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SMARCE1-related meningiomas: A clear example of cancer predisposing syndrome

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ABSTRACT

We report the case of a 16-year-old girl presenting with spinal clear-cell multiple meningiomas (CCMs). In view of this presentation, we sequenced a bioinformatic panel of genes associated with susceptibility to meningioma, identifying a germline heterozygous variant in *SMARCE1*. Somatic DNA investigations in the CCM demonstrated the deletion of the wild-type allele (loss of heterozygosity, LOH), supporting the causative role of this variant. Family segregation study detected the *SMARCE1* variant in the asymptomatic father and in the asymptomatic sister who, nevertheless, presents 2 spinal lesions. Germline heterozygous loss-of-function (LoF) variants in SMARCE1, encoding a protein of the chromatin-remodeling complex SWI/SNF, have been described in few familial cases of susceptibility to meningioma, in particular the CCM subtype. Our case confirms the role of NGS in investigating predisposing genes for meningiomas (multiple or recurrent), with specific regard to *SMARCE1* in case of pediatric CCM. In addition to the age of onset, the presence of familial clustering or the coexistence of multiple synchronous meningiomas also supports the role of a genetic predisposition that deserves a molecular assessment. Additionally, given the incomplete penetrance, it is of great importance to follow a specific screening or follow-up program for symptomatic and asymptomatic carriers of pathogenic variants in *SMARCE1*.

1. Introduction

Meningiomas are the most frequent neoplasm of the central nervous system (CNS) (Ostrom et al., 2021a). Their current WHO classification comprises fifteen subtypes and integrates histological features, histological subtypes and molecular analysis to establish three possible grades (grade 1/2/3) which correlate with the disease evolution and biological behavior (Louis et al., 2021; Central Nervous System Tumours, 2021). Overall, about 80% of meningiomas are slow-growing and histologically benign (grade1) whereas the remaining 20% demonstrate an increased proliferative activity and malignant morphology (grade 2/3) (Harter et al., 2017). As for other CNS cancers, the employment of new molecular testing is expected to improve the delineation of recurrence risk and prognosis (Maas et al., 2021; Nassiri et al., 2021; Sahm et al., 2017). Meningiomas originate from arachnoid cells and show a more prevalent intracranial than spinal localization (Ostrom et al., 2021a; Central Nervous System Tumours, 2021). The clinical presentation may vary depending on the site and the size of the lesion, possibly including headache, focal neurological deficit, seizures, cognitive decline, local pain, weakness, dysesthesia (Magill et al., 2018).

