


LETTER TO THE EDITOR

Familial Pediatric Clear Cell Meningioma With Germline *SMARCE1* Mutation in the United States

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To the Editor:

Clear cell meningioma (CCM) is a rare subtype of meningioma with WHO grade II histology. It is seen in children and young adults and tends to occur in cerebello-pontine angle and cauda equina regions. It has been shown to exhibit aggressive pattern of recurrence. This report focuses on the familial form of CCM with germline *SMARCE1* mutation, which has not previously been reported from the United States. We investigated the occurrence of familial CCM around the world in order to understand its genetic inheritance, biology, and relationship with other familial syndromes.

A 6-year-old girl presented with chronic cognitive decline, subacute headaches, emotional lability, and acute onset syncope with blurry vision. MRI brain showed an enhancing tumor infiltrating the left prepontine area, extending into left cerebello-pontine angle along the brainstem and middle cranial fossa. She underwent a two-staged neurosurgical resection, and pathology was consistent with meningioma, WHO grade II, clear cell variant. Tumor cytogenetics (single nucleotide polymorphism) revealed 2 chromosome aberrations, a 95 Mb gain on 13q12.11q34 and a 62 Mb gain on 20p13q13.33 as well as 3 areas of absence of heterozygosity on chromosomes 5 and 17, encompassing the *TERT*, *NF1*, and some portions of *SMARCE1* gene.

Family history was significant for multiple intracranial meningiomas in the patient's 25-year-old mother, that was diagnosed and being managed at a different tertiary care center. We reviewed the mother's pathology diagnosis at our institute, which confirmed CCM. Given this information, our pathologist opted to pursue somatic *SMARCE1* mutation test on the patient's tumor, which was positive. A pediatric geneticist was consulted to investigate the germline origin of this pa-

thology. Germline *SMARCE1* testing revealed a pathogenic variant (c.525delT) in both the patient and her mother. Of note, previous germline analysis of the *NF2* and *SMARCB1* genes was negative.

Clinically, the patient had significant postoperative neurological deficits and suffered from progression of residual tumor one year from initial diagnosis requiring tumor debulking and focal radiosurgery of 30 Gray. The patient is currently undergoing follow-up and has stable disease 2 years since the progression. The patient's mother continues to receive care at another hospital and has had progressive disease but to date has deferred treatment.

This is the first case report of a familial pediatric CCM with germline *SMARCE1* mutation from the United States. Our patient has CCM, which is a rare variant of meningioma. Pediatric patients seem to have this variant more commonly than adults. Given that CCM is WHO grade II category, it is known to be more aggressive with tendency for recurrence compared with the classical variant. Our patient has already seen recurrence of her tumor needing resection and radiosurgery. This tumor has predilection to occur in the posterior fossa and lower spine.

There was a previously published case report from the United States in 2000 with a child and her mother both diagnosed with spinal CCM, but they were unable to conduct a germline linkage analysis (*NF* and *VHL* were excluded) (1).

Familial CCM is more commonly associated with germline *SMARCE1* (BAF57) gene mutations than germline *NF2* mutations. A United Kingdom case series has described familial CCM with germline *SMARCE1* mutation in 14% cases of solitary meningioma. They have identified cases of multiple spinal CCM, with the presence of somatic *SMARCE1* mutation, as well as germline *SMARCE1* mutation in 4 of the 9 families studied (2). The UK group also reported

TABLE. Familial Pediatric Clear Cell Meningioma With Germline *SMARCE1* Mutation Cases Around the World

Publication (Author Name, Country, Year)	Patients (Age/Age Range in Years)	Location of Tumor	Pathology (Microscopy, Molecular)	Comments
Smith MJ et al, United Kingdom, 2013 (2)	6 (15–27)	Spinal	CCM; <i>SMARCE1</i> loss in tumor in 2 patients	4 families with germline <i>SMARCE1</i> mutation in all patients.
Raffalli-Ebezant et al, United Kingdom, 2015 (3)	1 (14)	CP angle	CCM, <i>SMARCE1</i> loss in tumor and germline	First reported case; mother with same germline mutation and has suspected spinal meningiomas (nonbiopsied).
Smith MJ et al, United Kingdom, 2014 (4)	4 (2–30)	1 cranial, 4 spinal	CCM, <i>SMARCE1</i> loss in tumor in 2 patients	<i>SMARCE1</i> germline mutation in all patients, related to CCM histology, not tumor location. Incomplete penetrance of disease in males.
Gerkes EH et al, The Netherlands, 2016 (7)	2 (10, 36)	CP angle, spine	CCM, <i>SMARCE1</i> loss in tumor and germline in 1 patient	Paternal grandmother at age 36 had spinal CCM, dad carrier of <i>SMARCE1</i> germline mutation.
Inoue T et al, Japan, 2018 (6)	3 (5, 8, 34)	Spinal, CP angle	CCM, <i>SMARCE1</i> loss in tumor in 1 patient	<i>SMARCE1</i> germline mutation in all 3 patients who were part of single family.
Navalkele P et al, United States	2 (6, 25)	CP angle	CCM, <i>SMARCE1</i> loss in tumor and germline in both patients	Recurrent tumor; young mother with same tumor.

