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Germline *SUFU* mutation carriers and medulloblastoma: clinical characteristics, cancer risk, and prognosis

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Abstract

Background. Germline mutations of suppressor of fused homolog (*SUFU*) predispose to sonic hedgehog (SHH) medulloblastoma. Germline *SUFU* mutations have been reported in nevoid basal cell carcinoma syndrome (NBCCS), but little is known about the cancer risk and clinical spectrum.

Methods. We performed a retrospective review of all patients with medulloblastoma and a germline *SUFU* mutation in France.

Results. Twenty-two patients from 17 families were identified with medulloblastoma and a germline *SUFU* mutation (median age at diagnosis: 16.5 mo). Macrocrania was present in 20 patients, but only 5 met the diagnostic criteria for NBCCS. Despite treatment with surgery and chemotherapy, to avoid radiotherapy in all patients except one, the outcome was worse than expected for SHH medulloblastoma, due to the high incidence of local relapses (8/22 patients) and second malignancies (n = 6 in 4/22 patients). The 5-year progression-free survival and overall survival rates were 42% and 66%. Mutations were inherited in 79% of patients, and 34 additional *SUFU* mutation carriers were identified within 14 families. Medulloblastoma penetrance was incomplete, but higher than in Patched 1 (*PTCH1*) mutation carriers. Besides medulloblastoma, 19 other tumors were recorded among the 56 *SUFU* mutation carriers, including basal cell carcinoma (BCC) in 2 patients and meningioma in 3 patients.

Conclusion. Germline *SUFU* mutations strongly predispose to medulloblastoma in the first years of life, with worse prognosis than usually observed for SHH medulloblastoma. The clinical spectrum differs between *SUFU* and *PTCH1* mutation carriers, and BCC incidence is much lower in *SUFU* mutation carriers. The optimal treatment of *SUFU* mutation–associated medulloblastoma has not been defined.

Keywords

germline *SUFU* mutations | infant | medulloblastoma | predisposition

Importance of the study

Germline *SUFU* mutations were described in patients with medulloblastoma for the first time in 2002 and are currently a matter of increasing interest. This condition may concern about 20% of all infants with SHH medulloblastoma. However, little is known about the clinical characteristics, risk of cancer, and prognosis of patients with germline *SUFU* mutations. Similarly, the optimal treatment for *SUFU* mutation–associated medulloblastoma has not been defined yet. In this manuscript, we report the largest cohort to date (22 patients with medulloblastoma and *SUFU* germline mutation from 17 families). Systematic molecular classification of the medulloblastoma at diagnosis should increase the discovery rate of patients with *SUFU* germline mutations. The findings of our report could have a major impact on the management of these patients and on genetic counseling.

Medulloblastomas are a composite group of tumors with distinct cells of origin as well as biological and clinical characteristics. Advances in molecular profiling have allowed the identification of 4 medulloblastoma subgroups: wingless (WNT), sonic hedgehog (SHH), Group 3, and Group 4.[1–7] The SHH subgroup is more frequent in young children (<3 y) and in adults, and is commonly associated with the desmoplastic/nodular histological subtypes (>50% of SHH medulloblastoma).[2] Genome sequencing of SHH medulloblastoma samples led to the identification of mutually exclusive somatic alterations in the Patched 1 (*PTCH1*),[8,9] suppressor of fused (*SUFU*),[10–13] and Smoothened (*SMO*)[14] genes. Moreover, a large proportion of somatic *SUFU* mutations are associated with germline mutations (6 of the 8 concerned patients in a large series of 133 patients with medulloblastoma). Conversely, only a small proportion of somatic *PTCH1* mutations (3%) are also present in the germline.[15]

Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome (NBCCS), has been described as a cancer-predisposition syndrome for medulloblastoma associated with *PTCH1* germline mutations.[16,17] Affected individuals show phenotypic abnormalities and high risk of developing multiple basal cell carcinoma (BCC).[18] NBCCS diagnostic criteria have been recently described by Jones et al (see Supplementary Table S1).[9,18–20]

Germline *SUFU* mutation has been identified more recently as a genetic condition that predisposes to medulloblastoma,[10] particularly to desmoplastic/nodular medulloblastoma[15,21] and almost exclusively in children before the age of 3 years. Thus far, a limited number of pediatric patients with medulloblastoma and a germline *SUFU* mutation have been described: 11 by different authors (Table 1) and 13 by our group.[10,12,13,21–27] Moreover, germline *SUFU* mutations have also been detected in 8 adult patients with NBCCS, but without personal or family history of medulloblastoma.[23,24,28] This suggests an overlapping between NBCCS and germline *SUFU* mutations.

