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Rhabdoid Tumor Predisposition Syndrome

Synonyms: Rhabdoid Predisposition Syndrome, RTPS

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Summary

Clinical characteristics

Rhabdoid tumor predisposition syndrome (RTPS) is characterized by a markedly increased risk for the development of rhabdoid tumors – rare and highly aggressive malignant tumors occurring predominantly in infants and children younger than age three years. Malignant rhabdoid tumors can occur in almost any anatomic location. They often occur in the central nervous system (i.e., atypical teratoid/rhabdoid tumor]); more than 50% occur in the cerebellum. Other common locations include extracranial malignant rhabdoid tumors (e.g., rhabdoid tumors of the head and neck, paravertebral muscles, liver, bladder, mediastinum, retroperitoneum, pelvis, and heart), rhabdoid tumor of the kidney, and possibly small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT). More than 70% of individuals with RTPS present before age 12 months with synchronous tumors that exhibit aggressive clinical behavior.

Diagnosis/testing

The diagnosis of RTPS is established in a proband with a rhabdoid tumor and/or a family history of rhabdoid tumor and/or multiple SMARCB1- or SMARCA4-deficient tumors (synchronous or metachronous), and a heterozygous disease-causing germline variant in *SMARCB1* (RTPS1) or *SMARCA4* (RTPS2) identified by molecular genetic testing.

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Management

Treatment of manifestations: Because of the rarity of RTPS, standards for management are evolving. Most individuals are treated using intensive multimodal therapeutic strategies – according to institutional preference – combining surgery, radiotherapy, and chemotherapy. The intensive multimodal treatment strategies required for clinically aggressive tumors in children with RTPS lead to a high rate of secondary complications. Consider risk-reducing treatment strategies (e.g., postpone or replace radiotherapy with high-dose chemotherapy or proton beam therapy; use targeted therapy concomitantly with, or before, standard chemotherapy).

Prevention of primary manifestations: Prophylactic risk-reducing bilateral salpingo-oophorectomy may be discussed following the end of family planning in women with *SMARCA4*-related RTPS because of the high risk of developing SCCOHT. The medical and ethical ramifications involved require an interdisciplinary approach including counseling and further research.

Surveillance: For all individuals with a disease-causing germline variant in *SMARCB1* or *SMARCA4* (regardless of age), whole-body MRI should be offered at diagnosis:

- **Birth to age six months.** Monthly (or at least every 2-3 months) thorough clinical examination including neurologic examination, ultrasound of the abdomen and neck, and head ultrasound or brain and spine MRI or whole-body MRI
- **Age seven to 18 months.** Every two to three months, thorough clinical examination including neurologic examination and ultrasound of the abdomen and neck. Consider brain and spine MRI as whole-body MRI resolution may not be sufficient for brain structures.
- **Age 19 months to five years.** Every three months, thorough clinical examination including neurologic examination, ultrasound of the abdomen and neck, and brain and spine MRI.
- **After age five years.** Every six months, thorough clinical examination including neurologic examination and annual whole-body MRI. Individuals with *SMARCA4*-related SCCOHT should have an abdominal and pelvic ultrasound every six months.

Evaluation of relatives at risk: It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual to identify as early as possible those who would benefit from prompt initiation of tumor surveillance.

Genetic counseling

RTPS is inherited in an autosomal dominant fashion. The vast majority of individuals with *SMARCB1*-related RTPS have a *de novo* disease-causing *SMARCB1* germline variant. Most reported individuals diagnosed with *SMARCA4*-related RTPS inherited a disease-causing variant from a parent without a history of a rhabdoid tumor or SCCOHT. Each child of an individual with a germline *SMARCB1*- or *SMARCA4* disease-causing variant has a 50% chance of inheriting this variant. The penetrance of *SMARCB1*-related RTPS may be extremely high in individuals who inherit a *SMARCB1* disease-causing variant. The penetrance of *SMARCA4*-related RTPS appears to be incomplete. The types of RTPS-related tumors vary among family members with the same disease-causing variant. Once the *SMARCB1* or *SMARCA4* disease-causing variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Rhabdoid tumor predisposition syndrome (RTPS) **should be suspected** in an individual with any of the following clinical or laboratory features.

Clinical features. Any rhabdoid tumor with the following features is particularly suspicious:

- Congenital presentation (i.e., prenatal diagnosis or symptoms within the first 28 days of life)
- Early-onset rhabdoid tumor (age <12 months)
- Advanced stage of rhabdoid tumor at diagnosis (e.g., $>M_1$ by Chang classification; Stage ≥II in extracranial malignant rhabdoid tumor [Harisiadis & Chang 1977])
- Synchronous rhabdoid tumors (>1 primary rhabdoid tumor)
- Family history of rhabdoid tumor, small-cell carcinoma of the ovary, hypercalcemic type, or other malignant entities such as cribriform neuroepithelial tumor, malignant peripheral nerve sheath tumor, myeloid sarcoma, epithelioid schwannoma, meningioma, benign myoepithelioma, chondrosarcoma, and/or ganglioglioma
- Family history of RTPS

Germline molecular genetic testing for RTPS is recommended in any individual with:

- A rhabdoid tumor (at any age), familial rhabdoid tumors, multifocal tumors, or congenital onset tumors;
- A SMARCB1-deficient tumor with a family history of rhabdoid tumor OR family history of nonspecified cancer in early childhood (age <5 years);
- A SMARCA4-deficient tumor with a family history of rhabdoid tumor OR family history of nonspecified cancer in early childhood (age <5 years).

