CCR PEDIATRIC ONCOLOGY SERIES

Cancer Surveillance in Gorlin Syndrome and Rhabdoid Tumor Predisposition Syndrome

William D. Foulkes[1], Junne Kamihara[2], D. Gareth R. Evans[3], Laurence Brugières[4], Franck Bourdeaut[5], Jan J. Molenaar[6], Michael F. Walsh[7], Garrett M. Brodeur[8], and Lisa Diller[2]

Abstract

Gorlin syndrome and rhabdoid tumor predisposition syndrome (RTPS) are autosomal dominant syndromes associated with an increased risk of childhood-onset brain tumors. Individuals with Gorlin syndrome can manifest a wide range of phenotypic abnormalities, with about 5% of family members developing medulloblastoma, usually occurring in the first 3 years of life. Gorlin syndrome is associated with germline mutations in components of the Sonic Hedgehog pathway, including Patched1 (*PTCH1)* and Suppressor of fused (*SUFU)*. *SUFU* mutation carriers appear to have an especially high risk of early-onset medulloblastoma. Surveillance MRI in the first years of life in *SUFU* mutation carriers is, therefore, recommended. Given the risk of basal cell carcinomas, regular dermatologic examinations and sun protection are also recommended. Rhabdoid tumors (RT) are tumors initially defined by the descriptive "rhabdoid" term, implying a phenotypic similarity with rhabdomyoblasts at the microscopic level. RTs usually present before the age of 3 and can arise within the cranium as atypical teratoid/rhabdoid tumors or extracranially, especially in the kidney, as malignant rhabdoid tumors. However, RTs of both types share germline and somatic mutations in *SMARCB1* or, more rarely, *SMARCA4*, each of which encodes a chromatin remodeling family member. *SMARCA4* mutations are particularly associated with small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). The outcome following a diagnosis of any of these tumors is often poor, and the value of surveillance is unknown. International efforts to determine surveillance protocols are underway, and preliminary recommendations are made for carriers of *SMARCB1* and *SMARCA4* mutations. *Clin Cancer Res; 23(12); e62–e67. ©2017 AACR.*

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Gorlin Syndrome

Introduction and clinical features

Gorlin syndrome (OMIM #109400), also known as Gorlin–Goltz syndrome, nevoid basal cell carcinoma syndrome (NBCCS), or basal cell nevus syndrome (BCNS), is a heritable cancer predisposition syndrome with an autosomal dominant pattern of inheritance. Gorlin and Goltz described a syndrome that included multiple basal cell carcinomas, jaw cysts, and bifid ribs in 1960 (1). The incidence of Gorlin syndrome is approximately one in 15,000 births (2). Affected individuals can have multiple phenotypic abnormalities, with characteristic features described in over 50% of individuals that may include coarse facial appearance, macrocephaly, and hypertelorism (3, 4). Diagnostic criteria for Gorlin syndrome have been previously proposed and refined by several groups (3, 5–7). These share the following major criteria: (i) multiple basal cell carcinomas or basal cell carcinoma occurring at a young age (less than 30 years old at diagnosis), (ii) jaw keratocysts, (iii) plantar or palmar pits, (iv) lamellar calcification of the falx cerebri, and (v) first-degree relative with Gorlin syndrome. Approximately 75% of individuals with Gorlin syndrome have a first-degree relative with the syndrome, with the remainder presumably representing *de novo* germline mutations. Full diagnostic criteria have been recently outlined by Jones and colleagues (8).