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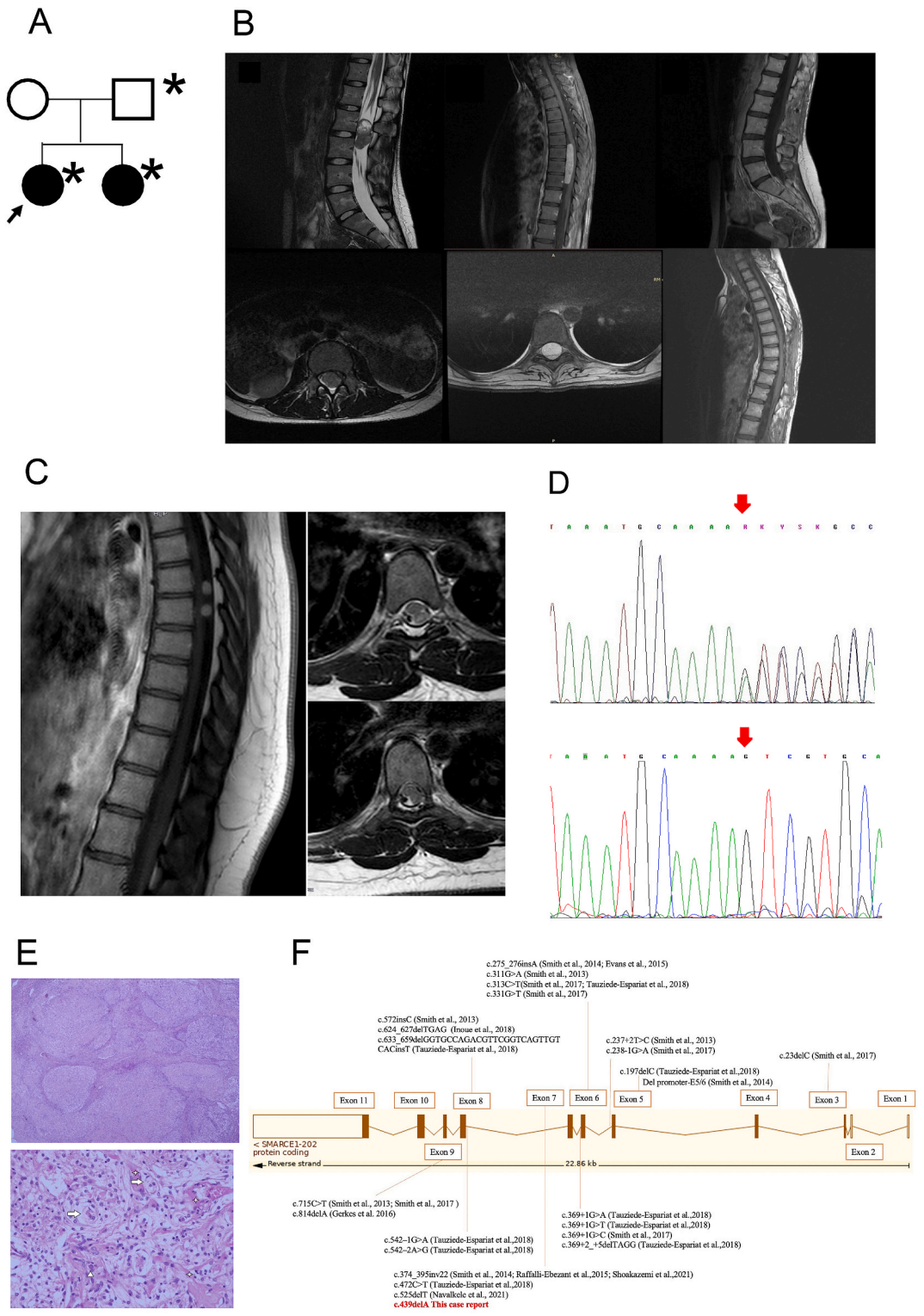

Fig. 1. A. Pedigree of the family CCM with the SMARCE1 mutation. Filled symbol for CCM affected and asterisks for mutation carriers.
B. Proband's MRI, from left to right: preoperative sagittal and axial MRI T2 weighted sequence showing L2L3 intradural tumor, occupying all the spinal canal; after surgical removal of the lumbar tumor, patient received a whole spine MRI showing a second cranial intradural tumor, compressing and dislocating posteriorly the spinal cord at D9-D11 level; final post-op sagittal MRI after surgical removal of both tumors.
C. Sister of the proband's MRI: sagittal MRI T1 weighted with CM and axial T2 weighted showing two spinal meningiomas.
D. Sanger sequencing of exon 7 of *SMARCE1* gene: in peripheral blood (above) it showed the variant c.439delA (p.Ser147fs) in heterozygosity; in the CCM bioptic sample (below) it showed a loss of heterozygosity (LOH) of the wild-type allele and the variant c.439delA (p.Ser147fs) in hemizygosis.
E. Histopathological examination of the spinal lesion of the proband: Neoplastic cells with clear vacuolated cytoplasm and spindled to roundish bland-appearing nuclei (above) arranged in nodular structures separated by thick fibro vascular septs (below); collagen bundles (asterisks) in the interstitial spaces (above); cellular whorls (arrows) and small psammoma body (head of the arrow) (above). H&E; original magnification 20×, 2×.
F. Pathogenetic variants of *SMARCE1* described to be associated with meningiomas.

The incidence of meningiomas increases with age, particularly over 65 years. The sex ratio is significantly skewed towards females (3:1), who are also more prone to develop non-malignant lesions (Ostrom et al., 2021a; Central Nervous System Tumours, 2021).