a case of 14-year-old girl with CP angle tumor, who underwent a two-stage resection without evidence of recurrence. She was found to carry a *SMARCE1* mutation by both somatic and germline analysis, making it the first case of *SMARCE1*-related intracranial CCM described in the literature. Her mother was also positive for this mutation (3). They also published another case series of both spinal and cranial *SMARCE1*-deficient CCM in individuals with germline *SMARCE1* mutation. This strengthened their assertion that CCM histology is a more accurate predictor of *SMARCE1* mutation status than the tumor location. In this series, they also identified at least one individual with asymptomatic spinal and cranial CCM following screening of family members. Their analysis revealed incomplete penetrance of this disease in males as evidenced by their report on a family with 2 affected female carriers and their unaffected father who also carried the familial *SMARCE1* mutation but did not develop CCM. Their data also demonstrated that in those who did develop CCM, it tends to affect younger pediatric patients in particular (4). The UK group has also conducted in-depth exploration of the *SMARCE1* mutation status leading to familial CCM and found that nonsense and frameshift mutations, especially in exon 6, tend to occur more frequently (5).

A Japanese study has described familial CCM in a single family with cases of both spinal and cranial (cerebello-pontine angle) *SMARCE1*-deficient tumors and a germline *SMARCE1* mutation (6).

A study from the Netherlands aimed to clarify concordance rate between disease manifestation and *SMARCE1* mutation status in cases of familial CCM through germline testing and screening of asymptomatic family members (7). Their methods included performing neurological exam and brain and full spine MRI every year until the age of 18 years and then every 3 years or sooner if symptoms arise. Standardized CCM screening in pediatric patients and young asymptomatic

family members is of paramount importance given the aggressive nature of this disease and the need to achieve safe maximal resection. As the penetrance of familial CCM is incomplete and the lifetime risk for familial CCM is unknown, further investigation is needed to determine appropriate screening for adults.

Somatic *SMARCE1* mutation has been described in breast, ovarian and prostate cancers. Germline *SMARCE1* mutation has been described in 14% of patients with CCM (Pathmanaban et al as described in reference [8]). *SMARCE1*-deficient familial syndrome so far afflicts the CNS, but its effect on other organ systems needs to be investigated in a systematic manner to determine if screening of additional organ systems is needed (7).

There are a number of familial syndromes associated with meningiomas, with neurofibromatosis type 2 (*NF-2*) being the most common. *NF2* gene mutation is also seen in 40%–60% of sporadic meningiomas and there seems to be predilection of hemispheric or lateral skull base location for meningiomas. Familial meningioma is also seen in 5% of patients with nevoid basal cell carcinoma syndrome (Gorlin syndrome) patients as a result of *SUFU* gene mutation, though *PTCH1* mutation is more commonly associated with the overall syndrome. Cowden syndrome and Cowden-like syndrome also have a propensity for meningioma development in 8% of patients with *AKT1* and *PI3KA* mutations. *WRN* mutations associated with Werner syndrome (adult progeria), also predisposes to familial meningioma at a younger age. Meningiomas (WHO grade II, malignant rhabdoid variant) are also part of the disease spectrum seen in *BAP1* tumor predisposition syndrome. *SMARCB1* (*INI1*) germline mutation results in rhabdoid predisposition syndrome and with specific predilection for meningioma of falx cerebri. Although mutations in these genes are uncommon in sporadic disease, with the exception of *NF2*, it has been suggested that

the study of the above genes could aid in clarifying the etiology of sporadic disease. In a comprehensive review of the known causes of hereditary meningioma, it was noted that many of these genes work in pathways that would play key roles in meningioma formation when mutated, such as those that control cellular proliferation, cell signaling, and DNA maintenance and repair. It was suggested that these pathways should be targeted in attempts to identify candidate genes as drivers in sporadic disease as well, which could lead to better understanding about the development and progression of sporadic disease (8).

A French study has found the use of *SMARCE1* antibody immunostaining to be quite sensitive in diagnosing loss of *SMARCE1* expression in CCM tumor cells. Tauziède-Espariat et al found this test to be specific for CCM alone in comparison to microcystic meningioma and variants that mimic CCM. This immunostain also stands alone as a sensitive test for CCM and correlates well with the targeted NGS for *SMARCE1* gene loss. This finding can make it a useful biomarker in routine practice for clear cell tumors, including CCM (9). This finding echoes the utility of studying hereditary causes of disease to aid in advances in diagnostics.

This review of familial cases from across the globe (Table), including the current case from the United States, highlights the role of molecular genetics in connecting recurrent pattern of tumor histology in familial setting to the genetic defect. Thus, *SMARCE1*-deficient hereditary CCM needs to be considered when more common defects, such as

NF2, are not identified during routine testing. Much work needs to be done to clarify the disease spectrum and presentation of *SMARCE1* syndrome by longitudinal follow-up of familial cohorts.

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