The aim of the present study was to describe medulloblastoma outcome in patients with germline *SUFU* mutations, as well as the clinical features and tumors associated with this genetic abnormality in order to better define the risks associated with these mutations.

Patients and Methods

Patients

We reviewed the clinical files, molecular data, and family history of all patients with medulloblastoma and germline *SUFU* mutation ($n = 22$) identified in France by the 2 reference genetics laboratories (Gustave Roussy and Institut Curie). The indication for germline *SUFU* mutation screening varied according to the center and period. Nevertheless, it was proposed systematically to patients with a medulloblastoma diagnosed before the age of 5 years and to patients with an SHH medulloblastoma and chromosome 10q loss of heterozygosity (LOH) in the tumor. Written informed consent was obtained for the genetic analysis during a genetic counseling consultation, according to good clinical practice guidelines. Blood samples were collected from the probands and all family members who agreed to the genetic testing. The family history of cancer was explored whenever possible. Clinical examination and dermatological screening were offered to all *SUFU* mutation carriers. A review of the available radiological exams was performed to detect radiological patterns included in the NBCCS criteria (see Supplementary Table S1).

Tumor Analysis

The most representative formalin-fixed paraffin-embedded (FFPE) specimens from all patients with available tumor

Table 1 Patients with medulloblastoma and germline *SUFU* mutation reported in the literature

Author (date)	Selection Criteria	Sex, Age, mo at MB	Histological Subtype	*SUFU* Mutation	Inheritance	Clinical Characteristics and Other Malignancies	Family History
Taylor (2002) 1 patient	MB	Male, 48 mo	Desmoplastic	IVS8 + 1G>A intron 8	NA	Severe developmental delay, frontal bossing, prominent jaw, and hypertelorism	No NBCCS, no family history of cancer
Taylor (2002) and NG (2005), 2 patients	MB	NA	Desmoplastic	c.143insA exon 1	NA	No physical abnormality. Meningioma in the radiation field	No family history of cancer
	MB	NA	Desmoplastic	IVS1-1A>T exon 2	Adopted	No physical abnormality at the clinical examination	NA
Pastorino (2009) 1 patient	NBCCS	8 mo	MBEN	c.1022 + 1G>A intron 8	Inherited from father	Macrocrania, frontal bossing, palmar and plantar pits. No BCC	Father: Macrocrania, bilateral pits on the soles, falx cerebri calcification
Slade (2011) 2 patients	MB	22 mo	Desmoplastic	c.846insC exon 7	NA		No NBCCS
	MB	23 mo	Desmoplastic	c.1022 + 1G>A intron 8	NA		No NBCCS
Smith (2014), 3 patients	NBCCS	Male, 23 mo	Desmoplastic	c.544G>T	Inherited from mother	BCC, falx cerebri calcification, meningioma, and grade 1 astrocytoma	BCC, falx cerebri calcification. Pancreatic and prostatic cancer (47 and 76 y)
	NBCCS	Male, 18 mo	Desmoplastic	c.550C>T	Inherited from mother	BCC, falx cerebri calcification	BCC, falx cerebri calcification. Ovarian fibroma (34 y)
	NBCCS	Female, 24 mo	Desmoplastic	E5-12del	Inherited from mother	BCC, falx cerebri calcification, squamous cell carcinoma cyst, meningioma, and ovarian fibroma	Falx cerebri calcification, pits, skeletal anomaly. Ovarian fibroma (10 y)
Robinson (2015), 1 patient	MB	Male, 29 mo	Desmoplastic				
Šoukalová (2016), 1 patient	MB	21 mo	Desmoplastic		Inherited from mother		Other brain tumors in the family

Abbreviation: NA: not available.

tissue samples were reviewed. Standard histological preparations—including immunostaining with anti–beta-catenin, anti–Yes-associated protein 1, anti–GRB2 [growth factor receptor bound protein 2]-associated-binding protein 1, and anti-p53 antibodies—were used to establish the medulloblastoma type according to the criteria defined by the 2007 and 2016 World Health Organization (WHO) classifications.[29,30] Medulloblastomas were classified into the 4 main molecular subgroups using a 22-gene signature assay and the nanoString nCounter Technology, as previously described.[31] RNA was extracted from FFPE tumor tissue samples obtained at diagnosis.

Screening for Germline SUFU Mutations

The *SUFU* coding exons and their exon/intron boundaries were sequenced using the BigDye terminator sequencing kit (Applied Biosystems) and an ABI Prism 3130xl automatic DNA sequencer with an ABI 3730 analyzer (Applied Biosystems). The primer sequences and PCR conditions are available on demand.