In childhood meningiomas are rare entities representing from 0.4% to 4.6% of primary CNS tumors (Ostrom et al., 2021a; Gao et al., 2009). Also the female-to-male ratio is different, being 1:1.9 or 1.6:1 before and after puberty, respectively. Moreover, some aggressive subtypes and the spinal localization are enriched in the pediatric population, on which the incidence of spinal tumors is 13% compared to approximately 4% in adults (Dudley et al., 2018). These epidemiological and biological differences suggest that adult and pediatric meningioma may account for distinct etiological mechanisms. Indeed, as for many other malignancies (Byrjalsen et al., 2020), pediatric meningiomas may be caused in a higher proportion by an underlying germinal pathogenic variant. Historically, the first condition associated with meningiomas was neurofibromatosis 2 (OMIM #101000) (Perry et al., 2001; Goutagny and Kalamarides, 2010). Germinal haploinsufficiency of the *NF2* gene is the most frequent genetic finding identified in familial meningiomas (Central Nervous System Tumours, 2021; Evans et al., 2005). In recent years a variable predisposition to meningiomas has been described for several other genes, among which *SMARCB1*, *SMARCE1*, *BAP1*, *PTCH1*, *SUFU*, *PDGFB, CREBBP*, *WRN*, *MEN1* (Lee and Lee, 2020; Kerr et al., 2018). A correlation with a specific histological subtype has been established for some of them. This is the case of the gene *SMARCE1*, whose involvement has been pointed out for the clear cell meningioma subtype (CCM) (Smith et al., 2013; Tauziede-Espariat et al., 2018; Sievers et al., 2021). This gene is located within the cytoband 17q21.2 and encodes the protein BAF57, an ATP-dependent component of the chromatin remodeling complex SWI/SNF. As for other genes belonging to this machinery, also *SMARCE1* exhibits allelic heterogeneity: germinal heterozygous pathogenic missense variants lead to the Coffin-Siris syndrome (CSS type 5, OMIM #616938) whereas germinal heterozygous pathogenic loss-of-function (LoF) variants cause familial susceptibility to CCM (OMIM #607174). The CCM subtype (grade 2) is rather rare, representing 0.3% of intracranial meningiomas and 1.4% of spinal meningiomas (Li et al., 2016). Moreover, it shows a preferential localization at the spine or cerebellopontine angle, an aggressive behavior with a tendency to relapse and a higher incidence in childhood and early adulthood (Central Nervous System Tumours, 2021; Li et al., 2016, 2019; Tao et al., 2018; Soni et al., 2021; Zhang et al., 2017, 2020; Rahman et al., 2021); for this latter point a few studies have found a mean age of diagnosis in middle adulthood (Soni et al., 2020; Wang et al., 2020; Zhang et al., 2018; Li et al., 2018), albeit still lower than what is generally reported for meningiomas.

In this report we describe the case of a 16-year-old girl presenting with spinal CCM multiple meningiomas. Whole exome sequencing (WES) coupled with a *in silico* tailored bioinformatic panel identified a pathogenic variant in *SMARCE1*. Further investigations on the somatic DNA highlighted the deletion of the wild-type allele due to an event of loss of heterozygosity (LOH), further supporting the causative role of this variant.

2. Methods

To histological purposes, the surgical specimen was routinely fixed in neutral buffered formol and embedded in paraffin. Some 5 μm sections were stained with hematoxylin and eosin (H&E) for the morphologic evaluation, whereas further 5 μm sections were mounted on electrostatic slides and used for the immunohistochemical analyses (standard avidin-biotin complex immunoperoxidase method and commercially available antibodies: Vimentin clone V9 Ventana-Roche, Tucson Arizona; EMA clone E29 and Ki67 clone MIB-1 DAKO, Carpinteria, California).

All genetic investigations were conducted in the diagnostic setting and after written consent.

Peripheral blood genomic DNA samples were extracted according to the manufacturer's instructions (QIAsymphony® DSP DNA, Qiagen, Hilden, Germania), and 4–5 paraffin-embedded (FFPE) tissue sections (5-μm-thick) DNA of meningioma were extracted with DNA MagCore Automated Nucleic Acid Extraction HF 16 Plus (RBC Bioscience Corp., New Taipei City, Taiwan).

