Clinical Case Report

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Familial cerebral cavernous malformation presenting with epilepsy caused by mutation in the CCM2 gene

A case report

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Abstract

Rationale: Cerebral cavernous malformation (CCM) of the familial type is caused by abnormalities in the CCM1, CCM2, and CCM3 genes. These 3 proteins forming a complex associate with the maintenance of vascular endothelial cell-cell junctions. Dysfunction of these proteins results in the development of hemangiomas and abnormal intercellular junctions.

Patient concerns: We report a 68-year-old man with familial cerebral cavernous malformation with initial presentation as convulsions at an advanced age. Brain magnetic resonance imaging revealed multiple cavernous hemangiomas in the right occipital lobe. The convulsions were considered to be induced by hemorrhage from cavernous hemangioma in the right occipital lobe.

Diagnoses: Genetic screening of the *CCM1*, *CCM2*, and *CCM3* genes revealed a novel mutation in the *CCM2* gene (exon4 c: 359 T>A, p: V120D). No abnormalities were found in *CCM1* or *CCM3*. Therefore, we diagnosed the patient with familial CCM caused by a *CCM2* mutation.

Interventions: This patient was treated with the administration of levetiracetam at a dosage of 1000 mg/day.

Outcomes: No seizures have been observed since the antiepileptic drug was administered. We performed brain magnetic resonance imaging (MRI) regularly to follow-up on appearance of new cerebral hemorrhages and cavernous hemangiomas.

Lessons: This report reviews cases of familial cerebral cavernous malformations caused by abnormalities in the *CCM2* gene. This mutation site mediates interactions with CCM1 and CCM3. The mutation occurs in the phosphotyrosine binding (PTB) site, which is considered functionally important to CCM2.

Abbreviations: CCM = cerebral cavernous malformation, del = deletion, fs = frame shift, LD-like motif = leucine-aspartic acid like motifs, MRI = magnetic resonance imaging, PCR = polymerase chain reaction, PTB = phosphotyrosine binding, PTC = premature termination codon, TGF-β1 = transforming growth factor-β1, uk = unknown, VEGF-A = vascular endothelial growth factor-A.

Keywords: CCM1, CCM2, CCM3, cerebral cavernous malformation, phosphotyrosine binding domain

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1. Introduction

Cerebral cavernous malformations (CCMs) are a type of low-flow vascular malformation; imaging studies have estimated their prevalence to be 0.4% to 0.8%.[1] Diagnosis of CCM is determined by imaging in 47% of cases, convulsions in 25%, intracerebral hemorrhage in 12%, and the identification of focal neurological defects in 15%.[2] CCMs are either sporadic or familial and recur in approximately 20% of patients. Mutations in the genes encoding CCM1, CCM2, and CCM3 have been associated with familial CCMs.[3] These 3 proteins, present in vascular endothelial cells, form a complex that regulates signal transduction proteins associated with the maintenance of adjacent vascular endothelial cell-cell junctions.[4] Dysfunction of these proteins results in the development of hemangiomas and abnormal intercellular junctions. The former increase in number and size over time, which increases the risk of intracerebral hemorrhage.[5,6] The development of interventions that target proteins associated with CCMs has therefore garnered increasing attention.[3]

Here, we report a case of familial CCM, first indicated by convulsions, in which we identified a novel mutation in the *CCM2* gene through genetic testing. We further summarize previously reported *CCM2* mutations, infer functionally impor-

tant sites of CCM2, and discuss potential interventions for progressive CCMs. The patient has provided informed consent for publication of the case.

2. Case presentation

A 68-year-old man was transported to the nearest hospital by an ambulance and was admitted due to impaired consciousness and a tonic seizure that had spread from the left leg while the patient was driving 3 months prior. Brain magnetic resonance imaging (MRI) revealed hemorrhages in the right occipital lobe and multiple CCMs. He was diagnosed with secondary convulsions caused by intracerebral hemorrhage. The patient received orally administered levetiracetam at a dosage of 1000 mg/day, and no convulsive seizure occurred thereafter. He was referred to our hospital and admitted for advanced examination. Family history revealed that his second son and grandson had both exhibited CCMs.