Large rearrangements of the 12 exons of the *SUFU* gene were analyzed by quantitative PCR using the Quantifast SYBR Green PCR kit (Qiagen) or Agilent Custom CGH + SNP microarray.

Mutation Interpretation

Mutations were confirmed by separate bidirectional sequencing using independent DNA samples from a second blood sample. Rare missense variants were classified as neutral or pathogenic in 3 steps: (i) literature data screening in the 1000-genome database; (ii) analysis of the possible splice consequences; and (iii) evaluation of the Grantham score. The interface software application Alamut version 2.6 (Interactive Biosoftware) was used for this purpose.[21]

Statistical Analyses

Progression-free survival (PFS), disease-free survival (DFS), and overall survival (OS) were calculated using the

Kaplan–Meier method. PFS was defined as the time from the date of diagnosis until the date of disease progression or first relapse or last contact. DFS was defined as the time from the date of diagnosis until the date of disease progression, first relapse, death from any cause (including death due to treatment-related toxicity), or last contact. OS was defined as the time from the date of diagnosis until death from any cause or last contact.

Results

Medulloblastoma Characteristics and Outcome

Between 1985 and 2015, a germline *SUFU* mutation was detected in 22 pediatric patients with medulloblastoma (MB+), who belonged to 17 families. Thirteen of these patients have already been described.[12,21] Patients and tumor characteristics are listed in Table 2. All children were younger than 3 years (first month of life in 2 patients) at the time of the medulloblastoma diagnosis (median age: 16.5 mo [range, 1–34]). All tumors (but for 3) had a desmoplastic histotype or extensive nodularity. Seven tumors could be analyzed (available samples) for expression-based subgrouping and were classified in the SHH subgroup. Immunostaining with anti-p53 antibody was negative in all tumors with available tissue samples (n = 11). *TP53* mutation screening was negative in all 3 patients who had a germline analysis.

Treatment varied according to the time of diagnosis and tumor extension. All patients had up-front surgery, at least to obtain one biopsy for histological confirmation of medulloblastoma, followed by chemotherapy. According to the published protocols,[32–34] most patients received chemotherapy with the aim of avoiding craniospinal radiotherapy. Only one child received craniospinal radiation therapy as part of the first-line treatment. No patient received specific SHH-targeted inhibitors.

The median follow-up for all patients was 4.9 years (range, 0.01–31). Eight patients presented at least one relapse after diagnosis (median interval: 12 mo [range, 7–24]). Recurrence was local in 6 patients and combined (local and metastatic) in 2 others. A second local relapse was reported in one patient who died. Two infants (2.A and 15) presented an early progression of the disease in the first month after the beginning of the chemotherapy. The 5-year PFS was 43.7% (95% CI: 20.4–64.9%) due to disease progression on therapy and relapses (Fig. 1).

Eight patients (36%) died after the diagnosis of medulloblastoma (median interval: 0.9 y [range, 0–8]) mostly due to tumor progression (5/8). Two infants died because of hemorrhagic complications just after the initial surgery, and one child due to chemotherapy-related toxicity. The 5-year DFS was 37.5% (95% CI: 17.4–57.7%) (13 events included deaths and relapses) (Fig. 1).

Overall, 14 patients were alive with a median follow-up of 9.2 years (range, 0.8–31) after the diagnosis of medulloblastoma, all in complete remission, including 5 patients in remission after a relapse and treatment including high-dose chemotherapy (HDC) and focal radiation. The 5-year OS was 67.0% (95% CI: 42.9–82.8%) (Fig. 1).

Associated Clinical and Radiological Signs

Five patients (23%) met the NBCCS criteria at the time of the analysis (Table 3). A significant macrocrania (>97th percentile) was observed in all children with available head circumference measurement at the time of diagnosis (n = 20). Moreover, frontal bossing and/or hypertelorism was described in 3 patients. Five patients from all patients with available brain CT scan (n = 16) presented falx cerebri calcification. Multiple melanocytic nevi were reported in 6 of 22 patients. Facial and dental anomalies were described in 4 patients: perinasal skin tag (n = 1), high arched palate (n = 2), and dental agenesis (n = 2 who received HDC, which also could cause dental agenesis). Odontogenic cysts and skeletal anomalies were not observed. Three children had a cognitive deficit worse than expected in patients treated for medulloblastoma in the first years of age.

Germline SUFU Mutation Screening

All mutations but one were truncating mutations (list in Table 4).

Family History

Overall, *SUFU* mutation inheritance could be tested in 14 of 19 nuclear families (parents and at least one affected child). In 3 patients, it was a de novo mutation, whereas it was inherited in 11 of 14 families (79%), from the father in 7 patients and from the mother in 4.