Whole Exome Sequencing (WES) DNA libraries were constructed, using a strategy based on enzymatic fragmentation followed by End repair, A-tailing, adapter ligation, and library amplification (Kapa Biosystems, Wilmington, MA), and they were hybridized with the protocol SeqCap EZ Exome v3 (Nimblegen, Roche, Basel, Switzerland), and sequenced by NextSeq550 (Illumina Inc., San Diego, CA). Reads alignment (Burrows-Wheeler Aligner, BWA), variants call (Genome Analysis ToolKit Unified Genotyper Module, GATK), annotation (Annotate Variation, ANNOVAR) and variants prioritization were performed using *in house* strategy according to with American College of Medical Genetics and Genomics (ACMG) guidelines (Nykamp et al., 2017). We assessed WES analysis by using a gene panel including 8 genes associated with familial susceptibility to meningioma with autosomal dominant inheritance (#607174): *NF2* (NM_000268.3), *SMARCB1* (NM_003073.4), *BAP1* (NM_004656.3), *SUFU* (NM_016169.3), *SMARCE1* (NM_003079.4), *MN1* (NM_002430.2), *PDGFB* (NM_002608.3) and *PTEN* (NM_000314.6).

Variants were confirmed by Sanger sequencing and primers were designed using Primer3Plus (www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi/) and PCR products were purified with ExoSAP-it (Thermo Fisher Scientific, Waltham, MA, USA), sequenced using Big Dye Terminator Cycle Sequencing Kit v3.1 Kit (Applied Biosystems, Foster City, CA, USA) and analyzed on an automated sequencer (ABI 3500Dx Genetic Analyzer, Applied Biosystems).

3. Results

The proband is a 16-year-old girl who presented with progressive weakness of the lower limbs associated with painful tactile hypoesthesia, lumbar pain, paresthesia and dysesthesia in the right lower limb (thigh/leg in the territory of L2/L3). Her neurological picture progressively worsened leading to the inability to stand and walk. A magnetic resonance imaging (MRI) of the lumbar and sacral spine highlighted an intradural extramedullary cystic and necrotic spinal tumor at the level of L2/L3 with a maximum diameter of 42 mm (Fig. 1B), suggestive in the first instance for a schwannoma of the cauda equina. She underwent L2 laminectomy and complete removal of the spinal lesion. Histopathological examination showed a proliferation of cells with clear cytoplasm and spindled to roundish bland-appearing nuclei with dispersed chromatin and inconspicuous nucleoli. Neoplastic cells were arranged in nodules separated by thick fibro vascular septa. Rare cellular whorls and psammoma bodies were present. Thick collagen bundles were visible in the interstitial spaces. Mitotic activity was inconspicuous. On immunohistochemistry, tumor cells were positive for EMA and vimentin. Ki-67 index was 3–5%. The diagnosis of CCM was then achieved. A postoperative lumbar spine MRI with contrast demonstrated a complete removal of the CCM without complications. The postoperative period was uneventful and in the following days her neurological symptoms ameliorated.

One month later, after complete recovery she presented dorsal backache. This time a cerebral and whole-spine MRI was carried out, showing a second D7-D10 intradural-extramedullary lesion, resembling the lumbar lesion previously removed. She was readmitted and underwent a Th9-11 laminectomy with ablation of the tumor, which was histologically confirmed to be a CCM. The proband was treated with anti-VEGF bevacizumab 7.5 mg/kg every 21 days for 8 months. This therapeutic choice was reached based on preliminary evidence of the slowing effects of bevacizumab on tumoral growth in small cohorts of patients with recurrent and refractory meningiomas (Yust-Katz et al., 2016; Franke et al., 2018; Kumthekar et al., 2022; Goldbrunner et al.,

Table 1
Overview of the SMARCE1-related pedigrees currently reported.