A physical examination on admission showed no abnormalities, such as hemangioma or nevus, on the body surface. No retinal hemangioma was observed in the fundus. A neurological examination showed alertness and consciousness, and the Hasegawa Dementia Scale-Revised and Mini-Metal State Examination scores were 26 and 27, respectively. There were no abnormalities in the central nervous system, cerebellar symptoms, pyramidal signs, signs of Parkinson's disease, autonomic symptoms, or sensory abnormalities. Posture/walking was normal, and no meningism was observed.

A urine test revealed no abnormalities. A blood test showed no liver dysfunction, kidney dysfunction, or glucose tolerance abnormalities. Autoantibodies were negative. A thoracoabdominal contrast-enhanced computed tomography scan showed no hemangioma or venous malformation. T1-weighted MRI of the brain showed a hemangioma of 20 mm in diameter in the right occipital lobe and a relatively new hemorrhage at the same site. T2-star imaging revealed new and old hemorrhages (Fig. 1). An MRI of the cervical, thoracic, and lumbar spines did not demonstrate any vascular anomalies, such as hemorrhage. An electroencephalogram showed neither abnormal basic waves nor any epileptiform wave patterns.

Using the PAXgene Blood DNA kit, peripheral venous blood was collected to extract genomic DNA; this was amplified by polymerase chain reaction (PCR) to determine the DNA sequence according to a previously reported method,[7] revealing a novel mutation in *CCM2* (c, 359; T>A; p, V120D). No abnormalities were found in either *CCM1* or *CCM3*. Based on the results, we diagnosed the patient with familial CCM caused by a *CCM2* mutation.