The familial history of cancer was obtained for all patients. In 3 families (inherited mutation), 2 (2.A and 2.B) and 3 (8.A, 8.B, and 8.C) siblings and 3 cousins (12.A, 12.B, and 12.C) had a medulloblastoma and were all described in this cohort. In 4 other families, 6 siblings, 1 uncle, and 1 nephew of a mutation-transmitting parent died inexplicably in the first years of life, often in a context of vomiting. We cannot exclude that a brain tumor might have been the cause of these early deaths.

SUFU Mutation Carriers and Other Tumors

Overall, 56 *SUFU* mutation carriers were identified: 22 MB+ and 34 relatives without medulloblastoma (MB–) (Table 4). Among the 14 MB+ who survived more than 2 years (median age at last follow-up: 10.2 y [range, 3.9–33.9]), 4 (27%) developed additional tumors (Table 5). Two patients had a single tumor (acute myeloid leukemia with chromosome 5 abnormality, and a thyroid papillary carcinoma without previous radiotherapy, respectively). One patient had multiple BCC and a meningioma (both in the radiation field), and another patient had a sex cord–gonadal stromal

Table 2 Medulloblastoma characteristics, treatment modalities, and outcome of patients with *SUFU* mutations and medulloblastoma

	Medulloblastoma				First-line Treatment		First Relapse		Outcome		
Patient	Sex, Age at Diagnosis, mo	Histopathologic Diagnosis	Molecular Diagnosis	Tumor spread	Quality of Surgical Resection	Other Treatment(s)	Pattern (time to relapse after the diagnosis, mo)	Treatment After Relapse	Other Events	Follow-up, y	Status
1	F, 17	DNMB	NA	Local	Complete	CC (BBSFOP*)	Local (23 mo)	HDC (misulban-Tt) + focal RT		27.7	Alive in CR2
2.A	M, 1	MBEN	NA	Local	Biopsy	CC (1 VPC)				0.04	Died because of PD without CR
2.B	M, 3	MBEN	NA	Local	Partial	No				0.03	Died because of postoperative complication without CR
3	M, 9	MBEN	NA	Local	Complete	CC (CCG-9921**, then BBSFOP*)	Local (15 mo)	HDC (Bu-Tt) + focal RT	Second local relapse and AML	7.8	Died because of AML
4	M, 15	MBEN	NA	Local	Complete	CC (HIT-SKK '92***)			Thyroid papillary carcinoma	10.5	Alive in CR1
5	M, 30	Classical MB with neuronal differentiation	NA	Local	Complete	CSI (55/35 Gy)			Multiple BCCs and meningioma	31.4	Alive in CR1
6	F, 31	DNMB	SHH	Local	Complete	CC (CCG-9921**)	Local and metastatic (14 mo)	CC (Temiri)		1.3	Died because of PD
7	M, 16	DNMB	SHH	Local	Complete	CC (HIT-SKK '92****)				6.9	Alive in CR1
8.A	M,30	Classical MB	NA	Local	Complete	CC (BBSFOP*)	Local (10 mo)	HDC (Bu-Tt) + focal RT	Metastatic relapse	14.4	Alive in CR3
8.B	M, 18	Classical MB	NA	Local	Partial	No				0.01	Died because of postoperative complication without CR
8.C	M, 27	MBEN	NA	Local	Complete	CC (BBSFOP*)	Local (14 mo)	HDC (Bu-Tt) + focal RT		4.4	Alive in CR2

(Continued)

Table 2 Continued

	Medulloblastoma				First-line Treatment		First Relapse		Outcome		
Patient	Sex, Age at Diagnosis, mo	Histopathologic Diagnosis	Molecular Diagnosis	Tumor spread	Quality of Surgical Resection	Other Treatment(s)	Pattern (time to relapse after the diagnosis, mo)	Treatment After Relapse	Other Events	Follow-up, y	Status
9	M, 11	MBEN	SHH	Metastatic	Partial	CC (3 VPC) + HDC (Mel, Mel, Bu-Tt)				0.5	Died as result of toxicity (VOD), in CR1
10	M, 8	DNMB	NA	Local	Partial	CC (BBSFOP*)				8.0	Alive in CR1
11	F, 19	DNMB	NA	Local	Complete	CC (HIT-SKK '92***)				0.8	Alive in CR1
12.A	F, 9	MBEN	NA	Local	Complete	4 VPC + HDC (Bu-Tt)			Sex cord–gonadal stromal tumor and meningioma	13.1	Alive in CR1
12.B	F, 34	DNMB	NA	Local	Complete	CC (BBSFOP*)	Local (7 mo)	HDC (Misulban-Tt) + focal RT		16.6	Alive in CR2
12.C	F, 19	DNMB	SHH	Local	Complete	CC (BBSFOP*)	Local and metastatic (9 mo)	HDC (Mel-Mel-Tt) + focal RT	Local and metastatic relapse	2.9	Died because of PD
13	F, 6	DNMB	NA	Metastatic	Complete	CC (HIT-SKK '92***)				2.4	Alive in CR1
14	F, 18	DNMB	SHH	Local	Complete	CC (BBSFOP*)	Local (9 mo)	HDC (Bu-Tt) + focal RT		16.7	Alive in CR2
15	M, 1	MBEN	NA	Local	Partial	CC (VP16)				1.4	Died because of PD without CR
16	F, 23	MBEN	SHH	Local	Complete	CC (HIT-SKK '92***)				3.9	Alive in CR1
17	9	MBEN	SHH	Local	Complete	CC (HIT-SKK '92***)				0.44	Alive in CR1