Note: (1) It remains to be determined whether adult-onset rhabdoid tumors are caused by disease-causing germline variants in *SMARCB1* or *SMARCA4*. (2) As morphologic rhabdoid features may not be present in all rhabdoid tumor biopsies because of inter- and intratumoral heterogeneity, any small blue round cell tumors in infants and young children should be evaluated for absence of nuclear SMARCB1 or SMARCA4 staining.

Laboratory features of tumor tissue

- **Immunohistochemistry.** Absence of SMARCB1 (INI-1) or SMARCA4 (BRG-1) staining indicating lack of functional protein in tumor tissue
- **Molecular genetic testing.** Somatic *SMARCB1* or *SMARCA4* disease-causing variants identified in a rhabdoid tumor. Note: Fresh-frozen tumor is preferable; formalin-fixed, paraffin-embedded samples may also be suitable.

Establishing the Diagnosis

There is currently no consensus regarding formal diagnostic criteria for RTPS.

The diagnosis of RTPS **is established** in any proband with both of the following:

- A rhabdoid tumor and/or a family history of rhabdoid tumor and/or multiple SMARCB1- or SMARCA4-deficient tumors (synchronous or metachronous) AND
- Identification of a disease-causing germline variant in *SMARCB1* or *SMARCA4* using molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **serial single-gene testing** and use of a **multigene panel**.

- **Serial single-gene testing** may be considered in individuals with absence of SMARCB1 or SMARCA4 identified on tumor immunohistochemistry:
    - **Absence of SMARCB1.** Sequence analysis and gene-targeted deletion/duplication analysis of *SMARCB1* may be performed first.
    - **Absence of SMARCA4.** Sequence analysis and gene-targeted deletion/duplication analysis of *SMARCA4* may be performed first.

- **A multigene panel** that includes *SMARCB1, SMARCA4*, and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel provides the best opportunity to identify the genetic cause of the condition while limiting identification of disease-causing variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) Multigene panel testing should include deletion/duplication analysis designed to detect smaller single-exon deletions and duplications and larger multiexon and whole gene deletions and duplications.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Rhabdoid Tumor Predisposition Syndrome

Gene [1]	Proportion of RTPS Attributed to Disease-Causing Variants in Gene	Proportion of Probands with a Disease-Causing Variant [2] Detectable by Method	
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
SMARCB1	~85%-95% [5]	~49% [6, 7]	~51% [6, 7]
SMARCA4	~5%-15% [8]	4/9 persons [6, 9]	5/9 persons [6, 9]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. In persons with RTPS confirmed by germline molecular testing, a germline *SMARCB1* pathogenic variant was identified in 84/90 persons [EU-RHAB – Author, personal communication], 29/35 persons [Author, personal communication], and 184/192 persons [Holsten et al 2018].
6. EU-RHAB – Author, personal communication
7. Bourdeaut et al [2011], Biegel et al [2014]
8. In persons with RTPS confirmed by germline molecular testing, a germline *SMARCA4* pathogenic variant was identified in 6/90 persons [EU-RHAB – Author, personal communication], 6/35 persons [Authors, personal communication], and 8/192 persons [Holsten et al 2018].
9. Hasselblatt et al [2014], Andrianteranagna et al [2021], Holdhof et al [2021]

Clinical Characteristics

Clinical Description

Rhabdoid tumor predisposition syndrome (RTPS) is characterized by a markedly increased risk of developing rhabdoid tumors.

Rhabdoid tumors are rare and highly aggressive malignant tumors occurring predominantly in infants and children younger than age three years. The term rhabdoid is derived from the histologic resemblance of tumor cells to rhabdomyoblasts. Rhabdoid tumors are characterized by heaps of cells with an eccentric nucleus and

prominent nucleoli, abundant cytoplasm with eosinophilic inclusion bodies, and distinct cellular membranes. Immunohistochemically, rhabdoid tumor cells are characterized by increased expression of vimentin (a nonspecific marker), epithelial membrane antigen, cytokeratins, and loss of SMARCB1 protein (a strong indicator for rhabdoid tumor) or, more rarely, of SMARCA4.

As morphologic rhabdoid features may not be present in all rhabdoid tumor biopsies because of inter- and intratumoral heterogeneity, any small blue round cell tumor in infants and young children should be evaluated for absence of nuclear SMARCB1 staining [Agaimy 2019].

