Correlation of the venous angioarchitecture of multiple cerebral cavernous malformations with familial or sporadic disease: a susceptibility-weighted imaging study with 7-Tesla MRI

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OBJECTIVE Multiple cerebral cavernous malformations (CCMs) are rare lesions that occur in sporadic or familial form. Depending on the disease form, the natural history and treatment of the lesions strongly vary. Molecular analysis of an underlying germline mutation (*CCM1–3*) is the most sensitive screening method to distinguish between sporadic and familial cases. However, based on the different pathomechanisms that are believed to be involved in either form, significant distinctions in the CCM-associated cerebral venous angioarchitecture should be detectable. This has not been systematically studied.

METHODS A consecutive series of 28 patients with multiple CCMs (681 total) diagnosed on 1.5-T MRI underwent genetic screening for *CCM1–3* mutations and high-resolution susceptibility-weighted imaging (SWI) of the cerebral venous angioarchitecture with 7-T MRI. Imaging data were analyzed to examine the CCM-associated venous angioarchitecture. Results were correlated with findings of molecular analysis for *CCM1–3* mutations.

RESULTS Two different SWI patterns (sporadic and familial) were found. The presence of associated developmental venous anomalies correlated with negative screening for germline mutations (11 sporadic) in all cases. All patients with confirmed familial disease showed normal underlying venous angioarchitecture. Additionally, a very unusual case of a probable somatic mutation is presented.

CONCLUSIONS The SWI results of the venous angioarchitecture of multiple CCMs correlate with sporadic or familial disease. These results are consistent with the theory that venous anomalies are causative for the sporadic form of multiple CCMs.

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KEY WORDS CCM; susceptibility-weighted imaging; SWI; high-field MRI; magnetic resonance imaging; cerebral cavernous malformations; familial disease; familial cavernomatosis; *CCM1–3*; vascular disorders

CEREBRAL cavernous malformations (CCMs) are low-flow focal vascular abnormalities, which are histologically characterized as closely packed thin-walled vessels filled with blood at different stages of thrombosis. Recurrent intra- or extralesional (micro)

hemorrhages and secondary iron deposits determine the clinical findings in patients with symptoms, mainly seizures or focal neurological deficits.¹⁵ Cerebral cavernous malformations affect approximately 0.5%²² of the population and occur mostly as a sporadic and less frequently

ABBREVIATIONS CCM = cerebral cavernous malformation; DVA = developmental venous anomaly; FA = flip angle; MLPA = multiplex ligation-dependent probe amplification; R = in-plane resolution; ST = slice thickness; SWI = susceptibility-weighted imaging.

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as an inherited autosomal-dominant (familial) form.²⁷ Whereas the former is usually characterized by single lesions, the latter presents with multiple lesions distributed throughout the entire CNS and/or other organ systems.³⁰ However, depending on the specific underlying germline mutation within *CCM1/KRIT1*, *CCM2/MGC4607*, or *CCM3/PDCD10*,²⁶ penetrance of the disease, age of the patient, and other factors (e.g., applied MRI technique), the number of detectable lesions strongly varies, ranging from a single or a few lesions to hundreds of CCMs.¹⁴ On the other hand, sporadic CCMs may present as multiple lesions as well (10%–15%), with an underlying germline mutation emerging in up to two-thirds of the cases.^{26,32}

Because a familial form has a significant impact on the natural history and treatment of the disease and especially a considerable social component compared with the sporadic form, early clarification during consultation of a patient with multiple lesions (≥ 2) is desirable. Molecular screening for known *CCM1–3* mutations is the most sensitive method but is often initiated only months to years later.^{7,26,32} Additionally, information on a potential family history may be fragmentary, especially because many CCMs remain asymptomatic.¹⁵ Consequently, the initial MRI diagnosis of multiple CCMs frequently leads to a prolonged situation of uncertainty for the patient and their family.

However, based on the distinct pathomechanisms suspected to be involved in the formation of sporadic and familial CCMs (venous malformation or developmental venous anomaly [DVA]²⁹-associated formation² or loss-of-function mutation [germline or somatic] in 1 of the 3 *CCM* genes with consecutive endothelial dysfunction,³³ respectively), specific differences in local venous angioarchitecture^{6,21,25} between these forms of multiple CCMs are expected to be detectable. This has not been systematically studied. We propose the following hypotheses: that 1) a differing distribution of multiple CCMs and 2) a differing adjacent venous angioarchitecture of multiple CCMs can be detected, and 3) that these will correlate with genetic screening for an underlying familial disease.