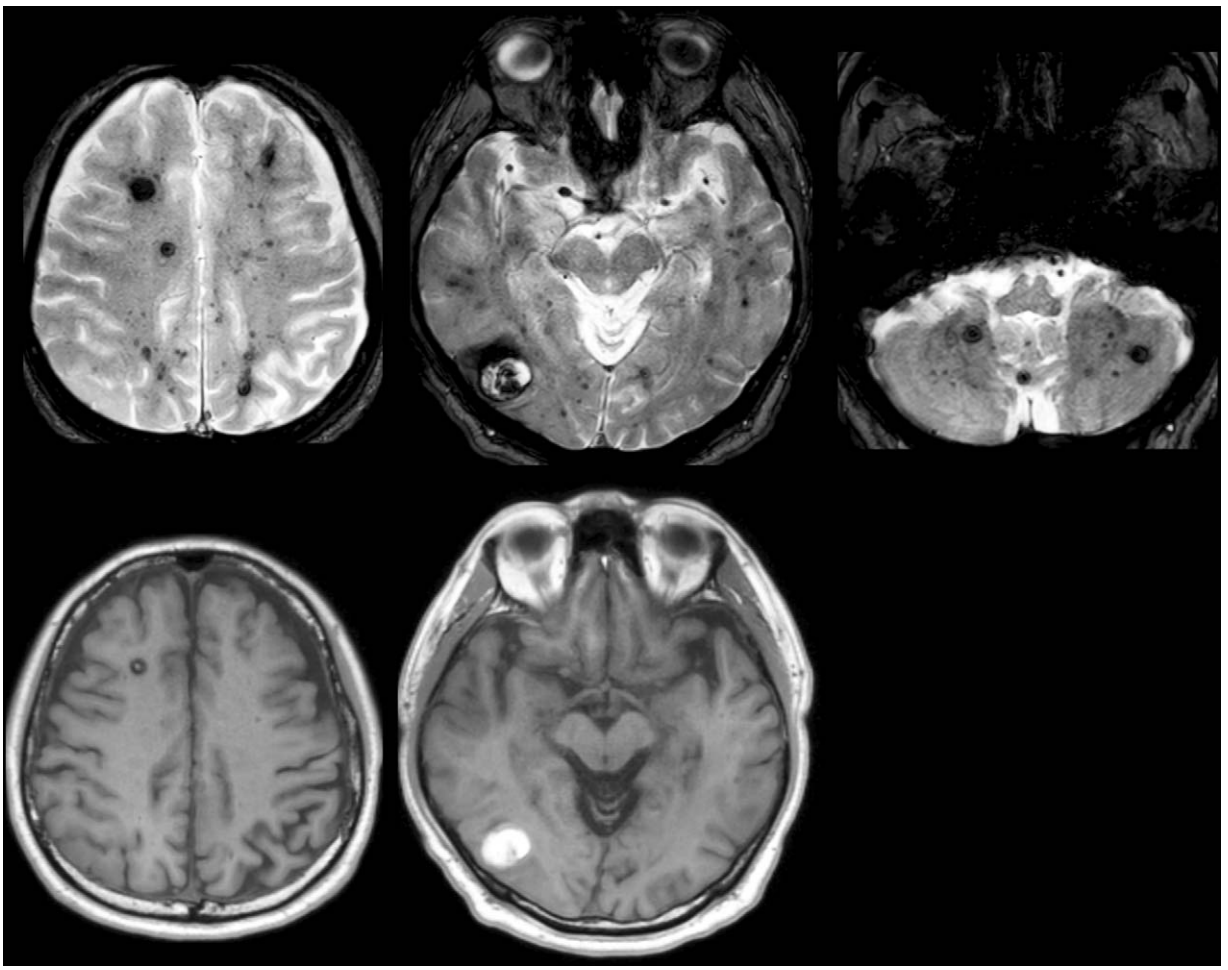

Figure 1. Brain magnetic resonance imaging (MRI). T2-star MRI revealed multiple micro-bleedings as low-signal spotty lesions (upper). T1-weighted MRI was used to visualize relatively new bleeding in the right occipital lobe as a high-signal lesion (lower).

No seizures occurred after the continuous administration of levetiracetam 1000 mg/day. In addition, regular brain MRI scans have been performed to monitor the cerebral cavernous hemangioma and check for the appearance of new hemorrhages.

3. Discussion

CCM2 is composed of 10 exons that encode a 444-amino acid protein (CCM2/malcavernin).[8] CCM2 features an N-terminal phosphotyrosine binding (PTB) domain and a C-terminal helical domain,[9–11] which bind to CCM1 (KRIT1). CCM2 is a scaffold protein that contributes to several signal transduction cascades, including the p38 mitogen-activated protein kinase (MAPK) and Rho-kinase signaling pathways, which maintain the integrity of blood vessels.[12,13] In addition, CCM2 binds to CCM3 with an leucine-aspartic acid like motifs (LD-like motif), which consists of amino acids 223 to 238, to form a complex of 3 proteins: CCM1, CCM2, and CCM3.[14]

Our search of the National Center for Biotechnology Information ((NCBI) URL: https://www.ncbi.nlm.nih.gov/gene/83605) database and The Human Gene Mutation Database (URL: http://www.hgmd.cf.ac.uk/docs/login.html) revealed that 57 abnormal sites on *CCM2* have been reported, 40 of which are pathogenic mutations.[7–9,15–22] As shown in Figure 2, these abnormalities are concentrated in the CCM1 binding site, the PTB domain, and the N-terminus, all of which are functionally important regions of CCM2.

When the function of CCM1, CCM2, or CCM3 is impaired by a genetic mutation, vascular endothelial cells in the central nervous system assume the features of mesenchymal and stem cells; this causes the loss of VE-cadherin organization and the polarity of vascular endothelial cells, impairment of endothelial intercellular adhesion, and abnormal vascular lumen, further inducing hemangioma and bleeding.

Effective treatment of familial CCMs associated with CCM2 has not been established. Hemangiomas progressively increase in number and grow larger over time, which elevates the risk of intracerebral hemorrhage.[5,6] Interventions preventing their increase and growth would further forestall the occurrence of intracerebral hemorrhage and improve functional prognosis. Based on pathological mechanisms underlying the formation of hemangioma, agents that can eliminate inflammation and oxidative stress, such as Vitamin D3 and Tempol, have been developed. This same approach has yielded agents that suppress the transforming growth factor-β1 (TGF-β1) signaling such as DMH1, LY364947, SB431542, and Sulindac; RhoA inhibitors, such as statins and Fasudil; and anti-angiogenic agents, such as rapamycin, sorafenib, and vascular endothelial growth factor-A (VEGF-A).[3,12] Statins such as simvastatin and atorvastatin are well known lipid-lowering medications, and are particularly