Individuals with Gorlin syndrome are at risk for developing both benign and malignant neoplasms. Multiple basal cell skin carcinomas are a hallmark of the syndrome, and they arise most frequently on the face, back, and neck (8). Men and women are equally affected, without any clear genotype–phenotype correlation for the timing or number of basal cell carcinomas that develop (8). These generally present in the teenage/young adult years, but these skin tumors have been reported in children as young as 2 years old (9, 10). Cardiac fibromas may develop in infants and ovarian fibromas in adolescent girls and women, and these may cause physiologic compromise of normal function, especially when calcified. Rhabdomyosarcomas and fetal rhabdomyomas have also been reported in Gorlin syndrome, although these histologies are quite rare (<10 reported cases of each), and they are notably absent from larger population-based

[1]Departments of Human Genetics, Medicine and Oncology, McGill University, Montreal, Québec, Canada. [2]Dana-Farber/Boston Children's Cancer and Blood Disorders Center and Harvard Medical School, Boston, Massachusetts. [3]Division of Evolution and Genomic Science, Department of Genomic Medicine, MAHSC, University of Manchester, Saint Mary's Hospital, Manchester, England. [4]Child and Adolescent Cancer Department, Gustave Roussy Institute, Villejuif, France. [5]Institut Curie, Integrated Cancer Research Site, Paris, France. [6]Princess Máxima Center for Pediatric Oncology, Amsterdam, the Netherlands. [7]Memorial Sloan Kettering Cancer Center, New York, New York. [8]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

Note: W.D. Foulkes and J. Kamihara share primary authorship.

G.M. Brodeur and L. Diller share senior authorship.

Corresponding Author: Lisa Diller, Pediatric Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02115. Phone: 617-632-5642; E-mail: Lisa_Diller@dfci.harvard.edu

doi: 10.1158/1078-0432.CCR-17-0595

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studies of Gorlin syndrome (11). A wide spectrum of other tumors has been reported, but the relative risk of these other tumors in Gorlin syndrome patients is unclear.

Importantly, approximately 5% of individuals with Gorlin syndrome develop medulloblastoma (5, 12). Cases occur at a mean age of 2 years old, significantly younger than in patients with sporadic medulloblastoma. They are predominantly of the desmoplastic subtype and are often the first manifestation of the syndrome (12–14). In one review of 36 cases, 24 medulloblastomas occurred by 2 years of age, with all but one (97%) of the remaining cases occurring by the age of 5 (14). In addition, patients who are survivors of medulloblastoma treated with therapeutic radiation have a high risk of developing a large number of basal cell carcinomas (>1,000) in the radiation field (15, 16).

Genes responsible for Gorlin syndrome

Germline mutations in genes of the sonic hedgehog (SHH) signaling pathway, including Patched1 (*PTCH1)* and Suppressor of fused (*SUFU)*, are implicated in Gorlin syndrome (17–21). Heterozygous germline mutations in *PTCH1* have been detected in the majority of individuals with Gorlin syndrome. Less frequently, germline mutations in *SUFU* are observed (20).

Derangements of the SHH pathway have also been linked to the pathogenesis of sporadic medulloblastoma, with inactivating somatic mutations in the SHH pathway identified in both adult and pediatric medulloblastomas, as well as in basal cell carcinomas and selected other malignancies. These inactivating mutations act to derepress or activate SHH pathway signaling, which is normally active only during brain development.

The *PTCH1* gene product is a receptor for SHH or other SHH-related ligands. SHH binding to PTCH1 results in an alteration in Smo (smoothened) activity; normal PTCH1 represses Smo and, when mutant, promotes Smo to activate the signaling complex comprised of Gli-1 (glioma-associated oncogene) and SUFU. Germline mutations in both *SUFU* and *PTCH1* are associated with LOH of the remaining allele in the tumor and activation of the SHH pathway. This activation results in unregulated expression of pathways involved in proliferation and inhibition of apoptosis (22).

Genotype–phenotype correlations of medulloblastoma risk

The risk of medulloblastoma in individuals with germline *PTCH1* mutations is low, estimated to be <2% from one large series in which two of 115 individuals with *PTCH1*-related Gorlin syndrome developed medulloblastoma (20). In contrast, *SUFU*-related Gorlin syndrome is highly associated with medulloblastoma predisposition, with three of nine Gorlin syndrome patients with germline *SUFU* mutations developing medulloblastoma in the same series (20). Germline nonsense mutations, missense mutations, and deletions in *SUFU* have been described in families with medulloblastoma (20, 23).