		Sex	Age of onset of symptoms and/or diagnosis	Germinal variants in *SMARCE1*	Protein	Number of lesions	Single or multiple lesions	Localization	Histological type	Somatic variants in *SMARCE1*
Proband	Pa	F	16 y AO	c.439delA	p.Ser147fs	2	M	Spinal	CCM	M2: c.439delA + LOH
Father	Pb	M	49 y AD	c.439delA	p.Ser147fs	0	/	/	/	/
Sister	Pc	F	15 y AD	c.439delA	p.Ser147fs	2	M	Spinal	NN	NN
Smith et al. (2013)	P1	F	27 y AO	c.715C > T	p.Arg239*	2	M	Spinal		NN
	P2	F	15 y AO	c.715C > T	p.Arg239*	1	S	Spinal		NN
	P3	F	30 y AO	c.237+2 T > C	p.?	2	M	Spinal		NN
	P4	F	26 y AO	c.237+2 T > C	p.?	3	M	Spinal		NN
	P5	M	26 y AO	c.311G > A	p.Trp104*	2	M	Spinal	CCM	M1: c.311G > A heterozygous M2 c.311G > A + LOH
	P6	F	17 y AO	c.572insC	p.Thr191Thrfs*14	1	S	Intracranial		c.572insC heterozygous
Smith et al. (2014)	P1	M	7 y AO	NN	NN	1	S	Spinal		c.624_627delTGAG, p.(Ser208Argfs*26) + LOH
	P2	F	22 y AO	NN	NN	1	S	Intracranial		c.357C > G, p.(Tyr119*) + LOH
	P3	M	10 y AO	NN	NN	1	S	Intracranial		c.688C > T, p.(Gln230*) + LOH
	P4	M	8 y AO	NN	NN	1	S	Spinal		Del promoter-E5/6 + LOH
	P5	M	2 y AO	c.275_276insA	p.Leu93Valfs*17	1	S	Spinal		c.275_276insA, p.Leu93Valfs*17 + LOH
	P6	F	14yAO	c.374_395inv22	p.(Glu125_Ala132 delinsGlyLeuHisArg PhelleValLeu)	1	S	Intracranial		c.374_395inv22, p.(Glu125_Ala132delins GlyLeuHisArgPhelleValLeu) + c.267delT, p.(Asp90Thfs*2)
	P7	F	NN	c.374_395inv22	p.(Glu125_Ala132 delinsGlyLeuHisArg PhelleValLeu)	2	M	Spinal, intracranial	NN	NN
	P8	M	17 y AD	c.374_395inv22	p.(Glu125_Ala132 delinsGlyLeuHisArg PhelleValLeu)	0	/	/	/	/
	P9	F	17 y AO	Del promoter-E5/6	No protein product	1	S	Spinal		Del promoter to E5/6 + c.757C > T, p.(Gln253*)
	P10	M	71 y AD	Del promoter-E5/6	No protein product	0	/	/	/	/
	P11	F	30 y AO	Del promoter-E5/6	No protein product	1	S	Spinal	NN	NN
	P12	F	25 y AO	Del promoter-E5/6	No protein product	2	M	Spinal, intracranial	NN	NN
Raffalli-Ebezant et al. (2015)	P1[a]	F	14 y AO	c.374_395inv22	p.(Glu125_Ala132 delinsGlyLeuHisArg PhelleValLeu)	1	S	Intracranial	CCM	c.374_395inv22, p.(Glu125_Ala132 delins GlyLeuHisArgPhelleValLeu) + c.267delT, p.(Asp90Thrfs*2)
	P2[a]	F	NN AD	c.374_395inv22	p.(Glu125_Ala132 delinsGlyLeuHisArg PhelleValLeu)	>1	M	Spinal Intracranial?	NN	/
Evans et al. (2015)	P1[b]	M	3 y AO ?	c.275_276insA	p.Leu93Valfs*17	1	S	Spinal	CCM	c.275_276insA, p.Leu93Valfs*17 + LOH
Gerkes et al. (2016)	P1	M	10 y AO	c.814delA	p.Arg272Glyfs*5	1	S	Intracranial		c.814delA, p.(Arg272Glyfs*5) + LOH
	P2	M	47 y AD	c.814delA	p.Arg272Glyfs*5	0	/	/		/
	P3	F	36 y AO	c.814delA	p.Arg272Glyfs*5	1	S	Spinal		/
	P4	M	5 y AD	c.814delA	p.Arg272Glyfs*5	0	/	/		/
	P5	F	12 y AD	c.814delA	p.Arg272Glyfs*5	0	/	/		/
	P6	F	39 y AD	c.814delA	p.Arg272Glyfs*5	0	/	/		/
Smith et al. (2017)	P1	M	16 y AO	c.238-1G > A	p.(?)	1	S	Intracranial	CCM	c.238-1G > A,p.(?) + c.957delC,p.(Pro320Leufs*122)
	P2	M	11 y AO	c.369+1G > C	p.(?)	1	S	Intracranial	CCM	c.369+1G > C,p.(?) + LOH
	P3	F	33 y AO	c.715C > T	p.(R239*)	1	S	Spinal	CCM	c.715C > T,p.(R239*) + LOH
	P4	F	19 y AO	c.23delC	p.(Pro9Hisfs*62)	1	S	Spinal	CCM	c.23delC,p.(Pro9Hisfs*62) + c.689_698delinsCCAGT,p.(Gln230Profs*13)
	P5	F	30 y AO	c.331G > T	p.(E111*)	1	S	Intracranial	CCM	c.331G > T,p.(E111*) + LOH