Primary rhabdoid tumor locations include the following:

- Central nervous system: atypical teratoid/rhabdoid tumor (AT/RT); >50% are cerebellar.
- Head and neck, paravertebral muscles, liver, bladder, mediastinum, retroperitoneum, pelvis, and heart: extracranial malignant rhabdoid tumor (eMRT)
- Kidney: rhabdoid tumor of the kidney (RTK)
- Ovary: small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT)

Rhabdoid tumors have been reported in nearly all anatomic locations [Brennan et al 2013, Frühwald et al 2020, Nemes et al 2021].

More than 70% of individuals with RTPS present before age 12 months with synchronous tumors that exhibit aggressive clinical behavior, often in one of the following clinical settings:

- Pre- or perinatally detected synchronous rhabdoid tumors [Negahban et al 2010, Fossey et al 2017, Nemes et al 2018, Schenone et al 2021]
- Infantile-onset or congenital rhabdoid tumor, presenting at a median age of five and a half months (range: prenatal to 60 months) compared to individuals with sporadic rhabdoid tumors (median age: 11.5 to 29.5 months; range: 1 day to 228 months) [Nemes et al 2018; Frühwald et al 2020; Nemes et al 2021; EU-RHAB – Author, personal communication].

  Note: A bias toward increased molecular testing in younger individuals may confound the data.
- Synchronous (multiple primary) rhabdoid tumors. Ninety-one percent (10/11) of individuals with synchronous tumors demonstrated disease-causing germline variants [Nemes et al 2018]. Individuals with RTPS have a higher incidence of multiple rhabdoid tumors. Twenty-two of 90 individuals (24.5%) with RTPS in the EU-RHAB registry presented with synchronous tumors at diagnosis [EU-RHAB – Author, personal communication].
- Family history of a rhabdoid tumor, epithelioid schwannoma, malignant peripheral nerve sheath tumor, myeloid sarcoma [Metts et al 2017], neuroblastoma [Coorens et al 2020], meningioma, benign myoepithelioma, chondrosarcoma, ganglioglioma, or cribriform neuroepithelial tumor [Bruggers et al 2011, Forest et al 2012, van den Munckhof et al 2012, Bosse et al 2014, Smith et al 2014, Evans et al 2018, Kehrer-Sawatzki et al 2018]. Rarely, AT/RTs occur in adult heterozygotes; for example, a sellar AT/RT-like tumor was described in a woman age 51 years whose daughter and brother had both died of malignant rhabdoid tumor [Voisin et al 2019].
- Family history of SCCOHT for *SMARCA4*-related RTPS (germline *SMARCB1* disease-causing variants have not been reported in individuals with SCCOHT) [Schneppenheim et al 2010, Witkowski et al 2013, Witkowski et al 2016]

  Note: No individual with SCCOHT published to date developed a malignant rhabdoid tumor (MRT) during infancy. Apart from SCCOHT, truncating germline disease-causing variants of *SMARCA4* have also been associated with undifferentiated uterine sarcomas and a single case of BRG1/SMARCA4-

deficient lung carcinoma [Moes-Sosnowska et al 2015, Lavrut et al 2016, Witkowski et al 2017, Lin et al 2019, Connor et al 2020].

- Clinically aggressive rhabdoid tumors. Tumor progression at the time of follow up was identified in 84.5% (76/90) of individuals with RTPS [EU-RHAB – Author, personal communication]. Progression occurred while on chemotherapy in 48% (35/73) of individuals with RTPS [Sredni & Tomita 2015; EU-RHAB – Author, personal communication].
- Rhabdoid tumor and syndromic features suggestive of 22q11.2 distal deletion syndrome (OMIM 611867)

Prognosis. Individuals with RTPS potentially have a worse prognosis than those with a sporadic rhabdoid tumor, although long-term survival has been reported in some individuals [Kordes et al 2014, Seeringer et al 2014b, Nemes et al 2018, Frühwald et al 2020].

Pathogenesis. Various studies have revealed three molecular subgroups in AT/RT characterized by distinct transcriptional histopathologic and clinical characteristics: ATRT-TYR, ATRT-SHH, and ATRT-MYC, in accordance with overexpressed pathways or genes [Birks et al 2011, Birks et al 2013, Torchia et al 2015, Johann et al 2016, Torchia et al 2016, Ho et al 2020].

While these molecular groups are widely accepted in AT/RT, the molecular subgroups of eMRT are still evolving. Chun et al [2016] demonstrated two distinct molecular subgroups in eMRT (subgroup 1 and subgroup 2). Within subgroup 1, significantly overexpressed genes were linked to BMP signaling and differentiation. In subgroup 2, the most significantly overexpressed genes were linked to cell adhesion and migration, WNT signaling, and differentiation.

