Two Cases of Familial Cerebral Cavernous Malformation Caused by Mutations in the *CCM1* Gene

Im-Yong Yang\textsuperscript{1}, Mi-Sun Yum\textsuperscript{1}, Eun-Hee Kim\textsuperscript{1}, Hae-Won Choi\textsuperscript{1}, Han-Wook Yoo \textsuperscript{1,2}, Tae-Sung Ko\textsuperscript{1}

Department of Pediatrics\textsuperscript{1}, Medical Genetic Center\textsuperscript{2}, Asan Medical Center, Children's Hospital, University of Ulsan College of Medicine

Running title: Familial Cerebral Cavernous Malformation

Corresponding author: Tae-Sung Ko

Department of Pediatrics, Asan Medical Center Children’s Hospital, University of Ulsan College of Medicine, 86, Olympic-ro 43-gil, songpa-gu, Seoul 138-736, Korea

TEL: +82-2-3010-3386, Fax: +82-2-473-3725, E-mail: tsko@amc.seoul.kr

This study did not receive any research funds.

This report has not been published previously.
Abstract

Cerebral cavernous malformation (CCM) is a vascular malformation characterized by abnormally enlarged capillary cavities without any intervening neural tissue. We report two cases of familial CCMs diagnosed with CCM1 mutation by genetic assay. A five-year old boy presented with a headache, vomiting, and seizure-like motion. Brain MRI revealed multiple, CCM lesions in the cerebral hemisphere. Subsequent mutation analysis of his father and other family members demonstrated c.940_943 del (p.Val314 Asn315delinsThrfsX3) mutations of the CCM1 gene. A 10-month-old boy who presented with seizure-like motions was reported to have had no perinatal event. His aunt was diagnosed with cerebral angioma. Brain and spine MRI revealed multiple angioma in the cerebral hemisphere and thoracic spinal cord. Mutation analysis of his father was normal, although mutation analysis of the patient and his mother demonstrated c.535C>T (p.Arg179X) mutations of the CCM1 gene. Based on this report, when a child with a familial history of CCMs exhibits neurological symptoms, the physician should suspect familial CCMs and consider brain imaging or a genetic assay.
Key Words: Familial cerebral cavernous malformation, Novel mutation, CCM1
Introduction

Cerebral cavernous malformation (CCM) is characterized by abnormally enlarged capillary cavities without intervening brain or spinal cord parenchyma. The prevalence of CCMs has been estimated to exist in 0.4% to 0.8% of the population in several reports\(^1\). CCMs can occur in the brain, spinal cord, retina or skin and can show numerous manifestations including headaches, focal neurologic signs, hemorrhagic stroke, seizures or sometimes even death\(^2\).

CCMs can present sporadically or be inherited and can be autosomal dominant with incomplete penetrance. Familial CCMs are associated with the mutation of three genes, i.e. \(CCM1\) (KRIT1), \(CCM2\) (MGC4607), and \(CCM3\) (PDCD10). The \(CCM1\) gene contains 16 coding exons that encode KRIT1, containing three ankyrin domains and one FERM domain. Until now, a strong founder effect has been reported in the Hispanic-American population, and with most families linked to the \(CCM1\) locus\(^3\).

Our study reports the first genetically proven, Korean CCM families with \(CCM1\) mutation.
Case Report

Case 1

A five-year old boy presented with headache, vomiting, and seizure-like motion, although he was without a history of trauma. On physical and neurological examination, he had no focal neurologic deficit.

The laboratory findings showed no evidence of electrolyte imbalance or other cause of his seizure. The electroencephalogram (EEG) performed one month after the seizure, revealed diffuse background slowings. Brain magnetic resonance imaging (MRI) revealed multiple CCM lesions in his cerebral hemisphere and involving the parietal and temporal lobes as well as basal ganglia (Fig. 1).

After obtaining his family history of neurologic disease, it was revealed that his grandmother had suffered from dizziness and vomiting, and the subsequent brain MRI revealed cerebral cavernous malformation and cerebellar infarction. Familial evaluation using genetic and brain MRI screening was performed. With complete radiologic penetrance of the CCMs, his father, one uncle, and two aunts were all seen to have
CCMs (Fig. 2). Mutation analysis of his family demonstrated c.940_943 del (p.Val314
Asn315delinsThrfsX3) frameshift mutation in exon 7 of the CCM1 gene of the affected
family members, and which had not been previously reported (Fig. 3).

Based on the diagnosis of CCM and the associated epilepsy, oxcarbazepine was
introduced and the patient had been seizure-free during three years of medication. At
this time, he has been seizure-free for two years after discontinuing the oxcarbazepine.

**Case 2**

A 10-month-old boy with no perinatal events, presented with seizure-like motion. His
aunt was diagnosed with cerebral angioma (Fig. 4). On neurologic examination, the
infant had no focal neurologic deficit and no evidence of developmental delay.

EEG recording revealed two episodes of electrical seizures with runs of spike discharges
from the left temporo-parietal area. An MRI of brain and the entire spine showed
multiple angioma in cerebral hemisphere and thoracic spinal cord (Fig. 5).

Familial screening for genetic analysis of CCM1 was done and the patient and his
mother demonstrated c.535C>T (p.Arg179X) heterozygous mutation in exon 5 of the

CCM1 gene (Fig. 6), and which was already known.

His seizures were well-controlled with the use of vigabatrin and zonisamide medications. At his four years of age follow-up, he was neurologically normal and has remained seizure-free without antiepileptic medications.
Discussion

Cerebral cavernous malformations (CCMs) may be both sporadic and familial. Some previous reports have described mutation of CCM genes in worldwide familial CCMs \(^{4-6}\). In this report, we describe one novel and one known mutation of the \(CCM1\) gene occurring in two, Korean family patients with CCMs with epilepsy.

