High Frequency of Germline SUFU Mutations in Children With Desmoplastic/Nodular Medulloblastoma Younger Than 3 Years of Age

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ABSTRACT

Purpose
Germline mutations of the SUFU gene have been shown to be associated with genetic predisposition to medulloblastoma, mainly in families with multiple cases of medulloblastoma and/or in patients with symptoms similar to those of Gorlin syndrome. To evaluate the contribution of these mutations to the genesis of sporadic medulloblastomas, we screened a series of unselected patients with medulloblastoma for germline SUFU mutations.

Patients and Methods
A complete mutational analysis of the SUFU gene was performed on genomic DNA in all 131 consecutive patients treated for medulloblastoma in the pediatrics department of the Institut Gustave Roussy between 1972 and 2009 and for whom a blood sample was available.

Results
We identified eight germline mutations of the SUFU gene: one large genomic duplication and seven point mutations. Mutations were identified in three of three individuals with medulloblastoma with extensive nodularity, four of 20 with desmoplastic/nodular medulloblastomas, and one of 108 with other subtypes. All eight patients were younger than 3 years of age at diagnosis. The mutations were inherited from the healthy father in four of six patient cases in which the parents accepted genetic testing; de novo mutations accounted for the other two patient cases. Associated events were macrocrania in six patients, hypertelorism in three patients, and multiple basal cell carcinomas in the radiation field after age 18 years in one patient.

Conclusion
These data indicate that germline SUFU mutations were responsible for a high proportion of desmoplastic medulloblastoma in children younger than 3 years of age. Genetic testing should be offered to all children diagnosed with sonic hedgehog–driven medulloblastoma at a young age.

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INTRODUCTION

Medulloblastoma, a malignant neoplasm arising in the cerebellum, is the most common malignant brain tumor occurring in childhood. Five histologic subtypes are recognized in the 2007 WHO classification: classic, anaplastic, large cell, desmoplastic/nodular, and extensive nodularity (MBEN).1,3

Microarray studies demonstrate that medulloblastoma subtypes can be characterized by specific pathway activations such as wingless (WNT) or by sonic hedgehog (SHH) signaling.4-7 These studies show that most desmoplastic/nodular medulloblastomas are found in the SHH group. Involvement of the SHH signaling pathway in the genesis of these tumors has also been well established mainly in the desmoplastic/nodular subtype with the presence of somatic mutations in Patched1 (PTCH1),8 Patched2 (PTCH2),9 suppressor of fused (SUFU),10 and/or smoothened (SMOH)11 as well as high-level amplification of the SHH effectors, transcription factors GLI1 and GLI2.12

The involvement of SHH pathway activation in a genetic predisposition to medulloblastoma has been demonstrated in individuals with Gorlin syndrome (GS), in which affected individuals carrying a mutation in the SHH receptor PTCH1 develop basal cell carcinomas and have a number of developmental abnormalities and an increased risk of medulloblastoma.13

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Several cases of germline mutations of the SUFU gene have been described\textsuperscript{10,14-17} in patients with nodular/desmoplastic or MBEN medulloblastoma. Some of the germline mutations described to date were inherited in families exhibiting several cases of medulloblastoma. In these families, the penetrance of these mutations is clearly incomplete.\textsuperscript{15} To evaluate the contribution of germline mutations of the SUFU gene in the genesis of sporadic medulloblastomas, we screened a large series of unselected patients with medulloblastoma for germ-line SUFU mutations.

### Patients and Methods

#### Patients

All consecutive patients treated for medulloblastoma in the pediatrics department of the Institut Gustave Roussy between 1972 and 2009 and for whom a blood sample with informed consent for genetic testing was available were included in the study. Blood samples were collected from the parents whenever possible. Patients with familial medulloblastoma in whom a germline SUFU mutation had already been reported were excluded from the analysis.

We performed a review of the slides of all patients for whom histologic samples were available. Standard histologic preparations stained with hematoxylin and eosin and reticulin preparations were used to evaluate several morphologic criteria as defined by the 2007 WHO classification, including desmoplasia, nodule formation, neuronal differentiation, and anaplastic or large-cell phenotype.\textsuperscript{1} Immunohistochemical studies systematically included: Mib-1; DAKO, Glostrup, Denmark), and betacatenin (clone 14; Ventana, Tucson, AZ). Medulloblastomas were classified as classic tumor or one of four subvariants: desmoplastic/nodular, MBEN, anaplastic, and large-cell medulloblastoma. Atypical teratoid/rhabdoid tumors were excluded based on their histologic appearance and the loss of nuclear immunoreactivity for INI1 (1/50, clone BAF47; BD Biosciences, San Jose, CA).