Abbreviations: NA: not available, CR1: first complete response, CR2: second complete response, CR3: third complete response, PD: progressive disease; CC: conventional chemotherapy; VP16: etoposide; VPC: etoposide-carboplatin; Tt: thiotepa; Mel: melphalan; Bu: busulfan; CSI: craniospinal irradiation; AML: acute myeloid leukemia; VOD veno-occlusive disease.
*Grill et al. *Lancet Oncol.* 2005; **Geyer et al. *J Clin Oncol Off J Am Soc Clin Oncol.* 2005; ***Rutkowski et al. *N Engl J Med.* 2005.

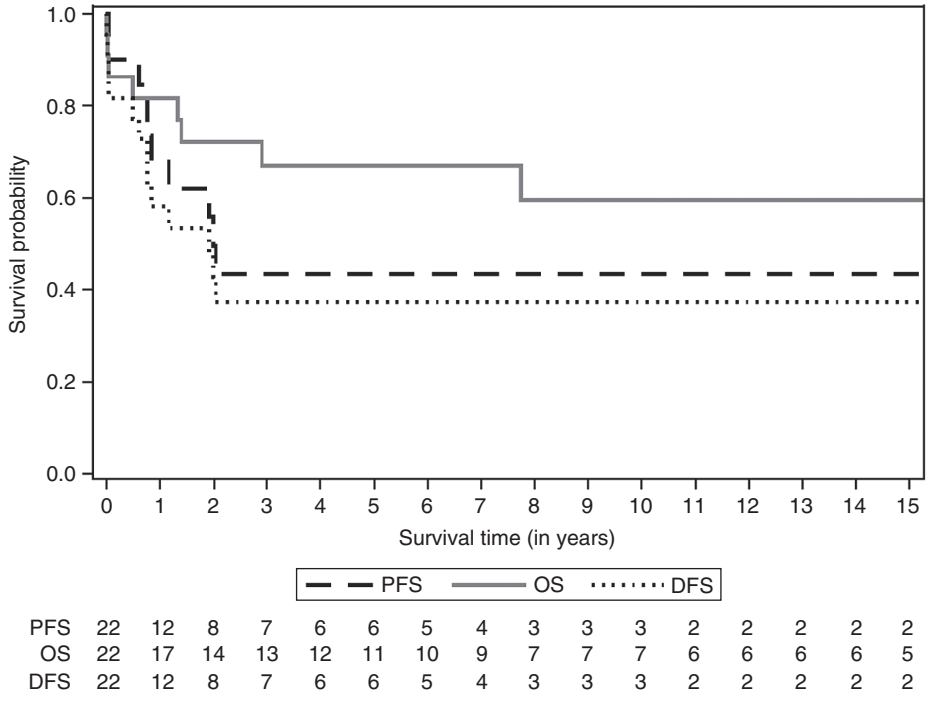

Fig. 1 Overall survival, disease-free survival, and progression-free survival of children with medulloblastoma and germline *SUFU* mutation ($n = 22$).

tumor and a meningioma (without previous radiotherapy). At the time of diagnosis of the second malignancy, the median age was 12.1 years (range, 7.7–33.9), and the median time from the medulloblastoma diagnosis was 11.3 years (range, 6.5–31.4).

The median age of the 34 MB– relatives was 51.3 years. None of them had a previous diagnosis of NBCCS. Overall, 7 of them reported 13 benign or malignant tumors, including one BCC (age at diagnosis: 71 y) (Table 5). The median age of these 7 relatives at the time of diagnosis of the first malignant tumor was 49.5 years.

Discussion

To date, this is the largest reported series of germline *SUFU* mutation carriers. Our main aim was to describe more precisely the clinical characteristics, the risk of cancer, and the outcome of medulloblastoma associated with a germline *SUFU* mutation.