Kufs et al\(^7\) first reported families affected by CCMs in 1928. Since then there have been many studies reporting the clinical and neuroradiological features, and after which the recent development of genetic linkage analysis has allowed the full description of CCMs. In recent, large studies, \(CCM1\) mutation showed a clinical penetrance of 62%, and several de novo mutations have also been reported\(^8\). In addition, according to Gault et al., biallelic \(CCM1\) (\(KRIT1\)) mutations, including somatic and germ-line truncating mutation of CCM lesions, may explain the CCM pathophysiology as that occurring in hamartomatous disease\(^9\).

Recent research data allowed significant progress in determining the function of \(KRIT1\) (CCM1) as a Notch activator which negatively regulates sprouting angiogenesis\(^{10}\). The
loss of KRIT1 leads to an induction of angiogenesis caused by impaired DELTA-NOTCH signaling, and disrupts the vascular polarity and lumen formation. Interestingly, exciting recent data suggest that the loss of KRIT1 or PDCD10 induce BMP6-SMAD signaling and endothelial-mesenchymal transition contributing to the development of CCM, and which leads us to search for another therapeutic option such as BMP6 or TGFβ inhibitors11).

In general, the natural course of CCMs is benign, although some patients may suffer from neurological deterioration, primarily related to hemorrhage. According to recently published reports, infratentorial CCM lesions, especially brainstem, are more hemorrhagic events than supratentorial lesions. A larger lesion (>1cm), early age at presentation (<35 years), and the co-existence of a developmental venous anomaly, are considered as other risk factors for hemorrhage2).

Usually, familial CCMs are more likely to hemorrhage, grow, and present with multiple lesions than those seen in sporadic cases. In addition, a recent study regarding genotype-phenotype correlations shows that CCM3 mutations are more likely to cause cerebral hemorrhage, particularly during childhood, and the increase of the number of
gradient-echo-sequence lesions with age differs according to the mutation, with a higher rate in CCM1 than in CCM2 mutations\textsuperscript{12}).

The management of CCMs includes conservative treatment, surgical resection, and stereotactic radiosurgery (SRS). In general, asymptomatic and small CMs that are silent may be observed conservatively. Follow-up MRI is recommended at one year, three years, and five years following the diagnosis for patients younger than 45 years. In contrast, epileptogenic CMs in patients with chronic epilepsy or hemorrhagic CMs are an indication for surgical resection. The goal of surgery is gross total resection because incomplete resection can increase re-bleeding with consequent mortality. For difficult cases, such as patients with deep-seated eloquent lesions, stereotactic radiosurgery may be recommended. However, the long-term results are controversial and radiation-induced morbidities are the principal drawback\textsuperscript{13}).

Several sporadic cases of cavernous malformation involving the central nervous system have been reported in the Korean population, but there are only a few studies with a genetic diagnosis and accompanying familial study. Lee ST et al\textsuperscript{14}) reported the occurrence of cerebral and multiple spinal CMs with CCM3 gene mutation, and Lee YW
et al\textsuperscript{15}) presented a novel mutation of the \textit{CCMI} gene related to CCM and multiple spinal CMs in Korea.

In our patients, thorough history-taking and genetic screening detected familial cases of CCMs. A novel mutation of the \textit{CCMI} gene was confirmed in case 1 families over three generations and a detailed history provided a clue to identifying a mutation of the \textit{CCMI} gene in case 2 and his mother.

In a child with multiple CCMs, family-history taking, brain imaging or genetic assay should be considered in order to evaluate for familial CCMs.

\textbf{Conflict of interest}

No potential conflict of interest relevant to this article was reported.
References


EndMT contributes to the onset and progression of cerebral cavernous 

Genotype-phenotype correlations in cerebral cavernous malformations patients. 

13. Kivelev J, Niemela M, Hernesniemi J. Treatment strategies in cavernomas of the 

mutation in the PDCD10 gene in a patient with cerebral and multiple spinal 

mutation in a patient with cerebral and multiple spinal cavernous malformations. 
Figure Legends

Fig. 1

(A) Gradient-echo axial MRI of the patient's father showing a cavernous malformation in the parietal, deep-white matter as well as multiple microbleeds in the brain.

(B) Brain MRI of the index patient showing multiple cavernous angiomas in the brain.

Fig. 2

The pedigree of patient 1's family with CCMs. Filled circles and squares indicate affected members; the index patient (arrow) and the father, uncle, aunts, and grandmother. Filled square or circle with a diagonal indicates deceased individuals; * = Affected, but cannot perform the genetic test.

Fig. 3
Mutation analysis of patient 1’s father demonstrated c.940_943 del (p.Val314
Asn315delinsThrfsX3) mutations of the CCM1 gene. This is a novel mutation of the
CCM1 gene in CCM patients.

Fig. 4

The pedigree of patient 2’s family with CCMs. Filled circles and squares indicate
affected members; the index patient and the mother. * = Affected, but cannot perform
the genetic test.

Fig. 5

(A) Brain MRI of patient 2 shows multiple, cavernous angiomas in the left perisylvian
and right parietal areas.

(B) Spine MR shows a cavernous angioma in the spinal cord at T7-8.
Fig. 6

(A) The normal DNA PCR sequencing.

(B) Mutation analysis of patient 2 and his mother demonstrated c.535C>T (p.Arg179X) mutations of the CCM1 gene.