Of the 148 patients potentially eligible for the study, 17 were excluded for the following reasons: parents refused genetic testing (n = 1), diagnosis of medulloblastoma was not confirmed (n = 5), and a genetic predisposition syndrome had already been diagnosed (n = 11); of these 11, four patients had a family history of medulloblastoma and a SUFU gene mutation that had already been identified (patient cases previously published\textsuperscript{13}), three had a PTCH germline mutation, two of them were diagnosed with GS after the occurrence of basal cell carcinomas as second malignancies, and two had a germline P53 mutation and family history of Li-Fraumeni syndrome.

Overall, 131 patients were included in the present study. The median age at diagnosis was 54 months (range, 1 to 204 months), with 43 patients younger than 3 years of age. The distribution of the histologic subtypes was as follows: classic (n = 71), desmoplastic/nodular (n = 20), MBEN (n = 3), large cell (n = 1), medulloblastoma with myogenic differentiation (n = 1), and undetermined (n = 35).

#### Screening for Germline Mutations

Genomic DNA was extracted directly from 400 μL of whole blood using the QIAamp DNA/Blood Mini Kit (Qiagen, Venlo, the Netherlands) automated in the QIACUBE System (Qiagen). For mutational screening, all the exons of the SUFU gene including exon-intron boundaries were amplified by quantitative polymerase chain reaction (Q-PCR) performed on a TaqMan (Applied Biosystems, Carlsbad, CA) analyzer to detect genomic rearrangements, followed by direct sequencing of Q-PCR products on an ABI3730 analyzer (Applied Biosystems; protocols and primers available on request). All nucleotide numbers refer to the wild-type cDNA sequence of SUFU (NM_016169.2) as reported in GenBank. The molecular alterations were designated according to the Human Genome Variation Society nomenclature.

#### Mutational Interpretation

All novel variants and mutations were confirmed by separate bidirectional sequencing in independent DNA extracted from a second blood drawing. Rare missense variants were classified as neutral or pathogenic in different steps: first, a screening of the literature and in the 1,000-genome database; second, a study of possible splice consequences; and third, an evaluation of the Grantham score, which predicts the effect of substitutions between amino acids based on chemical properties, including polarity and molecular volume, taking into account the phylogenetic conservation of the amino acid among 12 species\textsuperscript{14,15} (Appendix Table A1, online only). The interface software application Alamut version 2.0 (Interactive Biosoftware, Rouen, France) was used for this purpose. Sequencing of the SUFU gene was also performed in a series of samples from 96 healthy volunteers.

#### Splicing Analysis

An analysis of potential splicing aberrations was carried out for variations that were in silico predicted to create an alternative splicing site or to abolish a physiologic splicing site. cDNA was synthesized by real-time PCR from RNA extracted from wild-type controls and from lymphocytes from variant carriers. It was PCR amplified, and products were separated by high-resolution gel electrophoresis for fragment size analysis or sequencing. These experiments were run on an ABI 3730 analyzer, and data were analyzed using Gene Mapper (Applied Biosystems) or Seqscape (Applied Biosystems) software, respectively. Primers and protocols are available on request.

#### Tumor Analysis

In patients with a germline SUFU mutation, direct sequencing using ex-on-specific primers was performed on DNA extracted from frozen samples of the tumor when available.

#### Analysis of Relatives

Whenever possible, the analysis of relatives for a deleterious mutation was proposed to the parents of patients. Direct sequencing was performed using ex-on-specific primers. When possible, a clinical examination and