Therefore, we conducted a study to search for specific patterns in high-resolution MRI of multiple CCMs (≥ 2). To increase the sensitivity for delineation of CCM lesions and associated venous vascular structures,⁵ all MRI was performed at 7-T magnetic field strength¹³ using susceptibility-weighted imaging (SWI)^{10,20} and standard anatomical imaging protocols. After image analysis, the results were matched with findings from genetic examination that included screening for *CCM1–3* gene mutations.

Methods

The study was conducted at the Department of Neurosurgery and the Erwin L. Hahn Institute for Magnetic Resonance Imaging of the University of Duisburg-Essen, Germany, in accordance with all guidelines set forth by the approving institutional review board. The study was performed as part of a superordinate fundamental research study on high-field MRI. Informed consent according to the Declaration of Helsinki was obtained from every patient before examination. Sequence analysis of *CCM1–3*

genes was mainly performed at the Department of Human Genetics, University Medicine Greifswald, Germany, and in part at the Center for and Department of Human Genetics, University of Regensburg, Germany.

Patient Characteristics

All patients who were admitted to our department between 2010 and 2015 who showed multiple CCMs (≥ 2) on 1.5-T MRI (contrast-enhanced T1-weighted, T1-weighted, T2-weighted, and T2*-weighted) and who had undergone gene sequence analysis of *CCM1–3* were included in this study and underwent SWI with 7-T MRI. Patients with incomplete genetic screening, pregnant patients, and patients with a history of cranial radiation were excluded. Patients with the sporadic form of the disease and solitary lesions were analyzed in a previous study.⁶

Methods Used

Basic clinical data and medical history of all patients were assessed according to the reporting standards of CCM research.¹

The 7-Tesla MRI Protocol

In all patients, SWI was performed at 7 T (Magnetom 7T; Siemens Healthcare). Susceptibility-weighted imaging sequences were established in previous work.⁵ The whole-body ultra-high-field MR system was equipped with a single-channel transmitter/32-channel receiver head coil (Nova Medical), and a gradient system capable of 45 mT/m maximum amplitude and a slew rate of 220 mT/m/msec. The SWI parameters were as follows: TE 15 msec, TR 27 msec, flip angle (FA) 14°, in-plane resolution (R) 250 × 250 μm^2 , slice thickness (ST) 1.5 mm, and bandwidth 140 Hz/pixel. The SWI data were processed to phase, magnitude, susceptibility, and minimum intensity projection images. In addition, anatomical T1-weighted (TR 2500 msec, TE 1.4 msec, FA 6°, 0.7 mm isotropic), T2-weighted (TR 6000 msec, TE 99 msec, FA 29°, ST 3 mm, R 0.5 mm²), and time-of-flight angiography (TR 20 msec, TE 4.3 msec, FA 20°, ST 0.4 mm, R 0.2 mm²) sequences were acquired.

Image Analysis

All 7-T MR images (phase, magnitude, SWI, T1-weighted, and T2-weighted) were analyzed using an in-house workstation by 2 observers experienced in SWI analysis. The following criteria were assessed: number, location, type,²⁸ and size of the CCMs (≥ 1 CCM exceeding or not exceeding 10 mm). Size was determined using axial plane T2-weighted turbo spin echo. Also, distribution over 1, 2, or ≥ 3 regions of the brain (frontal, temporal, occipital, parietal lobe, insular lobe, basal ganglia, brainstem, and cerebellum) was determined. A distribution over > 2 regions of the brain was defined as a multifocal distribution.

In brain regions with CCMs, the local venous angioarchitecture was inspected for absence or presence of a typical DVA or anatomical abnormalities as specified previously,⁶ i.e., presence of transcerebral medullary veins or formation of venous radicles. In cases of a confirmed DVA, the number of collecting veins and presence of ste-

TABLE 1. Schematic representation of cerebral venous system sections

Venous System	Sections
Superficial veins	Superior Superficial sylvian Deep sylvian Inferior Inferior anastomotic Superior anastomotic
Deep veins	Great Basal Internal
Subependymal veins	Fissura transversa Lateral ventricle Cisterna tecti
Infratentorial veins	Medial pontine Lateral pontine Superficial cerebellar Deep cerebellar

nosis (vessel diameter reduction > 50%)¹² or an angulated course (< 90° angulation)¹² of collecting veins were assessed. Developmental venous anomalies were grouped as small, medium, or large based on involvement of 2, up to 4, or > 4 venous system sections, respectively. The classification of the venous system used as a physiological reference is shown in Table 1.³¹ Susceptibility-weighted and time-of-flight images were correlated to distinguish between arterial and venous vessels, e.g., for cases of arterialized venous malformations.