(*continued on next page*)

Table 1 (*continued*)

		Sex	Age of onset of symptoms and/or diagnosis	Germinal variants in *SMARCE1*	Protein	Number of lesions	Single or multiple lesions	Localization	Histological type	Somatic variants in *SMARCE1*
	P6	F	10 y AO	c.313C > T	p.(R105*)	1	S	Spinal	CCM	c.313C > T,p.(R105*) + c.831delA,(p.Lys277Lys*1)
Tauziede-Espariat et al. (2018)	P1	F	13 y AO	c.542–2 A > G	p.?	1	S	Intracranial	CCM	c.542–2 A > G, p.? + c.715C > T, p.(Arg239*)
	P2	F	18 y AO	c.472C > T	p.(Arg158*)	1	S	Intracranial	CCM	c.472C > T, p.(Arg158*) + c.925_929delGAGCA,p.(Glu309Serfs*2)
	P3	F	7 y AO	c.369+1G > A	p.?	1	S	Intracranial	CCM	c.369+1G > A, p.? + LOH by whole gene deletion
	P4	F	23 y AO	c.197delC	p.(Pro66Glnfs*5)	2	M	Intracranial, spinal	CCM	M1: c.197delC, p.(Pro66Glnfs*5) + LOH by isodisomy M2: c.197delC, p.(Pro66Glnfs*5) + c.624_627delTGAG,p.(Ser208Argfs*26)
	P5	M	72 y AO	c.542–1G > A	p.?	1	S	Intracranial	CCM	c.542–1G > A, p.? + c.547_548delGA, p.(Asp183*)
	P6	M	20 y AO	c.313C > T	p.(Arg105*)	1	S	Intracranial	CCM	c.313C > T, p.(Arg105*) + c.36911G > T, p.?
	P7	M	41 y AO	c.369+1G > T	p.?	1	S	Intracranial	CCM	c.369+1G > T, p.? + c.458 T > G, p.(Leu153*)
	P8	M	61 y AO	c.633_659del GGTGCCA GACGTTCGGTCAGTTGTCAC insT	p.(Val212Asnfs*3)	1	S	Intracranial	CCM	c.633_659delGGTGCCA-GACGTTCGGTCAGTTGTCACinsT,p.(Val212Asnfs*3) + LOH by whole gene deletion
	P9	M	45 y AO	c.369 + 2_+5delTAGG	p.?	1	S	Intracranial	CCM	c.369 + 2_+5delTAGG, p.? + c.370–4delTT, p.?
Inoue et al. (2018)	P1	M	5 y AO	c.624_627delTGAG	p. (Ser208Argfs*26)	1	S	Spinal	CCM	
	P2	M	34 y AO	c.624_627delTGAG	p. (Ser208Argfs*26)	1	S	Intracranial	CCM	
	P3	F	14 y AO	c.624_627delTGAG	p. (Ser208Argfs*26)	1	S	Intracranial	CCM	
Shoakazemi et al. (2021)	P1[a]	F	NN	c.374_395inv22	p.Glu125_Ala132del-insGlyLeuHis	1	S	Intracranial	CCM	
	P2[c]	M	17 y AD	c.374_395inv22	p.Glu125_Ala132del-insGlyLeuHis	2	M	Spinal, intracranial	CCM	
	P3[a]	F	NN	c.374_395inv22	p.Glu125_Ala132del-insGlyLeuHis	4	M	Spinal, intracranial	NN	
	P4	M	63 y AO	c.374_395inv22	p.Glu125_Ala132del-insGlyLeuHis	1	S	Spinal	CCM	
Navalkele et al., (2021)	P1	F	6 y AO	c.525delT	p.Ala176LeufsTer13	1	S	Intracranial	CCM	95 Mb gain on chr 13, 62 Mb gain on chr 20, 3 areas of LOH on chr 15 and 17 (*SMARCE1*)
	P2	F	25 y AD	c.525delT	p.Ala176LeufsTer13	>1	M	Intracranial	CCM	