SUFU and *PTCH1* mutations are the main genetic abnormalities associated with predisposition to SHH medulloblastoma. In *PTCH1* mutation carriers, the incidence of medulloblastoma is estimated to be lower than 2%.[18,24,35,36] In *SUFU* mutation carriers, the risk of medulloblastoma is difficult to evaluate due to the small number of families described to date and the difficulty to correct for the ascertainment bias because most families are recruited through a proband with medulloblastoma. In the present study, 14 children with germline *SUFU* mutation and medulloblastoma belonged to 9 families in which the *SUFU* mutation was shown to be inherited and that included 34 other mutation carriers without medulloblastoma (MB–) (Table 4). These results confirm our previous findings in a smaller cohort.[21] They also suggest that in the case of germline *SUFU* mutation, medulloblastoma penetrance is incomplete, with a risk of medulloblastoma probably lower than 30%, but still much higher than for *PTCH1* mutation carriers.[12] Although familial aggregation of medulloblastoma is rare,[37,38] in this study we found 7 families with medulloblastoma in several siblings or unexplained deaths in the first years of life. Therefore, we hypothesize that most cases of familial medulloblastoma could be explained by germline *SUFU* mutations, as already suggested.[25,28]

As previously described, all medulloblastomas were diagnosed in children younger than 3 years of age and the histological subtype was mainly desmoplastic or with extensive nodularity.[10,12,13,21–26] As expected, an involvement of the SHH-driven pathway was shown by immunostaining and with the nanoString nCounter Technology, when it could be explored. We recommend *SUFU* mutation screening in all children presenting with SHH medulloblastoma before 5 years of age, particularly in the case of chromosome 10q LOH, desmoplastic histotype, or extensive nodularity. If a *SUFU* somatic alteration is detected, germline mutation analysis should be proposed.

In this study, the 5-year DFS and OS rates were 37.5% and 67.0%, respectively. In order to take into account in this retrospective cohort accrued over 30 years the improvement

Table 3 Evaluation of the NBCCS criteria in patients with a medulloblastoma and germline *SUFU* mutation

	Sex, Age at MB, mo	Age at Last Follow-up, y	Falx Cerebri Calcification (age at CT scan)	Jaw Cysts or Dental Anomaly	BCC, Pits or Multiple Nevi	Macrocrania	Hypertelorism ± Frontal Bossing	Bifid Rib or Other Feature	NBCCS (age at diagnosis)
1	F, 17	28	NA	No	Nevi (50)	Yes	No	NA, syndactyly of 2/3 toes	No
2.A	M, 1	0	No (1 mo)	NA	No	Yes	No	NA	No
2.B	M, 3	0	NA	NA	No	Yes	No	NA	No
3	M, 9	9	No (1 y)	No	Nevi (20)	Yes	No	No	No
4	M, 15	11	NA	High arched palate, dental agenesis	Palmar/ plantar pits and nevi	Yes	No	No	Yes (8 y)
5	M, 30	34	Yes (26 y)	No	BCC and nevi	Yes	No	No	Yes (17.5 y)
6	F, 31	4	No (4 y)	High arched palate	No	Yes	Yes	No	No
7	M, 16	8	No (2 y)	No	No	Yes	No	No	No
8.A	M, 30	17	No (4 y)	NA	No	Yes	No	NA	No
8.B	M, 18	2	NA	NA	No	Yes	No	NA	No
8.C	M, 27	7	No (7.5 y)	NA	No	Yes	No	NA	No
9	M, 11	1	NA	No	No	Yes	No	NA	No
10	M, 8	9	No (1 y)	NA	No	Yes	Yes	No, perinasal skin tag	No
11	F, 19	2	Yes (2 y)	No	No	Yes	Yes	No	Yes (2 y)
12.A	F, 9	17	Yes (17 y)	No	No	Yes	No	No	Yes (17 y)
12.B	F, 34	19	NA	NA	Nevi	Yes	No	NA	No
12.C	F, 19	4	Yes, (3 y)	No	No	No	No	No	No
13	F, 6	3	No (1 y)	No	No	Yes	No	No	No
14	F, 18	18	Yes (16 y)	Dental agenesis	Nevi	Yes	No	No	Yes (16 y)
15	M, 1	2	No	NA	No	Yes	No	No	No
16	F, 23	6	No	No	No	No	No	No	No
17	M, 9	1	No (1 y)	NA	No	Yes	No	No	No