### Table 1. Germline Pathogenic SUFU Mutations

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Exon/Intron</th>
<th>Type of Mutation</th>
<th>Nucleotide Change</th>
<th>Consequence</th>
<th>Tumor Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intron 1</td>
<td>Splice → frameshift</td>
<td>c.182 + 3A&gt;T</td>
<td>p.Thr55fs</td>
<td>Not available</td>
</tr>
<tr>
<td>2</td>
<td>Exon 2</td>
<td>Frameshift</td>
<td>c.294_295dupCT</td>
<td>p.Tyr99fs</td>
<td>Not available</td>
</tr>
<tr>
<td>3</td>
<td>Intron 2</td>
<td>Frameshift</td>
<td>c.318-319dupCT</td>
<td>p.Tyr100fs</td>
<td>Loss of wild-type allele</td>
</tr>
<tr>
<td>4</td>
<td>Exon 3</td>
<td>Large duplication</td>
<td>c.318-319dupCT</td>
<td>p.Tyr100fs</td>
<td>Loss of wild-type allele</td>
</tr>
<tr>
<td>5</td>
<td>Exon 3</td>
<td>Missense</td>
<td>c.422T&gt;G</td>
<td>p.Met141Arg</td>
<td>Not available</td>
</tr>
<tr>
<td>6</td>
<td>Exon 9</td>
<td>Non-sense</td>
<td>c.1123C&gt;T</td>
<td>p.Gln375X</td>
<td>Not available</td>
</tr>
<tr>
<td>7</td>
<td>Exon 10</td>
<td>Frameshift</td>
<td>c.1149_1150dupCT</td>
<td>p.Cys384fs</td>
<td>Loss of wild-type allele</td>
</tr>
<tr>
<td>8</td>
<td>Intron 10</td>
<td>Splice → frameshift</td>
<td>c.1297-1G&gt;C</td>
<td>p.?</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Abbreviation: UV, unknown variant.

*In silico analysis of this UV was in favor of pathogenicity.
brain magnetic resonance imaging were performed in asymptomatic mu-
tation carriers.

RESULTS

SUFU Mutation Screening

Overall, we detected a SUFU germline mutation in eight of 131 patients (Table 1), including a large genomic duplication and seven point mutations. Among the seven, all but one were truncating muta-
tions. None of these mutations have been previously described, to our

knowledge. A transcript analysis was performed for the two intrinsic point mutations localized outside a canonic splice site. This allowed us
to classify them as pathogenic, because the c.182+3A>T mutation
induces deletion of 23 bases at the end of exon 1, and the c.318-10delT
mutation induces skipping of exon 3 (Fig 1). One mutation,
p.Met141Arg, is the first missense mutation described to date, to our
knowledge. This mutation is not described in the single nucleotide polymorphism databases (Children’s Hospital Informatics Program,
dbSNP) and was not found in our control population (n = 96). It is
located within a domain of SUFU highly conserved both in vertebrates

Fig 1. Transcript analysis of c.182+3A>T for (A) patient and (B) control and of c.318-10delT for (C) patient and (D) control.
and invertebrates. In this domain comprising a three-dimensional structure (highly twisted seven-stranded β-sheet), the substitution Met141Arg (Grantham score, 91) could induce loss of protein conformation, leading to the loss of interaction with partner proteins such as Gli1 or Gli3.19,20 Therefore, we classified this mutation as pathogenic.

Analysis of the corresponding tumors, performed in three patient cases, led to the demonstration of a loss of the wild-type allele in two and to the identification of a unknown variant with an in silico analysis in favor of pathogenicity in the third (Table 1). Additionally, 10 different germline unknown variants were identified in 10 patients, including two in patients with a germline SUFU mutation (Appendix Table A2, online only). In silico analysis performed in all patients was in favor of neutrality. None had been previously reported or identified in controls (Appendix Table A3, online only). Additionally, several variants also found in controls were classified as polymorphisms. Some of them might have been ethnographic polymorphisms, because they were identified more than once in patients of African origin.

**Clinical Characteristics of Patients With SUFU Germline Mutations**

Clinical characteristics of the eight patients in whom a germline SUFU mutation was identified are listed in Table 2. Median age at diagnosis was 17 months. The histologic subtype was nodular/desmoplastic in four patients, MBEN in three, and classic medulloblastoma in one. All patients had localized disease at diagnosis. One patient, now age 28 years, had been diagnosed with multiple basal cell carcinomas in the radiation field after 18 years of age. Despite a careful screening, none of the seven other patients were found to have obvious signs of GS, except for macrocrania (>97th percentile) at the time of diagnosis of medulloblastoma in six patients and hypertelorism in three. Because these children were young at diagnosis of the brain tumor, the increase in head circumference had been reported in most patient cases as resulting from hydrocephaly before the tumor diagnosis. However, head circumference was >95th percentile at birth for all transmitting fathers.