Young children with medulloblastoma but without obvious clinical features of Gorlin syndrome have also been found to be germline carriers of *SUFU* mutations. In one recent series, germline *SUFU* mutations were identified in eight of 131 medulloblastoma patients (23). Young age (<3 years) and specific histologic subtypes (extensive nodularity and desmoplastic/nodular types) were each associated with a higher likelihood of germline *SUFU* mutations (23).

Kool and colleagues (24) performed genomic profiling of 133 cases (83 pediatric and 50 adult) of SHH-related medulloblastomas (one of four major medulloblastoma subtypes), including matched germline testing when available. Among 60 tumors found to have *PTCH1* mutations, two germline *PTCH1* mutations were identified. Of 10 tumors with *SUFU* mutations, six were found to harbor the *SUFU* mutation in the germline (24).

Previously published tumor surveillance protocols for Gorlin syndrome family members

Carriers of germline mutations as well as those individuals meeting clinical criteria for Gorlin syndrome should be followed by a clinical geneticist or the equivalent for evaluation and management of a wide range of anatomic, skeletal, and other organ system abnormalities. Guidelines for early detection and prevention of benign and malignant neoplasms that occur in Gorlin syndrome have been proposed by others (3, 6, 25). These recommendations focus on dermatologic surveillance and avoidance of radiation, baseline echocardiogram to look for cardiac fibromas, jaw panorex for keratocyst identification, and ultrasound for ovarian fibromas. Annual brain MRIs have also been recommended until age 8 (6). However, with the identification of the different risks of medulloblastoma in *SUFU* versus *PTCH1* mutation carriers, Smith and colleagues have recommended MRI screening only among *SUFU* mutation carriers, with recommendations for these to occur on a frequent basis (20). Incidence of basal cell carcinomas may be less common in *SUFU* mutations carriers than in Gorlin linked to *PTCH1* mutation (23), and jaw keratocysts have been predominantly described among *PTCH1*, but not *SUFU*, carriers (20).

Expert consensus recommendations

Our recommendations for tumor surveillance of gene carriers and members of syndromic families (Table 1) are based upon review of the literature and discussion in the AACR Childhood Cancer Predisposition Workshop, held in Boston, Massachusetts, in October 2016, and include the following:

General recommendations in caring for medulloblastoma patients

Clinicians caring for pediatric patients newly diagnosed with medulloblastoma should complete a full physical/skin exam and

Table 1. Gorlin syndrome surveillance recommendations

***PTCH1* mutation carriers**
Basal cell carcinoma screening annually by age 10, with increased frequency after first basal cell carcinoma observed
Baseline echocardiogram in infancy, dental exams with jaw X-ray every 12 to 18 months beginning at age 8, and an ovarian ultrasound by age 18
Low risk of medulloblastoma: no radiographic screening unless concerning neurologic exam, head circumference change, or other unusual signs or symptoms
If medulloblastoma: radiation-sparing treatment given risk of radiation-induced skin cancers
***SUFU* mutation carriers**
Same as *PTCH1* mutation carriers, with the exception of no jaw X-rays, as keratocysts have not been described
Additional medulloblastoma screening: consider every-4-month brain MRI through age 3 and then every-6-month brain MRI until the age of 5[a]. Radiation-sparing treatments are again recommended if a brain tumor should occur.

[a]Data to support optimal frequency and timing of imaging are not currently available.

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an extended family history, including assessment of family members with a history of any of the major or minor criteria, especially basal cell carcinoma. Children with medulloblastoma, in particular children <3 years old or those whose tumors show nodular or desmoplastic histologic features and/or somatic changes in the SHH pathway, should undergo genetic testing for germline mutations in *PTCH1* and *SUFU*.