F Female.
M Male.
AO Age of onset of symptoms and diagnosis.
AD Age of diagnosis in asymptomatic family members.
NN unknown.
S Single lesion.
M Multiple lesions.
CCM Clear Cell Meningioma.
M1 first meningioma.
M2 second meningioma.

[a] Previously reported in Smith et al., 2014 as P6 and P7.
[b] Previously reported in Smith et al., 2014 as P5.
[c] Previously reported as asymptomatic P8 in Smith et al., 2014.

2021).

As the second CCM was identified only a month after the first one, it was very likely that they were synchronous CCMs. Given this co-occurrence, in addition to the young age, a genetic consultation was required. Family history revealed that the mother had removed two melanomas whereas the physical examination of the proband was normal. We offered to investigate the case by means of WES and, after exhaustive counselling, the girl and her parents consented. WES was performed as singleton due to the temporary absence of one of the parents. Quality control of WES showed that 91% of the targeted regions were covered by $\geqq 30\times$ reads with an average depth of 89x. Phenotype-driven gene panel analysis identified in the proband the heterozygous variant NM_003079.4: c.439delA; p.(Ser147fs*7) in exon 7 of *SMARCE1* (Clinvar VCV001740283.2). This variant is not reported in HGMD (The Human Gene Mutation Database) and is absent from the main population databases. Moreover, the Sanger sequencing of the bioptic CCM sample demonstrated a hemizygous status of c.439delA due the deletion of the wild-type allele (loss of heterozygosity, LOH).

Given the high confidence in the pathogenicity of this variant, this result posed a diagnostic dilemma for the proband's relatives as the segregation analysis implied predictive testing for CCMs. After extensive counselling, the parents agreed to be tested and the variant resulted to be transmitted from the healthy father; at the age of 49 years he recently underwent a whole-spine MRI which resulted normal. We counselled the family also regarding the proband's younger sister, who had a 50% risk of having inherited the variant. She and her parents decided to perform the segregation analysis, which identified the presence of the c.439delA variant also in her. A cranial and whole-spine MRI of the proband's sister was then performed, revealing little and asymptomatic spinal meningiomas at different levels. A follow-up program with a whole-spine MRI every four months was proposed to the proband's sister, but at the first revaluation disease progression was ascertained and medical treatment with anti-VEGF bevacizumab 7.5 mg/kg every 21 days was administered.

4. Discussion

Pediatric meningioma are rare tumors, accounting for 2,5% of all primary CNS malignancies in childhood (Ostrom et al., 2021b). Increasing evidence suggests that tumor occurrence in the pediatric population may imply a cancer predisposing syndrome (CPS) due to an underlying pathogenic germinal variants (Zhang et al., 2015; Sylvester et al., 2018; ICGC PedBrain-Seq Project ICGC MMML-Seq Project Gröbner et al., 2018). The molecular diagnosis can impact the clinical management, direct towards tailored therapies and be of extraordinary relevance for relatives. Different checklists or tools have been developed to help the physician to recognize such cases. Family history, cancer histology, somatic genetic findings, multiple malignancies, the co-occurrence with congenital anomalies and unexpected side effects after chemotherapy or radiotherapy are all clues for CPS (Jongmans et al., 2016; Goudie et al., 2017; Postema et al., 2017; Ripperger et al., 2017). Eventually, the appropriateness of genetic testing must be individualized, and to this end multidisciplinary management should include a genetic evaluation (Ripperger et al., 2017). Indeed, the family history may be silent, either due to *de novo* variants whose overall contribution in CPS is not defined yet (Kuhlen et al., 2019), or to incomplete penetrance. Moreover, as the field of CPS in childhood is quite recent, many conditions may not have been characterized yet.