In order to evaluate the influence of these mutations in patients with sporadic medulloblastoma, we screened a large series of patients with medulloblastoma for germline SUFU mutations and demonstrated that these mutations contribute to the pathogenesis of a large proportion of desmoplastic/nodular and MBEN medulloblastomas in children <3 years of age.

**Inheritance of the Mutations**

Mutations were inherited from the healthy father in four of six patient cases in which the parents agreed to undergo genetic testing; de novo mutations accounted for the two other patient cases. Pedigrees of the four families in which the mutations were inherited are shown in Figure 2. In all patients, the medulloblastoma was seemingly sporadic, with no known family history of medulloblastoma, even though the mutations were inherited from the previous generation in two of three families in which the grandparents were tested. However, in two families, several brothers and sisters of the transmitting father had died before the age of 3 years, and we cannot exclude that a brain tumor might have been the cause of these early deaths. Overall, eight healthy carriers were identified in these four families. None of them had obvious signs of GS except for a relative macrocephaly (95th percentile for height) in all transmitting fathers.

**Frequency of SUFU Germline Mutations According to Tumor Type and Age at Diagnosis**

A SUFU mutation was found in eight of 43 children <3 years of age at diagnosis, whereas no mutation was identified in any of the 88 patients age >3 years at diagnosis. A SUFU mutation was identified in all three patients with the MBEN subtype and in four (20%) of 20 patients with the desmoplastic/nodular subtype but in only one patient with classic histology. Altogether, of the 10 patients <3 years of age at diagnosis with a desmoplastic/MBEN histology, seven were diagnosed with a SUFU mutation.

![DISCUSSION](image)

Only a few patients with medulloblastoma carrying a germline SUFU mutation have been described so far, mostly in families with multiple cases of medulloblastoma and/or in patients with signs of GS (Table 3).10,15-17 To evaluate the incidence of these mutations in patients with sporadic medulloblastoma, we screened a large series of patients with medulloblastomas for germline SUFU mutations and demonstrated that these mutations contribute to the pathogenesis of a large proportion of desmoplastic/nodular and MBEN medulloblastomas in children <3 years of age.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age at Diagnosis (months)</th>
<th>Histology</th>
<th>Inheritance</th>
<th>Associated Symptoms</th>
<th>Outcome (follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>18</td>
<td>Desmoplastic</td>
<td>Inherited from father</td>
<td>Multiple naevi</td>
<td>Alive in CR (21 years)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>30</td>
<td>Classical MB with neuronal differentiation</td>
<td>Not tested</td>
<td>Macrocrania, multiple basal cell carcinomas since age 18 years</td>
<td>Alive in CR (25 years)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>33</td>
<td>Desmoplastic</td>
<td>Inherited from father</td>
<td>Macrocrania, hypertelorism</td>
<td>Died as a result of disease after local and metastatic relapse</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>16</td>
<td>Desmoplastic</td>
<td>De novo</td>
<td>Macrocrania</td>
<td>Alive in CR (14 months)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>9</td>
<td>MBEN</td>
<td>Inherited from father</td>
<td>Macrocrania, hypertelorism, perinarinal tag</td>
<td>Alive in first CR (39 months)</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>18</td>
<td>Desmoplastic</td>
<td>De novo</td>
<td>Macrocrania</td>
<td>Alive after local relapse (11 years)</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>11</td>
<td>MBEN</td>
<td>Not tested</td>
<td></td>
<td>Died as a result of toxicity</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>9</td>
<td>MBEN</td>
<td>Inherited from father</td>
<td>Macrocrania, hypertelorism</td>
<td>Alive after local relapse (28 months)</td>
</tr>
</tbody>
</table>

**Table 2. Clinical Characteristics of Patients With SUFU Mutations**

Abbreviations: CR, complete remission; MB, medulloblastoma; MBEN, MB with extensive nodularity.
The incidence of germline SUFU mutations identified in our series (6%) is quite similar to the that in initial findings reported by Taylor et al. They found somatic inactivating mutations of the SUFU gene in four of 46 sporadic medulloblastomas, three of which were also detected in lymphocyte DNA. Conversely, the recently published study by Slade et al identified only two patients with a germline SUFU mutation among 83 patients with sporadic medulloblastoma for whom genomic DNA was sequenced through both SUFU and PTCH1. The higher incidence in our series as compared with this last report may have partly resulted from a more complete genetic screening of the SUFU gene, including Q-PCR, which allowed the detection of a large genomic duplication. In addition, sequencing of intron-exon junctions led to the detection of two splice mutations localized outside canonic splice sites.