In a subgroup of patients for whom SW images at 1.5 T were available (n = 25), the following criteria were assessed and compared with findings at 7-T MRI: 1) number of CCMs, and 2) absence or presence of a DVA.

Molecular Genetic Analyses

Sanger sequencing analyses of individuals with CCMs were performed with informed consent as described in Spiegler et al.³² Mutation-negative individuals were subsequently screened for large *CCM1–3* alterations using multiplex ligation-dependent probe amplification (MLPA; SAL-

SA MLPA Kits P130 and P131, MRC Holland).⁸ GenBank and ENSEMBL accession numbers were as follows: *CCM1* (GenBank:NM_194456.1, Ensembl:ENST00000394507), *CCM2* (GenBank:NM_031443.3, Ensembl:ENST00000258781), and *CCM3* (GenBank:NM_145860.1, Ensembl:ENST00000392750). Sequences were analyzed in SeqPi-lot with the ENSEMBL data sets. DNA mutation numbering was based on the cDNA sequence, with +1 corresponding to the A of the ATG translation initiation codon.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 22 (IBM Corp.). Interval-scaled data were expressed as the mean and SD, and nominal data were expressed as absolute numbers and valid percent. Data were tested for normal distribution by conducting a Shapiro-Wilk test, in addition to histograms and Q-Q plots. Intergroup comparison was performed with the Fisher exact test for categorical variables and the Mann-Whitney U-test for continuous variables. To estimate the long-run probability of predicting a familial or sporadic disease based on the MRI data of our sample, the rule of 3 was applied (95% CI).¹¹

Results

Twenty-eight patients (15 women and 13 men) with a mean age of 42.7 ± 12.9 years (range 19–64 years) were included in the study (Tables 2 and 3). Six additional patients who presented with multiple CCMs between 2010 and 2015 did not meet the eligibility criteria. Genetic sequence analysis was performed in all 28 patients. Two patients were brothers from a family with known *CCM3* mutation (Cases 4 and 8; Table 3), and another 2 patients were mother and daughter from a family with known *CCM2* mutation (Cases 2 and 13). Twenty-four patients presented with at least 1 symptomatic hemorrhage, including 4 patients suffering from cavernoma-related epilepsy. Four patients were asymptomatic.

Image Analysis

At 7-T SWI, the overall number of CCMs was 681. The mean number of CCMs was 22.4 ± 40.0 (range 2–153). A

TABLE 2. Baseline clinical data, MRI findings, and genetic screening of patients with cluster-type MRI pattern

Case No.	Age (yrs)	Sex	No. of CCMs	Multifocal Distribution	Associated DVA	Family History	Genetic Screening
1	38	F	5	Yes*	Yes	No	Negative
2	57	M	4	No	Yes	No	Negative
3	55	F	8	No	Yes	No	Negative
4	52	F	4	No	Yes	No	Negative
5	45	F	5	No	Yes	No	Negative
6	44	F	3	No	Yes	No	Negative
7	36	M	3	No	Yes	No	Negative
8	57	M	6	No	Yes	No	Negative
9	61	M	5	No	Yes	No	Negative
10	41	F	3	No	Yes	No	Negative
11	34	M	6	Yes*	Yes	No	Negative

* Patient showed multifocal DVA with associated CCM involving both hemispheres and the posterior fossa.