Pediatric meningiomas are enlisted among malignancies to be always referred to exclude a CPS (Postema et al., 2017). It has long been known that isolated meningioma could be the onset sign of NF2 (Evans et al., 1999). Recent prospective data revealed that 38.1% of individuals aged 1–24 years with isolated meningioma were carrier of a CPS, of which 16.7% were *NF2*-related and 21.4% *SMARCE1*-raleted (Pathmanaban et al., 2017). Following the first report in 2013 (Smith et al., 2013), germinal LoF *SMARCE1* variants associated with CCMs were identified in few other papers (Table 1) (Tauziede-Espariat et al., 2018; Smith et al., 2014, 2017; Evans et al., 2015; Raffalli-Ebezant et al., 2015; Gerkes et al., 2016; Inoue et al., 2018; Navalkele et al., 2020; Shoakazemi et al., 2021). Our case recapitulates current challenges in the diagnostic process of pediatric meningioma. As the second CCM of the proband was detected only one month after the first resection, the two CCMs were very likely synchronous. This remark highlights the importance of performing whole-spine MRI to rule out multiple localizations, which are present in 7%–16% of individuals (Rahman et al., 2021) with CCMs and in 24% of germinal LoF *SMARCE1* variants carriers, and eventually introduce adjuvant therapy. The rapid recourse to genetic testing was prompted by the presence of multiple lesions, specific histotypes and suggestive family history, the latter eventually not linked to CCM pathogenesis.

The majority of carriers of a *SMARCE1* pathogenic variant had a positive family history consistent with an autosomal dominant predisposition to CCMs, although with incomplete penetrance (Smith et al., 2013; Gerkes et al., 2016); of the 45 subjects described so far, 88.8% have lesions that are MRI detectable. For those with an *a priori* negative family history, the segregation analysis revealed that the causative variant was inherited and somewhat penetrant in the kindred (Raffalli-Ebezant et al., 2015; Gerkes et al., 2016). Moreover, as already pointed out by other papers concerning *SMARCE1*-related CCM (Gerkes et al., 2016) (penetrance of 85% in males and 92% in females), an increased penetrance in female carriers is appreciable in our kindred as well, given the full penetrance of the two young sisters compared to the CCM-free 49-year-old father.

SMARCE1 appears to be intrinsically related to CCMs, as somatic variants are often identified in bioptic samples and loss of staining for BAF57/SMARCE1 at immunohistochemistry (IHC) represents a consistent and specific diagnostic marker for CCMs (Tauziede-Espariat et al., 2018; Sievers et al., 2021; Smith et al., 2017). In our case we could confirm the somatic *SMARCE1* LOH in the second CCM of the proband. Finally, the molecular diagnosis enabled us to provide the family an accurate counselling and extend segregation analysis to first-degree relatives, leading to the presymptomatic diagnosis and treatment of CCMs in the younger sister. As for treatment, although any tailored treatment for *SMARCE1*-related CCMs has not been validated yet, in our case the proband had no relapses after eighteen months of treatment with bevacizumab whereas for her sister whole-spine MRI documental CCMs stability after eight months of the same treatment.

In conclusion, the characterization of germline *SMARCE1*-related CCMs have allowed the early identification of high-risk subjects and the implementation of a tailored surveillance program.

CRediT authorship contribution statement

Erika Fiorentini: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Laura Giunti:** Resources, Data curation, Validation. **Andrea Di Rita:** Writing – original draft. **Simone Peraio:** Writing – original draft. **Carla Fonte:** Writing – review & editing. **Chiara Caporalini:** Resources. **Anna Maria Buccoliero:** Resources, Writing – review & editing. **Maria Luigia Censullo:** Investigation. **Giulia Gori:** Writing – review & editing. **Alice Noris:** Resources. **Rosa Pasquariello:** Investigation. **Roberta Battini:** Investigation. **Rossana Pavone:** Resources. **Flavio Giordano:** Conceptualization, Writing – original draft. **Sabrina Giglio:** Conceptualization, Writing – original draft. **Berardo Rinaldi:** Conceptualization, Writing – review & editing, Supervision.

Data availability

Data will be made available on request.

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