All patients in whom a germline mutation of the SUFU gene was identified were < 3 years of age at the time of medulloblastoma diagnosis. This finding is in accordance with those of previous reports in the literature, in which all 12 patients previously reported with a SUFU mutation were < 3 years of age at diagnosis. Focusing the analysis on patients age < 3 years at diagnosis leads to the identification of a group of patients with a high risk of carrying a SUFU mutation (eight of 43 patients; 18%).
nodular or MBEN subtype. The incidence of SUFU mutations in the group of patients with desmoplastic/nodular or MBEN subtype is 32% in the whole cohort and 70% in children age < 3 years at diagnosis. The rare MBEN subtype, accounting for fewer than 10% of all medulloblastomas, seems to be strongly associated with germline activation of the SHH pathway; in our series, all three patients diagnosed with the MBEN subtype were shown to have a SUFU mutation. This subtype has also been diagnosed in four of 12 patients previously reported with a SUFU mutation. One patient in whom a SUFU mutation was identified in our series was diagnosed with classic medulloblastomas subtype. This finding is consistent with the recent data that classified medulloblastoma according to the immunohistologic profile and showed that the involvement of the SHH pathway is not restricted to nodular/desmoplastic subtypes but can also be implicated in tumors of the classic subtype, especially in young children.

**PTCH1** mutations, which have been shown to be associated with GS, are usually considered to be the main genetic abnormalities associated with predisposition to desmoplastic/nodular medulloblastoma. Our finding suggests that SUFU germline mutations might be more frequent than **PTCH1** mutations in these patients. Only few data are available on the incidence of germline **PTCH1** mutations in patients with medulloblastoma; however, the recent report by Slade et al found no germline **PTCH1** mutations in a series of 78 patients with medulloblastoma, including 18 patients with the nodular/desmoplastic or MBEN subtype. The recent report from Garre et al provides significant data on the incidence of GS in patients with medulloblastoma. It identifies five cases of GS among 90 patients with medulloblastoma carefully screened for this syndrome. This incidence was shown to be higher (20%) in patients with medulloblastoma age ≤3 years at diagnosis and in patients diagnosed with desmoplastic variants (22.7%) or MBEN subtype (41%). However, the incidence of GS probably does not perfectly reflect the presence of a **PTCH1** mutation, because GS may be underdiagnosed in young children. Moreover, there is clearly some overlap between clinical features associated with **PTCH1** and SUFU mutations. Pastorino et al described a patient with GS associated with a germline SUFU mutation. In the present series, only one patient in whom medulloblastoma was associated with macrocrania and basal cell carcinoma met the diagnosis criteria for GS. However, six of eight patients and most healthy carriers had relative macrocrania. None of the SUFU mutation carriers presented with odontogenic cysts, falx calcification, or skin pits. Because no basocellular carcinomas were reported in any of the eight family members in whom a SUFU mutation was identified, the risk of basal cell carcinoma is probably much lower in SUFU mutations carriers than in those with GS associated with germline **PTCH1** mutations; 76.5% of women and 80% of men in the latter case are diagnosed with basal cell carcinoma by the age of 50 years. This risk, however, probably requires the limitation of sun exposure among SUFU mutation carriers and dermatologic follow-up.

Despite no obvious family history of cancer, we showed that SUFU mutations were inherited in four of six patients whose parents underwent genetic testing; only two de novo mutations were discovered. Altogether, eight healthy carriers were identified, confirming the incomplete penetrance of these mutations. However, even though no clear family history of cancer could be ascertained, several cases of unexplained deaths at a young age were described in two families in potential mutation carriers, and we cannot exclude the possibility that these deaths could have been related to misdiagnosed brain tumors before the era of modern radiology.