Genetic testing of at-risk family members

Because medulloblastoma is the most life-threatening tumor of childhood Gorlin syndrome, and in these individuals usually present by age 2, consideration of very early genetic diagnosis among family members (infants) is recommended. Phenotypic features of the syndrome may not be apparent in infants, as these develop over time. Thus, in families with known mutations, predictive, site-specific testing of *PTCH1* and/or *SUFU* should be performed in infants, and families who otherwise meet clinical criteria should be offered diagnostic testing. Genetic counseling to identify all young, at-risk family members should be performed. In addition, counseling and testing of family members anticipating childbearing are recommended.

PTCH1 mutation carriers

Basal cell carcinoma screening should be conducted annually beginning by age 10, and more frequent exams should be performed after the first basal cell carcinoma is observed. Germline mutation carriers should undergo a baseline cardiac echo in infancy, annual dental exams with jaw X-ray starting at age 8, and an ovarian ultrasound at age 18. No radiographic brain imaging is recommended given the low risk of medulloblastoma, but in the setting of concerning neurologic exams, head circumference changes, or other unusual signs or symptoms, the possibility of a posterior fossa tumor should be considered, with appropriate imaging. If medulloblastoma occurs, radiation-sparing treatment techniques should be considered given the risk of radiation-induced skin cancers.

Medulloblastoma screening recommendations for *SUFU* mutation carriers

There are currently little data to support the optimal surveillance frequency and modality for medulloblastoma screening. However, given the young age of onset, some centers recommend frequent MRIs in infants with a pathogenic germline mutation in *SUFU*. We suggest a brain MRI every 4 months through age 3 and then changing to every 6 months until the age of 5. As in *PTCH* mutation carriers, if medulloblastoma occurs, radiation-sparing treatment techniques should be considered given the risk of radiation-induced skin cancers.

Summary and future directions

Gorlin syndrome is a medulloblastoma predisposition syndrome associated with germline mutations in genes in the SHH pathway. International collaborative efforts are needed to validate the screening recommendations above, in particular to better understand risk and timing/frequency of medulloblastoma surveillance.

Given major interest in the application of targeted therapies in medulloblastomas, particularly for the treatment of the SHH subtype with SHH inhibition, it is likely that paired tumor/germline testing will lead to the identification of a greater number of individuals with germline mutations in *PTCH1*, *SUFU*, or other SHH pathway genes. As individuals who may not otherwise fit conventional Gorlin syndrome phenotypes may be identified, and our molecular understanding of the syndrome grows, expansion and refinement of current clinical criteria are likely to evolve.

Rhabdoid Tumor Predisposition Syndromes

Introduction

Rhabdoid tumors (RT) are aggressive soft tissue tumors that generally present between 1 and 3 years of age, but they can arise in older patients (26). Atypical teratoid/rhabdoid tumors (AT/RT) arise in the central nervous system (CNS), and malignant RTs (MRT) arise in extracranial tissues, most often the kidney. The "rhabdoid" cells present in these tumors were so named because they are composed of cells with eosinophilic cytoplasm that histologically resemble developing rhabdomyoblasts (27). However, the cellular component can be variable and may consist of undifferentiated "small round blue cells," with mesenchymal and epithelial components. In some cases, the rhabdoid component may be completely absent from the tumor, and the tumor cells consist solely of the small cell embryonal component (26), so the diagnosis in these cases relies upon loss of the relevant protein (see below). The exact incidence of RTs is difficult to determine because the tumors are rare and, until recently, were difficult to diagnose with confidence. However, one study of 106 children with extracranial MRTs in the United Kingdom calculated the annual incidence to be 0.6 per 1 million children, with the incidence decreasing with increasing age: 5 per million in the first year of life, down to 0.04 per million at age 10 to 14 years (28). MRTs make up 14% of all soft tissue sarcomas diagnosed in the first year of life (28), and they constitute 18% of all renal cancers in infants, but this number decreases to approximately 2% in children between ages 1 and 14 (28). AT/RTs are considerably more frequent, accounting for 6% to 7% of all CNS neoplasms in patients below age 7 (29). A study on AT/RT patients in the United States calculated an incidence of 0.7 AT/RTs per million, and as high as 5.4 per million in children below 1 year of age (29).

