A Japanese Pedigree of Familial Cerebral Cavernous Malformations — A Case Report —

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ABSTRACT

Familial cerebral cavernous malformations (FCCM) are autosomal-dominant vascular malformations. At present, 3 cerebral cavernous malformation genes (KRIT1/CCM1, MGC4607/CCM2, and PDCD10/CCM3) have been identified. Few genetic analyses of Japanese FCCM have been reported. A Japanese pedigree of 4 patients with FCCM has been reported that includes the genetic analysis of one of the patients. All 4 patients showed multiple lesions in the brain. Surgical removal was performed at our hospital due to enlargement or hemorrhage of the intracranial lesions in a 21-year-old female (Case 1) and a 30-year-old male (Case 2). The histological diagnoses were cavernous malformations. A 62-year-old female (Case 4), the mother of Cases 1, 2, and 3, suffered from intramedullary hemorrhage at T6-7 and surgical removal was performed at another hospital. Only one patient, a 32-year-old female (Case 3), did not show symptoms. The genetic analysis of Case 2 demonstrated heterozygous partial deletions of exons 12-15 of the KRIT1 gene.

Key words: Cerebral cavernous malformation, Familial cerebral cavernous malformation, Genetic analysis, Japanese

Cerebral cavernous malformations (CCM) are congenital vascular anomalies of the central nervous system that show a prevalence of 0.1-0.5% in the general population22). The lesions are characterized by abnormally enlarged capillary cavities without intervening brain parenchyma23). CCM occurs in both a sporadic and an inherited form. The proportion of familial cerebral cavernous malformations (FCCM) has been estimated to be as high as 50% in Hispano-American CCM patients22) and close to 10-40% in Caucasian patients12,22). FCCM are characterized by the presence of multiple lesions and are inherited in an autosomal-dominant fashion11,12,22). While 3 CCM genes have been identified (KRIT1/CCM1, MGC4607/CCM2, PDCD10/CCM3)1,4,13,14,24), few reports have conducted a genetic analysis of Japanese FCCM. In this study, we present a Japanese pedigree of FCCM and report the genetic analysis of 1 patient.

CASE REPORTS

Case 1 (III:5, Fig. 1) : A 21-year-old female with a history of loss of consciousness at 19 years old suffered general convulsion and was admitted to our hospital. Neurological and physical examination revealed no abnormalities, especially in the skin and mucosa. Computed tomography (CT) demonstrated 3 high-density areas in the bilateral frontal and right temporal lobe (Fig. 2A). T2-weighted magnetic resonance imaging (MRI) revealed 3 cores of mixed signal intensity areas with hypointensity rims in the bilateral frontal and right temporal lobe, and T2 star-weighted MRI revealed one small hypointensity area in the right cingulate gyrus (Fig. 2B-C). Bilateral carotid angiography showed no vascular anomalies. The right temporal lesion was removed surgically at 3 months after the first admission. Twenty-one months after the first surgery, two lesions in the bilateral frontal lobe were removed surgically due to their enlargement (Fig. 3A). Six months after the second surgery, she suffered intracerebral hemorrhage from the residual lesion in the right cingulate gyrus (Fig. 3B), and T2 star-weighted MRI revealed a small de novo lesion in the left midbrain (Fig. 3C). Emergency surgery was performed to evacuate a hematoma and the residual lesion in the right

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Case 2 (III:3, Fig. 1): A 30-year-old male with no medical history, the elder brother of Case 1, suffered from loss of consciousness and was admitted to our hospital at 6 years after the first admission of Case 1. Neurological and physical examination revealed no abnormalities, especially in the skin and mucosa. T2-weighted MRI revealed 3 cores of mixed signal intensity areas with hypointensity rims in the right frontal, right parietal and right caudate nucleus (Fig. 4A), and T2 star-weighted MRI revealed 5 small hypointensity areas in the bilateral cerebral hemisphere (Fig. 4B). T2-weighted MRI sagittal views revealed no lesion in the spinal cord. Bilateral carotid angiography showed no vascular anomalies. At 5 months after onset, two lesions in the right frontal and right parietal lobe were removed surgically due to their enlargement (Fig. 4C). The histological diagnoses were cavernous malformations. He was diagnosed with FCCM from his familial history. He was discharged from the hospital with no neurological deficit. We recommended that other family members receive MRI examinations and we obtained informed consent for the genetic analysis from Case 2. We performed the genetic analysis by outsourcing to GeneDX®, a genetic testing company founded in 2000 by 2 scientists from the National Institutes of Health in the United States. A blood sample was submitted to GeneDX. Genetic analysis demonstrated the following. First, the sequence cingulate gyrus was removed. Histological diagnoses were cavernous malformations in all of the lesions. She was discharged from the hospital with no neurological deficit. Follow-up MRI showed the lesion in the midbrain was unchanged, and no more de novo lesions were observed at 4 years after the third surgery (Fig. 3D).
analysis of exons 14, 16, and 18 of the KRIT1 gene and their flanking splice sites revealed no mutation. Second, the detection of deletions and duplications of the KRIT1, MGC4607, and PDCD10 genes was performed by exon-focused oligonucleotide array comparative genomic hybridization analysis. The analysis revealed heterozygous partial deletions of exons 12-15 of the KRIT1 gene. The reference genomic sequence coordinate was chromosome 7: 91850937-91856230, based on the Genome Reference Consortium build 37 (GRCh37). Hybridization data were analyzed with Genomic Workbench v5 software (Agilent Technologies). No additional deletions were detected in the MGC4607 or PDCD10 genes. Third, the sequence analysis of exons 1-10 of the MGC4607 genes and their flanking splice sites revealed no mutation.