of supportive care over time leading to reduction of the risk of death due to treatment-related toxicity, we calculated 5-year PFS. The 5-year PFS was 43.7% (95% CI: 20.4–64.9%). This contrasts with the usual good prognosis of SHH medulloblastoma with most current treatment protocols (5-year PFS and OS rates higher than 70% and 80%, respectively).[26,34] This was mostly due to the high rate of local relapse. In addition, 4 patients were diagnosed with 6 second malignancies. The spectrum (meningioma, BCC, thyroid carcinoma) was similar to that reported by Tsui et al in a cohort of 376 patients with unselected medulloblastoma/primitive neuroectodermal tumors. In this cohort, the cumulative incidence of second malignancies, 20 years after the first diagnosis, was 12%, which is much lower than the incidence observed in our cohort.[39] The best therapeutic strategies for infants with medulloblastoma are currently under discussion, particularly the question of whether patients with a germline *SUFU* mutation require a specific therapeutic approach. Radiotherapy is probably efficient because only one local relapse in the field of focal radiation occurred among the 8 patients who underwent radiotherapy. However, its use in this genetic context is still debated because of the risk of second malignancies. Therapy with a targeted inhibitor of the SHH pathway, which is clearly involved in the malignant transformation, could offer an alternative therapeutic option to the classic chemoradiotherapy approach for SHH medulloblastoma. Vismodegib (GDC-0449) and sonidegib (LDE-225) inhibit SHH signaling by binding to SMO. They are approved for use in BCC[40–43] and have demonstrated good efficacy as monotherapy in a subset of patients with SHH medulloblastoma (prolonged stabilization in 41% of them).[27] However, mutations in SHH pathway genes downstream of SMO (*SUFU, GLI2*, or *MYCN*) make these tumors intrinsically resistant to SMO targeting drugs.[11,15,27,43–45] Indeed, preclinical data confirmed the resistance to targeted SMO inhibition in cells harboring a *SUFU* mutation.[15] Moreover, the only patient with a germline *SUFU* mutation–associated medulloblastoma and treated with an SHH pathway inhibitor did not experience any response.[27] In addition, these agents may induce early growth plate fusion, restricting their use to skeletally mature patients. This highlights

Table 4 Pathogenic germline *SUFU* mutations

No of family	Type of Mutation	International Denomination	Inherited	MB+	MB–	Mutation Previously Described
1*	Splice	c.182 + 3A>T	Inherited from father	1	2	(21)
2*	FS	c.71del p.Pro24Argfs*72	Inherited from mother	2	5	(12)
3*	Splice	c.1297-1G>C	Inherited from father	1	2	(21)
4	FS	c.71del p.Pro24Argfs*72	Inherited from father	1	1	
5*	FS	c.294_295dup p.Tyr99Serfs*23	NA	1		(21)
6*	Splice	c.318-10del	Inherited from father	1	2	(21)
7*	Large duplication	Exon 3 duplication c.318-?_454+?dup	De novo	1	0	(21,26)
8	FS	c.567_571delinsT p.Gln189Hisfs*5	Inherited from father	3	2	
9*	FS	c.1149_1150dup p.Cys384Serfs*3	NA	1		(21)
10*	MS	c.422T>G p.Met141Arg	Inherited from father	1	1	(21)
11	Large deletion	Exon 9–12 deletion c.1023-?_1455+?del	NA	1		
12*	FS	c.71dup p.Ala25Glyfs*23	Inherited from their mothers**	3	18	(12)
13	FS	c.1096_1117delinsGAA p.Leu366Glufs*14	Inherited from father	1	1	
14*	NS	c.1123C>T p.Gln375*	De novo	1	0	(21)
15	Splice	c.1022 + 1G>A	NA	1	0	(13,23)
16	Splice	c.1022 + 1G>A	NA	1	0	(13,23)
17	Large deletion	Exon 3–12 deletion c.318-?_1455+?del	NA	1	0	(24)

Abbreviations: S: splice, FS: frameshift, MS: missense, NS: nonsense, NA: not available.
*Families and *SUFU* mutations already described by our group. **The 3 children with medulloblastoma are not siblings, but relatives.

the need of a prospective evaluation of the best treatment for these patients with poor prognosis.