In a more recent integrative analysis of genomic, transcriptomic, and epigenomic profiles of 301 malignant rhabdoid tumors, five DNA methylation groups were identified based on anatomic site, *SMARCB1* variants, gene expression pathways, DNA methylation-based pathway enrichment, and immune cell infiltration [Chun et al 2019]. Group 2 and group 5 of this integrative subgrouping correspond to the subgroups AT/RT-TYR and AT/RT-SHH as previously described in Johann et al [2016] and Ho et al [2020].

- Group 1 – AT/RT-MYC-like (ATRT-MYC and a subgroup of eMRT)
- Group 2 – AT/RT-TYR
- Group 3 – RTK-like
- Group 4 – Extrarenal MRT-like
- Group 5 – AT/RT-SHH

Notably, subgroup 2 (identified by differential gene expression analyses) largely corresponded to group 3 (RTK-like), while there was no clear equivalent for subgroup 1.

Groups 1, 3, and 4 (AT/RT-MYC-like, RTK-like, and extrarenal MRT-like) overexpressed *HOX* and other homeobox-containing genes involved in mesodermal development.

Groups 2 and 5 (AT/RT-TYR and AT/RT-SHH) largely corresponded to the respective AT/RT subgroups and were characterized by an expression of melanosomal features (AT/RT-TYR) and a proneural gene expression profile (AT/RT-SHH).

These results suggest that eMRTs share molecular features with AT/RT-MYC. Another feature distinguishing AT/RT-TYR and AT/RT-SHH from most other pediatric brain tumors is genome-wide hypermethylation – a characteristic that is not present in eMRT subgroups 1 and 2 and AT/RT-MYC.

Information on the specific molecular characteristics of SMARCA4-deficient eMRT has been sparse until very recently. A recent study shed light on the specific transcriptomic and DNA methylation characteristics of these entities [Andrianteranagna et al 2021]. While SMARCB1-deficient eMRT clustered together with AT/RT-MYC,

the SMARCA4-deficient counterparts tended to form a separate cluster. Along a similar line, the transcriptomic characteristics of SMARCA4-deficient eMRT differed from SMARCB1-deficient eMRT. The molecular characteristics of the different eMRT subgroups are depicted in Figure 1.

Note: Current data suggest the value of subgroup determination for diagnostic and therapeutic decision making. A study by Brocks et al [2017] described an induction of cryptic transcription start sites (and thus putative neoantigens) following exposure to DNA demethylating agents. Whether this characteristic may also be found in a priori hypomethylated tumors remains to be studied.

Phenotype Correlations by Gene

SMARCA4. SCCOHT has been reported in individuals with *SMARCA4*-related RTPS and has not been reported in individuals with germline RTPS-associated *SMARCB1* disease-causing variants.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

SMARCB1. Penetrance of *SMARCB1*-related RTPS may be extremely high (>90% by age 5 years) [Holsten et al 2018, Nemes et al 2018]. However, these data may be based on selection bias, and larger series of systematically screened trios (parents and affected offspring) are needed to accurately define penetrance. Rarely a *SMARCB1* disease-causing variant is inherited from an unaffected parent or a parent with late-onset or undiagnosed RTPS [Ammerlaan et al 2008]. Germline mosaicism may account for up to half of the families with sibs affected by RTPS.

SMARCA4. Even less is known about the penetrance of *SMARCA4*-related RTPS. Penetrance is incomplete, as most individuals with *SMARCA4*-related RTPS have inherited the disease-causing variant from an unaffected, healthy parent [Schneppenheim et al 2010; Hasselblatt et al 2014; Andrianteranagna et al 2021; Holdhof et al 2021; EU-RHAB – Author, personal communication].

Nomenclature

RTPS may also be referred to as familial posterior fossa brain tumor syndrome.

RTPS1 refers to the predisposition associated with germline *SMARCB1* disease-causing variants.

RTPS2, as initially described by Schneppenheim et al [2010], refers to the predisposition associated with disease-causing germline *SMARCA4* variants, and could also be used to refer to *SMARCA4*-related cancers including SCCOHT.

Prevalence

Among newly diagnosed individuals with rhabdoid tumors, 25%-35% will have a disease-causing germline variant in *SMARCB1* [Bourdeaut et al 2011, Eaton et al 2011, Hasselblatt et al 2014, Frühwald et al 2020, Nemes et al 2021].

The incidence of rhabdoid tumors may be estimated according to the following data:

- The age-standardized annual incidence rate is between 5 (eMRT) and 8.1 per million (AT/RT) in children younger than age one year and decreases to between 0.6 and 2.2 per million at ages one to four years [Brennan et al 2013, Dho et al 2015, German Childhood Cancer Registry 2019, Frühwald et al 2020, Nemes et al 2021].