Case 3 (III:2, Fig. 1): Case 3 was a 32-year-old female with no symptoms. She was the elder sister of Cases 1 and 2. T2 star-weighted MRI revealed 14 small hypointensity lesions in the bilateral cerebral hemisphere, left cerebellar hemisphere, and brain stem at 7 years after the first admission of Case 1 (Fig. 5A-B). Follow-up MRI showed no change at 2 years after the first examination.

Case 4 (II:2, Fig. 1): Case 4 was a 62-year-old female with no symptoms. She was the mother of Cases 1, 2 and 3. T2 star-weighted MRI revealed 55 small hypointensity lesions in the bilateral cerebral hemisphere, left cerebellar hemisphere, and brain stem (Fig. 6A-B). She had also been followed up at our hospital. However, she did not receive MRI examination of the spinal cord. At 1 year after the diagnosis, she suffered from paraplegia and was transferred to another hospital. T1-weighted and T2-weighted MRI revealed intramedullary hemorrhage at T6-7 and surgery was performed at that hospital. It was assumed that she had a lesion of CM lesion in the spinal cord. Her husband had multiple cutaneous vascular malformations on his face, head and neck, although MRI revealed no lesions of CM lesions in the brain or the spinal cord. Therefore, detailed family histories were taken from her
after the diagnosis. Her younger brother had previously shown the presence of a multiple mass lesion in the brain at the other hospital. Her younger sister had not received MRI. Her mother had received MRI, which revealed no abnormal lesions in the brain. Her father may have died from stroke, but the details were unclear. The family tree is shown in Fig. 1.

**DISCUSSION**

We have reported a Japanese pedigree of FCCM that includes 4 cases. These cases indicate four important clinical issues. First, all 4 cases had multiple lesions, and T2 star-weighted MRI was useful for the diagnosis. Second, the probability of showing symptoms was high (3/4) in all of these cases. Third, inheritance seemed to be autosomal-dominant from their family tree. Finally, genetic analysis of Case 2 demonstrated heterozygous partial deletions of exons 12-15 of the KRIT1 gene.

There are few case reports of Japanese FCCM compared with patients from other countries, such as Italy, the United States, Brazil, Switzerland, Spain and Portugal. In addition, only one report conducted genetic analysis of Japanese FCCM. Thus, the pathogenesis, natural history, inheritance fashion, and gene mutations related to Japanese FCCM are unclear. A previous review of 17 Japanese pedigrees and 37 cases of FCCM reported 17 cases of multiple lesions, although T2 star-weighted MRI may reveal more cases with multiple lesions. The same review showed that surgical removals were performed in 22 cases due to hemorrhages, focal deficits, or epilepsies, which indicated a high probability of showing symptoms of FCCM. FCCM is reported to be inherited in an autosomal-dominant fashion, thus many unrecognized cases of FCCM may exist in Japanese multiple CCM. Taking detailed family histories is important for a precise diagnosis. Currently 3 CCM genes have been identified: KRIT1 (Krev Interaction Trapped 1) at 7q21.2 (CCM1); MGC4607 at 7p13 (CCM2); and PDCD10 (Programmed Cell Death 10) at 3q25.2-q27 (CCM3). KRIT1 accounts for 40%-56% of FCCM, MGC4607 accounts for 20%-33% of FCCM, and PDCD10 accounts for 6%-10% of FCCM. Other CCM genes or a significant fraction of CCM mutations that are not detected by routine direct DNA sequence analysis account for 5%-30% of FCCM cases. There are several reports on large deletions or duplications within the three known CCM genes, and deletions of CCM2 were the most frequent, with similar location and type of CCM mutation in the same pedigree in many cases. Oligonucleotide array comparative genomic hybridization has been used to identify deletions and duplications that are not detected by routine direct DNA sequence analysis.

**Table 1. Reported cases of genetic analysis of Japanese FCCM**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age (years)/gender</th>
<th>Location</th>
<th>Exon</th>
<th>Type</th>
<th>procedure</th>
</tr>
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<tbody>
<tr>
<td>Tsutsumi et al (2013)</td>
<td>60/F</td>
<td>CCM1</td>
<td>Exon 16</td>
<td>HD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>37/F</td>
<td>CCM1</td>
<td>Exon 16</td>
<td>HD</td>
<td></td>
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<tr>
<td></td>
<td>30/F</td>
<td>UV</td>
<td>UV</td>
<td>UV</td>
<td>surgery</td>
</tr>
<tr>
<td></td>
<td>46/F</td>
<td>UV</td>
<td>UV</td>
<td>UV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65/M</td>
<td>CCM3</td>
<td>Exon 5</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>Exon 1</td>
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<td>CCM2</td>
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<td>D</td>
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<tr>
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<td>79/M</td>
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<td>Exon 2</td>
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</tr>
<tr>
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<td>29/M</td>
<td>UV</td>
<td>UV</td>
<td>UV</td>
<td></td>
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<tr>
<td></td>
<td>15/M</td>
<td>UV</td>
<td>UV</td>
<td>UV</td>
<td>surgery</td>
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<tr>
<td>Present case</td>
<td>30/M</td>
<td>CCM1</td>
<td>Exon12-15</td>
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<td>surgery</td>
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</tbody>
</table>

CCM2 or CCM3. The author assumed that cases associated with CCM1, CCM2, or CCM3 mutations may have benign clinical courses in contrast to previous reports\textsuperscript{20}. However, this assumption was invalid for our cases. In our cases, the larger genomic deletion spanning exons 12-15 may relate to symptomatic CCA. Further genetic analyses of Japanese FCCM are important in order to clarify the relationship between mutation patterns and their clinical courses.

**CONFLICTS OF INTEREST DISCLOSURE**

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices mentioned in this article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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