Genes responsible for RT predisposition

The vast majority of RTs are characterized by loss-of-function mutations in *SMARCB1*, with few other genetic abnormalities. In recent years, however, it has become apparent that a small fraction of RTs are characterized by loss-of-function mutations in *SMARCA4* instead. These genes respectively encode the SMARCB1 (also called INI1 or BAF47) and SMARCA4 (also called BRG1) proteins, which are both members of the SWI/SNF chromatin remodeling complexes. Mutations in these genes result in loss of expression of the encoded proteins. Indeed, immunohistochemical detection of SMARCB1 loss is now included in the diagnostic criteria of malignant RTs.

RTs can present in a familial setting, with up to 35% of cases due to germline mutations (30, 31). Patients who carry a germline mutation in *SMARCB1* have RT predisposition syndrome type 1 (RTPS1; OMIM #609322), whereas those with *SMARCA4* germline mutations have RT predisposition syndrome type 2 (RTPS2; OMIM #613325). These mutations are inherited in an autosomal dominant manner, with a second "hit," in the form of either a somatic mutation or LOH of the wild-type allele in the tumor. Although the penetrance of germline *SMARCB1* and *SMARCA4* mutations is still unknown, it appears that *SMARCA4* mutations

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Table 2. Conditions associated with SMARCB1 and SMARCA4 germline mutations

SMARCB1 carriers	Mutation type
Rhabdoid tumor	LoF[a]
Schwannomatosis	LoF and missense
Multiple meningiomas	Missense
Nicolaides–Baraitser syndrome	Missense
Coffin–Siris syndrome	Missense
MPNST	LoF
SMARCA4 carriers	**Mutation type**
MRT	LoF
AT/RT	LoF
SCCOHT	LoF
Coffin–Siris syndrome	Missense

Abbreviations: LoF, loss of function; MPNST, malignant peripheral nerve sheath tumor; SCCOHT, small cell carcinoma of the ovary, hypercalcemic type.
[a]One missense mutation has been seen (31).

are less penetrant for AT/RT than *SMARCB1*. It has been suggested that all patients who present with RTs be tested for the presence of germline mutations (26). In addition, relatives of proven germline carriers should be tested for the familial mutation.

RTs are frequently fatal, but in rare cases, RTs can present in families, and relatives of patients may develop RTs or other tumors (32–34). Indeed, *SMARCB1* mutation carriers may be at risk for developing other tumors, including schwannomas, malignant peripheral nerve sheath tumors, cribriform neuroepithelial tumors, meningiomas, and other rare tumors (Table 2; refs. 35–39). Furthermore, germline carriers are at risk for developing second primary tumors (31). In a study of 100 patients with *SMARCB1*-mutated AT/RTs and MRTs, six of the 35 germline (17%) carriers had two primary tumors, most cases being synchronous occurrences (31). Eight patients had inherited mutations from unaffected parents, two of whom had gonadal mosaicism. However, two carrier fathers had developed schwannomas, and one carrier mother developed a benign CNS lesion (31).

SMARCA4 female mutation carriers have a higher risk of developing small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), which can be regarded as a special type of MRT and was found to be very similar to RTs in clinical, histologic, genomic, and epigenomic characteristics (40–42). Although these tumors represent a distinct clinical entity, the similarities to MRT have led some to suggest that SCCOHT be considered part of the rhabdoid tumor predisposition syndrome (RTPS) spectrum of tumors (Table 3).

No specific genotype–phenotype correlations have been identified that associate location of mutation and organ of RT presentation. Missense (and most often gain-of-function) mutations in *SMARCB1* and *SMARCA4* are most often associated with rare developmental syndromes, including Coffin–Siris syndrome (43, 44) and Nicolaides–Baraitser syndrome (45). However, missense *SMARCB1* and *SMARCA4* mutations have been identified in RTs and SCCOHT (31, 46), and loss-of-function mutations have been seen in developmental disorders (47). Both missense and nonsense *SMARCB1* mutations have been seen in schwannomatosis, but the nonsense mutations may be localized to specific regions of the gene and are thought to be hypomorphic loss of function (48).