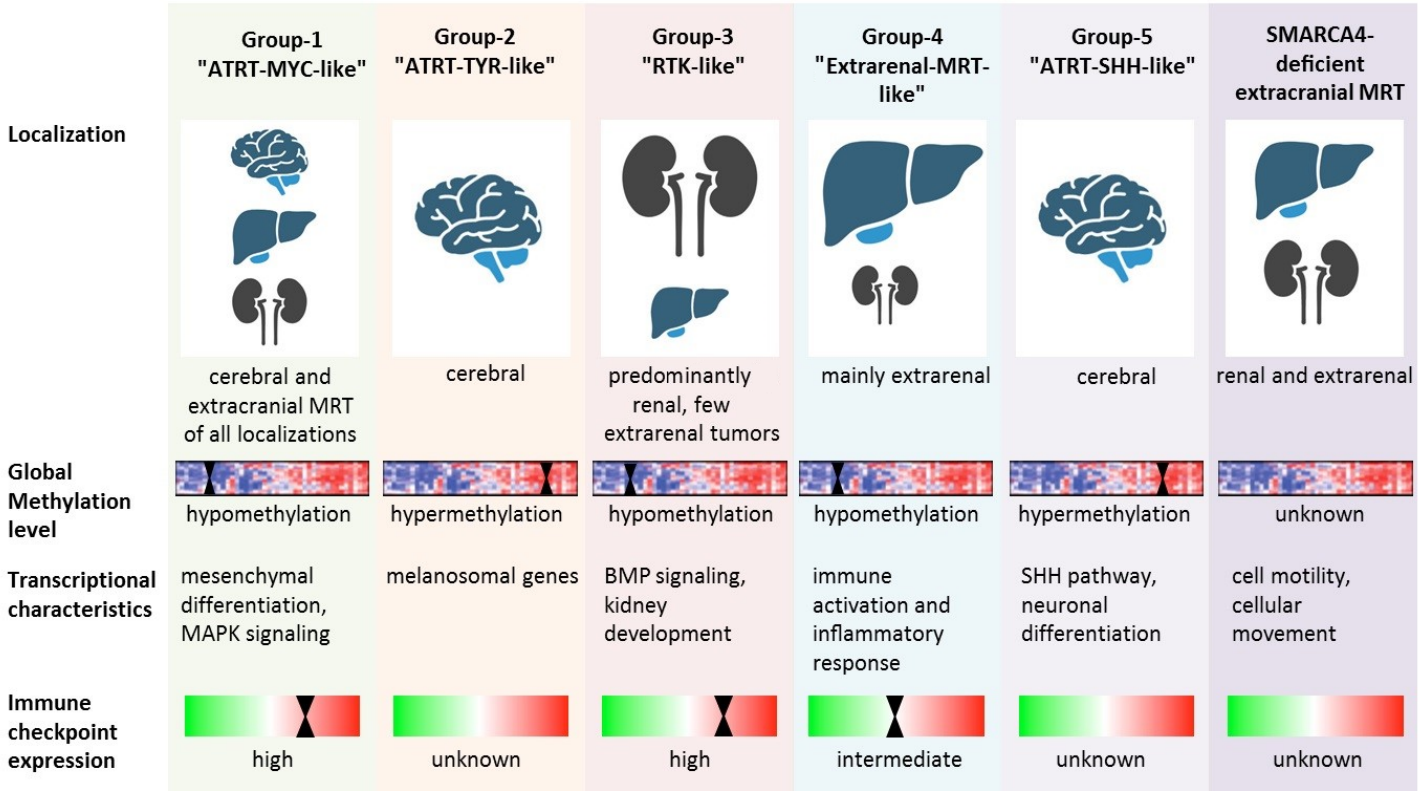

Figure 1. Overview of molecular features of the malignant rhabdoid tumor subgroups

Reprinted from Nemes et al [2022]

- In the United States, annual incidence among children younger than age 15 years is 0.89 per million for AT/RT, 0.32 per million for eMRT, and 0.2 per million for RTK [Heck et al 2013, Nakata et al 2020].

Genetically Related (Allelic) Disorders

Other phenotypes caused by germline disease-causing variants in *SMARCB1* and *SMARCA4* are summarized in Table 2. Of note, rhabdoid tumors have not been observed in any of these phenotypes.

Table 2. Allelic Disorders

Gene	Phenotype
SMARCB1	Schwannomatosis is characterized by a predisposition to develop multiple schwannomas &, less frequently, meningiomas [Gossai et al 2015, Kehrer-Sawatzki et al 2018].
	Coffin-Siris syndrome
	Coffin-Siris syndrome / Nicolaides-Baraitser syndrome intermediate phenotype
SMARCA4	Coffin-Siris syndrome [Errichiello et al 2017, Li et al 2020]

Sporadic tumors occurring as single tumors in the absence of other findings of rhabdoid tumor predisposition syndrome (RTPS) may harbor a somatic disease-causing variant of *SMARCB1* or *SMARCA4* that is not present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Demonstration of loss of the SMARCB1 or SMARCA4 protein (in tumor tissue) as a result of inactivation or loss of one allele of *SMARCB1* or *SMARCA4* (tumor tissue and constitutional samples) may suggest the diagnosis of rhabdoid tumor predisposition syndrome (RTPS). For example, an individual with a constitutional deletion of *SMARCB1* and an epithelioid sarcoma was reported by Le Loarer et al [2014]. In such cases the absence of a clinical and family history of rhabdoid tumor(s) distinguishes these individuals from those with RTPS.