TABLE 3. Baseline clinical data, MRI findings, and genetic screening of patients with scattered-type MRI pattern

Case No.	Age (yrs)	Sex	No. of CCMs	Multifocal Distribution	Associated DVA	Family History*	Genetic Screening	CCM1-3 Mutation
1	51	M	153	Yes	No	Yes	Positive	CCM1:c.1258G>T
2	21	F	2	No†	No	No	Positive	CCM2:c.30G>A
3	54	F	85	Yes	No	No	Positive	CCM1:c.1730+4_1730+7delAGTA
4	23	M	23	Yes	No	Yes	Positive	CCM3:c.334_337delCAAA
5	45	F	21	Yes	No	Yes	Positive	CCM2:c.55C>T
6	45	M	14	Yes	No	Yes	Positive	CCM1:c.1890G>A
7	19	F	4	No†	No	Yes	Positive	CCM1:c.730-1G>A
8	28	M	19	Yes	No	Yes	Positive	CCM3:c.334_337delCAAA
9	33	F	85	Yes‡	No	No	Negative	—
10	25	M	11	Yes	No	No	Positive	CCM2:205-1G>A
11	47	M	4	Yes	No	No	Positive	CCM3:c.63_64dupCC
12	64	M	132	Yes	No	No	Positive	CCM1:c.1391G>A
13	53	F	6	Yes	No	No	Positive	CCM2:c.30G>A
14	56	M	3	Yes	No	Yes	Positive	CCM1:c.12_20del
15	24	F	4	Yes	No	Yes	Positive	CCM1: deletion_of_entire_gene
16	43	F	3	Yes	No	Yes	Positive	CCM1:c.1780_1783delins
17	47	F	6	Yes	No	No	Negative	—

— = not applicable per negative screening.

* At initial diagnosis.

† Not applicable for patients with 2 lesions only or very few lesions.

‡ Lesions exclusively localized to 1 hemisphere (see Fig. 3).

multifocal distribution was found in 17 cases. Association of the CCMs with a typical DVA was found in 11 cases. Further CCMs associated with local venous abnormalities were not detected. In 16 cases, at least 1 CCM exceeded 10 mm. According to the Zabramski classification,³⁴ Type Ia/b was found in 19 patients (33 CCMs), Type II in 14 patients (30 CCMs), Type III in 2 patients (4 CCMs), and Type IV in 1 patient. Six hundred thirteen lesions were visible as a small signal cancellation on SWI only. IntraleSIONAL or extralesional macro hemorrhage (> 10 mm) was found in 9 cases.

Developmental venous anomalies showed 2.5 ± 1.9 (range 1–7) collecting veins. In 9 DVAs a stenosis was confirmed, and in 9 DVAs an angulated course of the collecting vein was confirmed. Eight were categorized as large, and 3 as medium. Further details are shown in Table 4.

According to MRI criteria, the patients were subdivided into 2 groups: (multi)focal distribution without associated DVA (scattered type; Fig. 1) and focal distribution with associated DVA (cluster type; Fig. 2). For details, see Tables 2 and 3. A schematic of the patterns is provided in Fig. 3.

At 1.5-T SWI (n = 25), the overall number of detected CCMs was lower compared with 7-T MRI (mean 33.2 ± 41.3 vs 39.8 ± 49.2 lesions). Fewer lesions were detected in 6 patients. The detection rate of DVA was similar between the 2 imaging modalities.

Molecular Genetic Analysis

Sanger sequencing and MLPA revealed a *CCM1-3* mutation in 15 patients, of whom 6 showed no previous family history. However, 1 of these 6 inherited the mutation from her mother, who was discovered to have 6 asymptomatic CCMs at the age of 52 years (Cases 2 and 13; Table 3). In 13 patients without previous family history, Sanger sequencing and MLPA did not reveal a mutation. For details see Tables 2 and 3.

Type of MRI Pattern

The cluster-type MRI pattern was not associated with a positive molecular screening for *CCM1-3* in any case. The scattered-type MRI pattern showed a positive genetic screening in 15 of 17 cases. This difference was statistically significant (Fisher's exact test, $p < 0.0001$).

The overall number of CCMs was lower in the cluster-

TABLE 4. Specifications of DVAs

Case No.	Location (IT vs ST)	No. of CVs	Stenosis	Angulated Course	Drainage (deep vs sup)	Size
1	Both	7	Yes	Yes	Deep	Large
2	ST	3	No	Yes	Sup	Large
3	IT	3	Yes	Yes	Both	Large
4	Both	2	No	Yes	Deep	Large
5	IT	1	Yes	Yes	Sup	Large
6	IT	1	Yes	No	Sup	Large
7	ST	1	Yes	Yes	Sup	Medium
8	ST	1	Yes	Yes	Deep	Medium
9	IT	3	Yes	Yes	Sup	Large
10	ST	1	Yes	No	Sup	Medium
11	Both	4	Yes	Yes	Both	Large

CV = collecting vein; IT = infratentorial; ST = supratentorial; sup = superficial.