Recommended surveillance protocols for RTs

No formal recommendations for surveillance of carriers have been established yet, as penetrance remains unclear and RTs can arise in multiple tissues. When considering screening for *SMARCB1*-related RTs, it is important to note the following points: (i) the very young age at diagnosis of RT; (ii) the difficulties of screening for these aggressive tumors associated with rapid onset; (iii) the potential risk for second malignancy, the spectrum of which is unknown; and (iv) the extreme rarity of familial cases. We recommend surveillance guidelines as summarized in Table 4. The recommendations for known carriers of truncating germline SMARCB1

Table 3. Clinicopathologic characteristics of RTPS spectrum tumors

	MRT (intra-/extracranial)	SCCOHT (ovarian RT)
Median age of onset	20 months (birth through adulthood, with most cases in infancy/early childhood)	24 years (14 months–56 years)
5-year survival	10%–30%	~33%
Cell type	Rhabdoid cells prominent, small cell component usually present, rhabdoid cells may be difficult to identify	50% small cell, 50% large cell (resembling rhabdoid cells)
Germline mutations (%)	35%	43%
Genes mutated/protein expression lost	SMARCB1 (>98%) SMARCA4 (<2%)	SMARCA4 (>98%) SMARCB1 (<2%)

Table 4. Suggested surveillance for rhabdoid tumors

	Organ	Type of mutation	
Gene	**at risk**	**Germline truncating**	**Germline missense**
SMARCB1	Brain	MRI q 3 months to age 5 years	No screening, generally no/very low risk
	Abdomen	Consider WBMRI to age 5 years, undetermined frequency. Ultrasound q 3 months	No screening, generally no/very low risk[a]
SMARCA4	Brain	No data available, risks likely very low	
	Abdomen	No data available, risk likely low to very low	
	Ovary	No data available, abdominal ultrasound q 6 months may be justified, role, if any, of MRI unknown. Preventive oophorectomy may be justified outside of the pediatric age range	

Abbreviations: q, every; WBMRI, whole-body MRI.
[a]Schwannomas may result from missense mutations and may justify MRI.

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mutations include every-3-month MRI of the brain, as well as ultrasound of the abdomen/kidneys during early infancy through age 5. Whole-body MRI may be considered, but there are little data to guide clinicians in terms of best timing and schedule for this.

For female relatives of *SMARCA4* mutation carriers, there are no official recommendations, but periodic ultrasounds have been suggested for younger women, and prophylactic oophorectomies are recommended for older women (49). The penetrance for SCCOHT in germline carriers of SMARCA4 is not well established. For female carriers of a germline mutation, genetic counseling and prophylactic oophorectomy should be considered after completion of puberty. The risk of SCCOHT and the decision to undergo prophylactic surgery will be individualized and informed by the family history, the age of the patient, the patient's reproductive plans, and by emerging data that will help with estimation of risk. *SMARCA4*-deficient SCCOHT has not been seen in women over age 60 (42), so screening recommendations can be altered in older women.

Conclusions

Germline mutations in *SMARCB1* and *SMARCA4* lead to RTPS, with risk of developing intra- and extracranial RTs, extremely aggressive tumors with young age of onset. The ongoing and detailed characterization of AT/RT and MRT (50, 51) will likely lead to further biological insights that can better delineate molecular subtypes of these tumors and may lead to novel therapeutic avenues. Despite this progress, how best to approach early cancer surveillance for germline carriers at risk for these rare and aggressive tumors is likely to remain an area of significant clinical challenge.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

W.D. Foulkes would like to thank Dr. Leora Witkowski for her contribution to this article.

Received February 28, 2017; revised April 17, 2017; accepted April 28, 2017; published online June 15, 2017.

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William D. Foulkes, Junne Kamihara, D. Gareth R. Evans, et al.

Clin Cancer Res 2017;23:e62-e67.

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