosome 9q21 [3] [4]. Although the inheritance of ChAc has been recognized as autosomal recessive, single heterozygous *VPS13A* mutations have been occasionally found in patients with ChAc. Dobson-Stone et al. reported 57 different *VPS13A* mutations in 43 patients with ChAc and 7 of the 43 patients possessed only a single heterozygous

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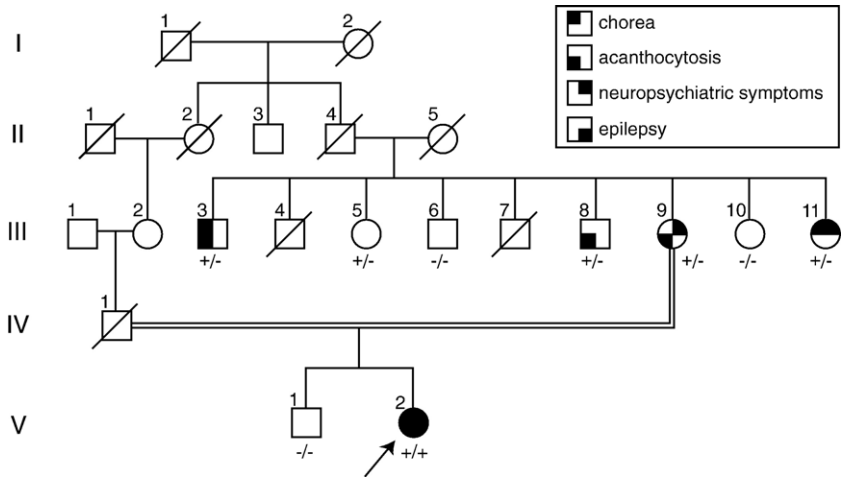

Fig. 1. Pedigree of a Japanese family. An arrow indicates the proband. Blackened symbols indicate individuals with symptoms of ChAc; blackened symbols at the upper left, lower left, upper right, and lower right indicate chorea, acanthocytosis, neuropsychiatric symptoms, and epilepsy, respectively. The combinations of plus and minus signs indicate the genotypes of *VPS13A* mutations; a plus sign (+) indicates the mutant allele of *VPS13A* point mutation, 3889C>T (Arg1297Ter), and a minus sign (−) indicates the normal *VPS13A* allele.

VPS13A mutation [5]. Heterogeneous phenotypes in terms of age of onset and symptoms were observed among patients with the same mutations [2].

We herein describe the clinical findings from a Japanese family harboring a 3889C>T (Arg1297Ter) nonsense mutation in the *VPS13A* gene and the genetic analyses of this pedigree, in which some of the family members with a heterozygous mutation showed signs and symptoms potentially attributable to a heterozygous *VPS13A* mutation. Then, we analyzed the polymorphism in the genes responsible for neurodegenerative choreiform diseases such as Huntington's disease, Huntington disease-like 2, McLeod syndrome, spinocerebellar ataxia 17, and ChAc.

2. Materials and methods

2.1. Patients and family members

We investigated a large family originating from Kagoshima Prefecture, Japan (Fig. 1). Nine family members including the proband with ChAc caused by a homozygous mutation in the *VPS13A* gene (V-2), heterozygous carriers of the mutation (III-3, -5, -8, -9, and -11), and noncarriers (III-6, -10, and V-1) were examined in the present study.

2.2. Genetic analysis

All patients and family members were referred by their primary psychiatrist or neurologist and provided written informed consent. The research protocol and consent form were approved by the Institutional Review Board of Kagoshima University. Genomic DNA (gDNA) was extracted from the leukocytes by standard methods and total RNA was extracted with a QIAamp® RNA blood mini kit (Qiagen, Hilden, Germany). Complementary DNA (cDNA) was prepared by reverse transcription of messenger RNA (mRNA) using BD PowerScript™ Reverse Transcriptase (BD Biosciences Clontech, Palo Alto, CA, USA) and random hexamers.

2.3. Mutation analysis

Mutations in *VPS13A* were detected in cDNA and gDNA corresponding to regions encoding transcripts A and B using an ABI PRISM 3100 Avant Genetic Analyzer (Applied Biosystems, Foster, CA, USA) [3,4]. All translated regions in *XK* were analyzed from gDNA by cycle sequencing analysis [6–8].

2.4. Genotyping using polymerase chain reaction for triplet repeats — polymorphisms or expansion

Genotyping of triplet repeats was performed using fluorescent dye-labeled primer sets. Polymerase chain reaction (PCR) products were run on an ABI 3100 Avant Genetic Analyzer and analyzed using the fragment analysis software GeneMapper version 3.7 (Applied Biosystems). The following primers were used for identification of the triplet repeats in *HD*: 5'-CCTTCGAGTCCCTCAAGTCCTTC-3' and 5'-GGCTGAGGAAGCTGAGGAG-3' (for detecting CAG triplets), 5'-AGCAGCAGCAGCAACAGCC-3' and 5'-GGCTGAGGAAGCTGAGGAG-3' (for detecting CTG triplets) [9–11]. Those for *JPH3* were 5'-AGATGCCACCG-CATTCGG-3' and 5'-GGTTCCCTGCACAGAAACCAT-3'. Those for *TBP* were 5'-GACCCCACAGCCTATTCAGA-3' and 5'-TTGACTGCTGAACGGCTGCA-3'. Those for genotyping the *VPS13A* triplet repeat polymorphism were 5'-TACAGGGAGTGGATTATGA-3' and 5'-AATACAAT-TATTTTGCTTTATGA-3'.

2.5. Clinical assessment

Neuropsychiatric signs and symptoms were assessed by a group of psychiatrists. Psychiatric diagnosis was based on