Table 3. Hereditary Disorders in the Differential Diagnosis of Rhabdoid Tumor Predisposition Syndrome

Gene(s)	Disorder	MOI	Key Features	Additional Features / Comment
TP53	Li-Fraumeni syndrome	AD	Cancer predisposition syndrome assoc w/ high risk for diverse spectrum of childhood- & adult-onset malignancies	SMARCB1- or SMARCA4-deficient malignant brain tumors w/complex copy number alterations & germline *TP53* variants [1]
ANKRD11 (or 16q24.3 deletion incl *ANKRD11*)	KBG syndrome	AD	Macrodontia (esp of upper central incisors), characteristic facial features, short stature, DD/ID, & behavioral issues	Paratesticular rhabdoid tumor [2]
BAP1	*BAP1* tumor predisposition syndrome	AD	↑ risk for a number of cancers & a specific skin lesion, *BAP1*-inactivated melanocytic tumor	Meningioma, particularly a high-grade rhabdoid subtype, may be assoc w/*BAP1*-TPDS. [3]
DICER1	*DICER1* tumor predisposition	AD	↑ risk for PPB, pulmonary cysts, thyroid gland neoplasia, ovarian tumors incl sex cord-stromal tumors (e.g., embryonal rhabdomyosarcoma), & cystic nephroma	ERMS of the cervix most commonly occurs in pubertal & postpubertal adolescent girls & young women.

AD = autosomal dominant; *BAP1*-TPDS = *BAP1* tumor predisposition syndrome; DD/ID = developmental delay / intellectual disability; ERMS = embryonal rhabdomyosarcoma; MOI = mode of inheritance; PPB = pleuropulmonary blastoma

1. Hasselblatt et al [2022]

2. Behnert et al [2018]

3. Prasad et al [2021]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with rhabdoid tumor predisposition syndrome (RTPS), the following are recommended:

- For all individuals (regardless of age), a whole-body MRI should be offered at diagnosis.
- Individuals who have not yet developed a rhabdoid tumor should be referred to a pediatric oncologist or tumor surveillance program.
- In those with a tumor, prior to planning therapy consider consulting a radiologist to assist in the selection and review of subsequent imaging, to evaluate the size and location of the primary tumor, and to evaluate for the presence of synchronous tumors and/or metastases (whole-body MRI).
- For individuals with atypical teratoid/rhabdoid tumor (AT/RT), examine cerebrospinal fluid and determine classification according to Chang staging [Harisiadis & Chang 1977].
- Refer to genetic counseling to inform affected individuals and their families about the nature, mode of inheritance, and implications of RTPS to facilitate medical and personal decision making.

Treatment of Manifestations

Because of the rarity of RTPS, standards for management are evolving. Most individuals are treated using intensive multimodal therapeutic strategies combining surgery, radiotherapy, and chemotherapy according to institutional preference:

- The Children's Oncology Group has employed a combination of surgery, two cycles of induction chemotherapy (cisplatin, cyclophosphamide, etoposide, vincristine, methotrexate), three cycles of high-dose chemotherapy (HDCT) with stem cell rescue (thiotepa, carboplatin) as consolidation therapy, and radiotherapy according to age and stage [Reddy et al 2020].
- The Dana-Farber Consortium has tested combination therapy with surgery, radiotherapy, and chemotherapy (vincristine, dactinomycin, cyclophosphamide, cisplatin, doxorubicin, temozolomide and intrathecal methotrexate, cytarabine, and hydrocortisone) [Chi et al 2009].
- The EU-RHAB registry recommends using combination therapy for rhabdoid tumors of any location (e.g., AT/RT, rhabdoid tumor of the kidney, extracranial malignant rhabdoid tumor), including gross total resection, conventional chemotherapy (vincristine, dactinomycin, cyclophosphamide, doxorubicin, ifosfamide, carboplatin, etoposide), intrathecal methotrexate, and permissive use of HDCT with stem cell rescue (carboplatin, thiotepa) and radiotherapy (in individuals age >18 months). The feasibility of intensive multimodal regimens even in the youngest individuals including those affected by RTPS has been demonstrated [Seeringer et al 2014a, Bartelheim et al 2016, Furtwängler et al 2018, Benesch et al 2020, Frühwald et al 2020, Nemes et al 2021].
- The Canadian Brain Tumour Consortium retrospectively evaluated children diagnosed with rhabdoid tumors between 1995 and 2007. Among 40 individuals, 22 received conventional chemotherapy and 18 received HDCT regimens; 15 received adjuvant radiation. Notably, six of 12 long-term survivors never received any radiotherapy [Lafay-Cousin et al 2012].
- Zaky et al [2014] evaluated the Head Start III experience for newly diagnosed individuals with AT/RT. Between 2003 and 2009, 19 individuals were treated with a combination of surgery and five courses of induction chemotherapy followed by consolidation with myeloablative chemotherapy and autologous hematopoietic progenitor cell rescue and radiotherapy according to age and stage. In five individuals, toxicity-related deaths occurred; ten individuals died as a result of disease progression. The three-year overall survival (OS) and event-free survival rates were 26±10% and 21±9%, respectively.
- Schrey et al [2016] summarized HDCT data by an individual pooled data analysis of 12 manuscripts and 389 publications including prospective and retrospective studies focused on the treatment of children diagnosed with AT/RT. Data of 332 individuals demonstrated an improved outcome in those treated with HDCT with stem cell rescue and radiotherapy.
- Fischer-Valuck et al [2017] evaluated data of 361 children diagnosed with AT/RT between 2004 and 2012. The five-year OS rate was 29.9%. For individuals with localized disease treated with multimodal therapy (surgery, chemotherapy, and radiotherapy), it was significantly higher, with a five-year OS rate of 46.8%. Individuals younger than age three years at diagnosis showed a significantly worse OS rate (5-year OS = 27.7%) compared to older individuals (5-year OS = 37.5%) and were also significantly less likely to receive multimodal therapy (specifically, the radiotherapy component). The authors suggest early radiotherapy as an important factor for long-term cure.