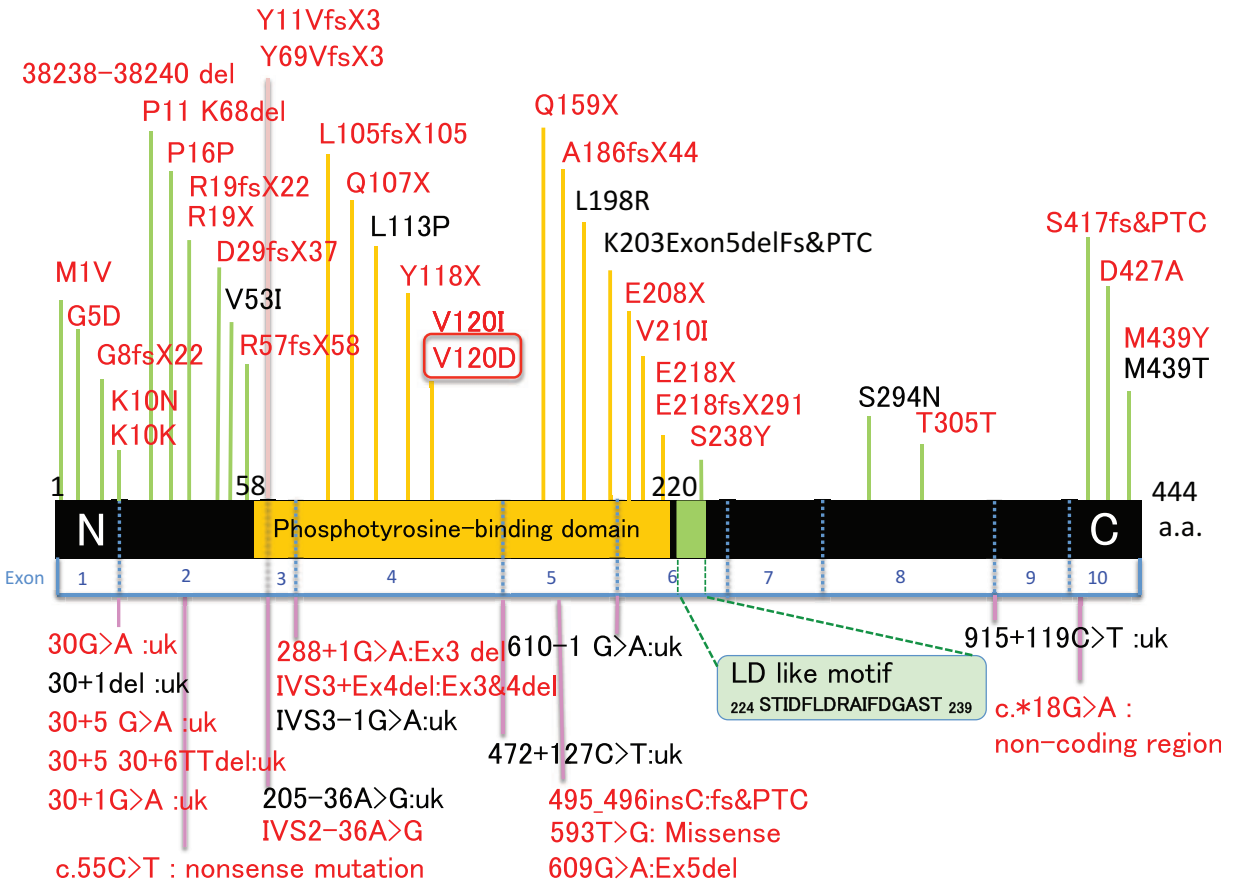

Figure 2. Reported mutations in *CCM2* and consequent abnormalities in CCM2. The phosphotyrosine binding (PTB) domain (58–220 amino acids) and the LD-like motif (224–239 amino acids) in the CCM2 protein and exons are shown: protein abnormalities, upper; genetic mutations, lower. Pathogenic mutations are shown in red. Pathogenic mutations are concentrated in the region from the N-terminus to the vicinity of the PTB domain. The genetic variants were expressed in accordance with the guidelines of the Human Genome Variation Society (HGVS) in 2000. del: deletion; fs: frame shift; PTC: premature termination codon; uk: unknown.

practical from the perspective of drug repositioning; clinical trials using these agents are currently underway.[3]

4. Conclusion

We present a case of familial CCM with a novel mutation in *CCM2* (c, 359; T>A; p, V120D). Forty abnormal pathogenic sites have been reported in *CCM2*. These mutation sites are predominantly found in the N-terminus, PTB site, and the LD-like motif of CCM2, which mediate interactions with CCM1 and CCM3. Because these regions are considered functionally important to CCM2, their dysfunction may account for the development of CCMs.

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