FIG. 1. A scattered-type MRI pattern is shown. **A:** A 7-T T2-weighted image depicting multiple supratentorial CCMs in a typical popcorn-like appearance with hemosiderin rim (arrows). **B:** A 7-T SW image (minimum intensity projection) revealing additional small CCMs but normal underlying venous anatomy. This represents a typical example of a random-type pattern of multiple CCMs. **C and D:** Normal venous cortical (black arrows) and subcortical (white arrows) ultrastructures are shown. The CCMs appear as bubble-like lesions without larger outflow vessels.

type group compared with the random-type group (4.7 ± 1.5 vs 33.8 ± 48.5 ; Mann-Whitney U-test, $p = 0.07$). Other categorical variables (hemorrhage size > 10 mm and CCM type) showed no significant difference. Based on the rule of 3, the long-run probability to fail in the prediction of sporadic versus familial disease based on the MRI data of our sample is, from a mere statistical perspective, approximately 10.7% (95% CI).¹¹

Discussion

In this study, the MRI pattern of multiple CCMs

FIG. 2. A cluster-type MRI pattern is shown. **A:** 7-T T2-weighted images depicting multiple CCMs of the brainstem in a typical popcorn-like appearance with hemosiderin rim (white arrows). **B–D:** A 7-T SW images (minimum intensity projection) revealing the large underlying DVA with caput medusae formation. This represents a typical example of a cluster-type pattern of multiple CCMs. Note the completely disarranged venous architecture with enlarged venous radicles (C, white arrows) and angulated and stenosed (D, white arrow) collecting vein. DN = dentate nucleus.

clearly differed between suspected sporadic (negative genetic screening) and confirmed familial (positive genetic screening) forms of the disease. Disease distribution in suspected sporadic CCMs was limited to 1 or 2 regions of the brain, except in those patients with multifocal DVAs (Cases 1 and 11; Table 2). In confirmed familial disease, CCMs were distributed over multiple regions of the brain, except for 2 cases in which only a few lesions (2 and 4 CCMs, respectively) were present (Cases 2 and 7; Table 3). Accordingly, overall, fewer lesions were found in sporadic cases compared with familial cases. However, half of patients with confirmed familial disease showed a lesion burden of < 10 CCMs.

Most importantly, the presence of a typical DVA with the CCMs located in the draining territory of the collecting vein was associated with a negative genetic screening in all cases, indicating a sporadic disease. An associated typical DVA or local venous abnormality was not found in any of the confirmed familial cases. These differences were statistically significant. There was no difference in the number of lesions showing acute hemorrhage (Types Ia and Ib vs Types II, III, and IV) or in the size of the lesions between the 2 groups. Based on the repetitive patterns of distribution over the brain and association/nonassociation with DVA, we suggest naming the patterns cluster-type (sporadic form) and scattered-type (familial form).

FIG. 3. A schematic of scattered-type (A) and cluster-type (B) MRI patterns of multiple CCMs. Copyright Bixia Chen. Published with permission.

FIG. 4. Case illustration. A 7-T SWI image (minimum intensity projection) of multiple CCMs, localized to 1 hemisphere with normal underlying venous anatomy.

Our results indicate that in patients with cluster-type distribution, the existence of an underlying familial form of the disease is extremely unlikely. On the other hand, a scattered-type distribution is suggestive of familial disease. Still, in 2 cases of scattered-type MRI, routine genetic screening was negative for a *CCM1-3* mutation along with a negative family history. Interestingly, one of these patients (Case 9; Table 2) shows an extraordinary pattern of multiple CCMs exclusively localized to 1 hemisphere (Fig. 4). Such a pattern of distribution would be rather suggestive of an underlying somatic mutation. A somatic mutation occurs during development and propagates in subsequent tissues. Recently, McDonald et al. reported evidence for somatic mosaicism in a similar case.¹⁸

Nevertheless, for patients with scattered-type MRI, definite diagnosis of a germline mutation requires genetic analysis. Such analysis nowadays identifies increasing numbers of already published mutations but may also very rarely be hampered by diagnostic gaps. These gaps may be explained by the existence of undetected mosaicism, an additional fourth *CCM* gene,¹⁶ or deep intronic mutations that could activate alternative or cryptic splice sites.²³ These technical limitations are generally thought to be responsible for an underlying mutation remaining undiscovered.^{21,26,32} We attribute the negative genetic screening of Case 17 (Table 3) to such diagnostic gaps.