Except for basocellular carcinoma in one patient, there was no case of cancer after 3 years of age in these families. Of note are the descriptions of a meningioma in the radiation field in a patient case described by Taylor et al and several cases of cancer (breast cancer at 37, meningioma at 38, and leiomyosarcoma at 63 years of age) in mutation carriers in our previous publication on familial medulloblastoma, suggesting that the risk of cancer associated with SUFU mutations may not be restricted to medulloblastoma during the first years of life, even though the risk of cancer is much lower after 3

<table>
<thead>
<tr>
<th>Author</th>
<th>Date of Study</th>
<th>Age at Diagnosis of MB</th>
<th>Histologic Subtype</th>
<th>Associated Symptoms</th>
<th>Inheritance of Mutation</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al</td>
<td>2002</td>
<td>4 years</td>
<td>Desmoplastic</td>
<td>Developmental delay</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ng et al</td>
<td>2005</td>
<td>NA</td>
<td>Desmoplastic</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pastorino et al</td>
<td>2009</td>
<td>8 months</td>
<td>MBEN</td>
<td>Meningioma in radiation field</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Brugieres et al</td>
<td>2010</td>
<td>&lt; 1 month</td>
<td>MBEN</td>
<td>None</td>
<td>Inherited</td>
<td>c.72delC</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>MBEN</td>
<td>None</td>
<td>Inherited</td>
<td>c.72delC</td>
<td>c.72delC</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 months</td>
<td>MBEN</td>
<td>None</td>
<td>Inherited</td>
<td>c.72insC</td>
<td>c.72insC</td>
</tr>
<tr>
<td></td>
<td>6-12 months</td>
<td>Desmoplastic/nodular</td>
<td>None</td>
<td>Inherited</td>
<td>c.72insC</td>
<td>c.72insC</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 months</td>
<td>Desmoplastic/nodular</td>
<td>None</td>
<td>Inherited</td>
<td>c.72insC</td>
<td>c.72insC</td>
</tr>
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<td>12-24 months</td>
<td>MB NOS</td>
<td>None</td>
<td>Inherited</td>
<td>c.72insC</td>
<td>c.72insC</td>
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<tr>
<td>Slade et al</td>
<td>2011</td>
<td>22 months</td>
<td>Desmoplastic/nodular</td>
<td>None</td>
<td>NA</td>
<td>c.846insC</td>
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<td></td>
<td>23 months</td>
<td>Desmoplastic/nodular</td>
<td>None</td>
<td>Inherited</td>
<td>c.1022 + 1G&gt;A</td>
<td>c.1022 + 1G&gt;A</td>
</tr>
</tbody>
</table>

**Abbreviations:** MB, medulloblastoma; MBEN, MB with extensive nodularity; NA, not available; NOS, not otherwise specified.
years of age. Because all transmitting parents were fathers in the families in which the mutations were inherited, the role of a parental imprinting could be discussed. However, this possibility can probably be ruled out, because in our previous report on familial medulloblastoma, most medulloblastomas occurred in children who had inherited the SUFU mutation from their mother.\textsuperscript{15}

Because the aim of this study was to assess the role of germline SUFU mutations in apparently sporadic medulloblastoma, families with several cases of medulloblastoma were excluded. However, the risk of medulloblastoma in siblings exists\textsuperscript{15} and justifies a proposal of SUFU mutation screening in all patients affected by medulloblastoma in the first years of life. Additional studies should aim to assess carefully the risk of cancer associated with these mutations to enable genetic counseling for families carrying such mutations. Meanwhile, in these families, all young children carrying a SUFU mutation should be offered careful follow-up, including brain magnetic resonance imaging during the first years of life. The possibility of offering prenatal diagnosis in a new pregnancy is still a matter of debate because of the incomplete penetrance of the mutations.

In conclusion, our report suggests that germline SUFU mutations are responsible for more than 50\% of seemingly sporadic desmoplastic/MBEN medulloblastomas in patients diagnosed at $<3$ years of age. This has prompted us to recommend genetic testing for all children affected by SHH-driven medulloblastoma before this age of onset.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The author(s) indicated no potential conflicts of interest.

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Provision of study materials or patients: Laurence Brugière, Stéphanie Puget, Christelle Dufour

Collection and assembly of data: Laurence Brugière, Audrey Remenieras, Pascale Varlet, Sébastien Forget, Véronique Byrde, Johny Bombled, Stéphanie Puget, Christelle Dufour

Data analysis and interpretation: Laurence Brugière, Audrey Remenieras, Gaëlle Pierron, Olivier Caron, Olivier Delattre, Brigitte Bressac-de Paillerets

Manuscript writing: All authors

Final approval of manuscript: All authors

**REFERENCES**