Note: RTPS most commonly affects infants; therapy presents a complex challenge because of the vulnerability of infants. The use of aggressive multimodal treatment on the developing nervous system and other organ systems in a young individual may profoundly affect neurodevelopmental outcome and lead to significant short- and long-term side effects. Intensive induction chemotherapy may often achieve a good response, and individuals may proceed with radiotherapy or (tandem) HDCT followed by autologous stem cell support.

The intensive multimodal treatment strategies required for clinically aggressive tumors in children with RTPS lead to a higher rate of secondary complications. Therapies and interventions that may prevent secondary complications include consideration of risk-reducing treatment strategies (e.g., postponing or replacing radiotherapy with HDCT or proton beam therapy; targeted therapy used concomitantly with – or before – standard chemotherapy). It remains to be determined whether a subgroup of children may be cured by surgery and chemotherapy alone, thus avoiding the potential severe side effects of radiotherapy to the developing brain.

Prevention of Primary Manifestations

Prophylactic risk-reducing bilateral salpingo-oophorectomy may be discussed following the end of family planning in women with *SMARCA4*-related RTPS because of the high risk of developing small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT). The medical and ethical ramifications involved necessitate an interdisciplinary approach including counseling and further research [Berchuck et al 2015, Pejovic et al 2019].

Surveillance

Surveillance guidelines for individuals with RTPS have been provided by Teplick et al [2011], Foulkes et al [2017], and Frühwald et al [2021].

Birth to age six months. Monthly (or at least every 2-3 months) thorough clinical examination including neurologic examination, ultrasound of the abdomen and neck, and head ultrasound or brain and spine MRI or whole-body MRI (imaging modality is based on resources and need for anesthesia). Clinically suspicious regions should initially be evaluated by ultrasound. Note: This intensive surveillance may only be possible in a research setting; recommendations are based on the high risk of tumors within this age group.

Age seven months to 18 months. Every two to three months, thorough clinical examination including neurologic examination and ultrasound of the abdomen and neck; consider brain and spine MRI. Clinically suspicious regions should initially be evaluated by ultrasound. Note: Whole-body MRI resolution may not be sufficient for brain structures; MRI of the central nervous system will then need to be done separately.

Age 19 months to five years. Every three months, thorough clinical examination including neurologic examination, ultrasound of the abdomen and neck, and brain and spine MRI. Clinically suspicious regions should initially be evaluated by ultrasound.

After age five years the risk of developing a new rhabdoid tumor dramatically decreases [Eaton et al 2011]. It remains worthwhile, however, to screen individuals with RTPS for other manifestations (e.g., schwannomas, SCCOHT). A practical approach would include:

- Every six months, thorough clinical examination including neurologic examination;
- Annual whole-body MRI;
- Abdominal and pelvic ultrasound every six months in individuals with *SMARCA4*-related SCCOHT.

Note: (1) Current data do not allow for a determination of how long surveillance should continue. (2) Recommendations are subject to continuous updates; the authors recommend close monitoring of the evolving literature.

Agents/Circumstances to Avoid

Limit exposure to DNA-damaging agents including radiation (e.g., x-ray, CT, external beam radiotherapy), tobacco, UV light, and chemotherapy to minimize the lifetime risk of developing late-onset secondary cancers. Imaging tests utilizing radioactive compounds should be used only if absolutely necessary for essential health care. This recommendation is based on the increased risk of adverse effects in young developing children, not increased risk as a result of a *SMARCA4* or *SMARCB1* pathogenic variant.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk relatives of an affected individual by molecular genetic testing for the *SMARCB1* or *SMARCA4* disease-causing variant in the family.