In our department, we still generally recommend genetic screening in patients with multiple CCMs, especially in younger patients or in families with symptomatic rela-

tives. On the other hand, we already inform patients about the lower probability of a familial disease if a cluster-type MRI pattern is shown.

The association of DVA and multiple CCMs in sporadic and familial cases has been reported before. The series of Mondéjar et al.,²¹ in which pathogenic mutations were screened for in familial and sporadic cases in Spain and Portugal, included 4 cases that presented multiple CCMs with associated DVA. None of these carried a pathogenic mutation in the *CCM* genes. The MRI study of Petersen et al.²⁵ reported a nonassociation of DVA in familial cases as well. However, the series included families with *CCM1/KRIT1* mutation only (genetic screening was not available in all patients), compiled both solitary and multiple lesions, and did not provide SWI or further analysis of MRI patterns.

Susceptibility-weighted imaging, especially when performed with high-field-strength MRI, is more sensitive for CCM lesions and DVA compared with clinical routine imaging (T2* weighted) and can be applied at submillimeter resolution.⁵ This minimizes the possibility of missing any vascular lesions. However, in the present study, relevant MRI data (detection of DVA and detection of CCM lesions) did not show a significant difference between 1.5-T and 7-T MRI, indicating that this information will be available from routine clinical protocols in most cases (at least for large or medium DVAs, as found in this study; very subtle DVAs may be missed at lower field strength). A clear advantage of SWI for the detection of DVAs is that no exogenous contrast agent is necessary.

Finally, our findings (cluster-type pattern) support previous assumptions that DVAs may be associated with the formation of sporadic CCMs, as judged by their systematic co-occurrence and close topographical relationship. There exist various reports of de novo CCM formation adjacent to the draining territory of a DVA.^{3,4,17} Furthermore, our own group has found systematic association of CCM and DVA in a consecutive series of sporadic, mainly solitary, lesions.⁶ These findings argue for a divergent pathogenesis of sporadic and familial CCMs.^{24,33} Awad et al. discussed this in further detail in their hemorrhagic angiogenic proliferation hypothesis.² According to the hypothesis, structural and hemodynamic conditions within the DVA are causative factors. In fact, in this series, we could confirm the presence of specific angioarchitectural factors of the DVAs (stenosis and angulated course of draining veins) that are believed to be involved in the formation of concurrent CCMs.¹²

In contrast, familial CCMs are derived from systematic endothelial dysfunction due to a loss-of-function mutation within *CCM1-3*; the most common form (*CCM1/KRIT1*) involves the RhoA and Rho kinase system.⁹ Pharmacological therapy affecting this system, a suggested future therapeutic option for familial cases,¹⁹ may thus not be suitable for the much more common sporadic cases.

Our study examines high-resolution SWI combined with genetic screening in a prospective consecutive series of patients with multiple CCMs for the first time. The main study limitation is a relatively small sample size. However, multiple CCMs are rare, accounting for only 15% of all CCMs, which generally leads to small series.

Conclusions

Our results indicate a systematic association of multiple CCMs with DVAs in the sporadic form of the disease. If such a cluster-type pattern is diagnosed on MRI, familial disease, with its severe clinical implications, thus seems rather unlikely. This is of high relevance in the counseling of patients. Especially when combined with routine genetic screening, the presence of these specific MRI patterns may therefore further ensure the diagnosis of a familial or sporadic disease in patients with multiple CCMs.

Finally, our results are consistent with the theory that DVAs are causative for the formation of (1 form of) sporadic CCMs, which has a significant impact on the natural history and treatment of the disease. Of course, because these findings are preliminary and based on a small sample size, they must be verified in future studies.

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Disclosures

The authors report no conflict of interest concerning the materi-

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Conception and design: Dammann Acquisition of data: Dammann, Wrede, Matsushige, Maderwald, Umutlu, Quick, Hehr, Rath, Ladd, Felbor. Analysis and interpretation of data: Dammann, Wrede, Zhu, Umutlu, Rath, Felbor. Drafting the article: Dammann, Wrede, Quick, Felbor, Sure. Critically revising the article: Zhu, Matsushige, Quick, Hehr, Ladd, Sure. Approved the final version of the manuscript on behalf of all authors: Dammann. Study supervision: Sure.

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