Besides patients with medulloblastoma, only a few other *SUFU* germline mutation carriers have been described so far (Table 1), and their phenotype is still largely unknown. As the clinical phenotypes of *SUFU* and *PTCH1* mutation carriers overlap, *SUFU* has been described as one of the genes involved in NBCCS. However, clinical manifestations and tumor incidence seem to differ between *SUFU* and *PTCH1* mutation carriers. One of the confounding factors is probably the age at observation, because the established diagnostic criteria for NBCCS are informative when evaluated in adults,[18,46] whereas they are often not all present in children until the teenage years.[46,47] In our series, 5 patients met the diagnostic criteria for NBCCS (medulloblastoma, macrocrania, and one additional feature). Macrocrania was more often observed in our patients than in patients with NBCCS; however, it could have been associated just with the brain tumor, because macrocrania is described in more than 50% of infants with brain tumors. Three patients had a severe cognitive impairment. A germline *SUFU* mutation was reported in a patient with severe developmental delay.[10] However, given the impact of medulloblastoma treatment on neurocognitive development, it is difficult to clearly associate this feature with the genetic background. Thus, for macrocrania and cognitive deficit, the respective role of the tumor and the predisposition syndrome may be difficult to assess in infants. As previously described in patients with *SUFU* mutations, no odontogenic cyst and very few pits were observed in our cohort.[24] In view of the low incidence of BCC (only 2/56; 3.5%) in our series, the risk of BCC is probably much lower in *SUFU* mutation carriers than in NBCCS associated with germline *PTCH1* mutations. This incidence is also lower than the BCC rate described in patients with a germline *SUFU* mutation in the context of NBCCS: 7 of 18 patients (39%), among whom 3 with a previous medulloblastoma and 4 without.[10,13,22–25] This confirms that the clinical manifestations in germline *SUFU* mutation carriers vary depending on the recruitment process. Patients recruited based on the diagnosis of medulloblastoma mostly do not show physical abnormalities and very few have a history of BCC.[10,13,22,25] Conversely, germline *SUFU* mutation carriers identified in NBCCS cohorts mostly present the specific NBCCS features, including BCC, except for the jaw cysts.[23,24] As patients in our series are still very young,

Table 5 Tumors observed in *SUFU* mutation carriers

Other Tumors in the 22 MB+ Patients	*n* Patients (pts)	Age at Diagnosis, y
Acute myeloid leukemia	1	7.8
Thyroid papillary carcinoma	1	7.7
Sex cord–gonadal stromal tumor	1	13.9
Meningioma	2 (2 pts)	10.3 and 33.9
Multiple BCC	1	17.5
Other tumors in 7/34 relatives harboring *SUFU* germline mutations from 3 families		
BCC	1	71
Meningioma	1	48
Carcinoma:		
Breast cancer	2 (2 pts)	37 and 71
Bladder cancer	1	73
Sarcomas[1]	4 (2 pts)	46, 47, 53, and 71
Neurofibroma	2 (1 pt)	46 and 47
Multiple colon polyps	1	NA
Liver adenoma	1	NA

[1] No germline *TP53* mutation.

NBCCS features may still appear later, although none of the relatives with germline *SUFU* mutations had NBCCS or developed a BCC before the age of 30.

We also observed several other cancers in *SUFU* mutation carriers, suggesting that the cancer risk associated with *SUFU* mutation might not concern only medulloblastoma during the first years of life. In addition to meningioma (3/56 carriers), already known to be associated with *SUFU* mutations,[48,49] a large tumor spectrum was observed in our series: carcinomas (breast, bladder, and thyroid papillary carcinomas), sarcomas, acute myeloid leukemia, and low-grade tumors (sex cord–gonadal stromal tumor, liver adenoma, and colonic polyps). Few associations of carcinoma or fibroma with germline *SUFU* mutation have been described so far.[24] Because of the large oncological spectrum and the incomplete penetrance of medulloblastoma, genetic counseling, including the question of prenatal diagnosis, is challenging in families with *SUFU* mutations. Young children with a germline *SUFU* mutation should be offered a structured follow-up, including regular brain MRI exams during the first years of life.[50]

Conclusion

The risk of medulloblastoma associated with germline *SUFU* mutations is still difficult to evaluate but is probably higher than for *PTCH1* mutations. The prognosis for these patients is worse than usually observed in SHH medulloblastoma due to the high risk of local relapses. Future international studies exploring the oncogenic pathways involved in each patient could help to improve the early diagnosis of *SUFU* predisposition syndrome and allow the definition of specific therapeutic guidelines for this group of patients. So far, for early detection of medulloblastoma, frequent MRIs in infants with a pathogenic germline mutation in *SUFU* are recommended (brain MRI every 4 mo until age 3 and then every 6 mo until age 5). If medulloblastoma occurs, the best therapeutic strategies are currently under discussion for patients with a germline *SUFU* mutation. Given the worse prognosis, we should consider these as patients with high-risk medulloblastoma. So, chemotherapies should probably be more intensive than those currently used. Taking into account the high risk of local relapse, the good local control after radiation treatment, and the low incidence of BCC in all mutation carriers in this series, radiotherapy should be discussed according to the age of the patient. International databases are needed to describe more comprehensively the spectrum of this predisposition syndrome that has some overlap with NBCCS.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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