- Early detection of individuals who are heterozygous for an *SMARCB1* or *SMARCA4* disease-causing variant allows prompt initiation of surveillance and treatment.
- Family members who have not inherited the disease-causing variant and their subsequent offspring have risks similar to the general population.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

The following clinical trials are currently recruiting unless otherwise indicated.

Table 4. Overview of Clinical Trials in Pediatric Malignant Rhabdoid Tumors Including Rhabdoid Tumor Predisposition Syndrome

Inhibitor Group	Inhibitor	ClinicalTrials.gov NCT Number	Phase	Study Completion
Epigenetic inhibitors	CUDC-907	NCT02909777	1	2022
	Vorinostat (SAHA)	NCT04308330	1	2022
	Tazemetostat	NCT02601937	1	2022
	Tazemetostat	NCT03155620	2	2027
	Tazemetostat	NCT03213665	2	2024
	Decitabine + Pembrolizumab	NCT03445858	1	2025
Cell cycle inhibitors	Abemaciclib	NCT02644460	1	2022
	Palbociclib	NCT03526250	2	2025
	Palbociclib	NCT03709680	1	2025
	Abemaciclib	NCT04238819	1	2023
Kinase inhibitors	Alisertib	NCT02114229	2	2027
	Sirolimus	NCT02574728	2	2022
	Everolimus + Lenvatinib	NCT03245151	1, 2	2022
	Adavosertib	NCT02095132	1, 2	2021
	Regorafenib	NCT02085148	1	2023
	Neratinib	NCT02932280	1,2	2024
	Pazopanib	NCT03628131	1, 2	2025
	Larotrectinib	NCT03834961	2	2022
	Ponatinib	NCT03934372	1, 2	2024
	Cabozantinib	NCT02867592	2	2021
	Cabozantinib	NCT03611595	1	2021
	Lenvatinib	NCT04447755	2	2024
Pathway-specific compounds	Tegavivint	NCT04851119	1, 2	2028

Table 4. continued from previous page.

Inhibitor Group	Inhibitor	ClinicalTrials.gov NCT Number	Phase	Study Completion
Immunotherapy	4-1BBζ B7H3-EGFRt-DHFR (selected) + 2nd-generation 4-1BBζ CD19-Her2tG	NCT04483778	1	2040
	2nd-generation 4-1BBζ EGFR806-EGFRt + 2nd-generation 4-1BBζ CD19-Her2tG	NCT03618381	1	2038
	AGAR T cells	NCT04377932	1	2040
	CAR T cells	NCT04715191	1	2040
	Nivolumab	NCT03465592	1, 2	2026
	Nivolumab + Entinostat	NCT03838042	1, 2	2023
	Nivolumab + Ipilimumab	NCT04416568	2	2025
	Nivolumab	NCT03585465	1, 2	2028
	Pembrolizumab	NCT02332668	1, 2	2022
	REGN2810	NCT03690869	1, 2	2025
	Avelumab	NCT03451825	1, 2	2021
	Atezolizumab	NCT04796012	2	2023
	Pembrolizumab + Decitabine	NCT03445858	1	2025
	Niraparib + Dostarlimab	NCT04544995	1	2030
Other compounds	ALRN-6924	NCT03654716	1	2022
	Idasanutlin	NCT04029688	1, 2	2024
	SGT-53	NCT02354547	1	2021
	CLR 131	NCT03478462	1	2024

Based on Nemes & Frühwald [2018], Nemes et al [2022]

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Rhabdoid tumor predisposition syndrome (RTPS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The vast majority of individuals diagnosed with *SMARCB1*-related RTPS have the disorder as the result of a *de novo* germline disease-causing variant [Biegel et al 2014]. Rarely, a *SMARCB1* disease-causing variant is inherited from an unaffected parent or a parent with late-onset or undiagnosed RTPS [Ammerlaan et al 2008].
- Most reported individuals diagnosed with *SMARCA4*-related RTPS inherited a disease-causing variant from a parent without a history of a rhabdoid tumor or small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) [Schneppenheim et al 2010; Hasselblatt et al 2014; Andrianteranagna et al 2021; Holdhof et al 2021; EU-RHAB – Author, personal communication].
- If a proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If a phenotypically healthy parent is found to have a *SMARCB1* or *SMARCA4* disease-causing germline variant, the parent should be offered surveillance.
- If the *SMARCB1* or *SMARCA4* disease-causing variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* disease-causing variant.
  - The proband inherited a disease-causing variant from a parent with germline (or somatic and germline) mosaicism. Parental germline mosaicism in *SMARCB1*-related RTPS has been reported [Bruggers et al 2011, Eaton et al 2011, Biegel et al 2014, Gigante et al 2016]. Germline mosaicism may account for up to half of the families with sibs affected by RTPS.

    Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a disease-causing variant that is present in the germ cells only.
- The family history of most individuals with RTPS may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance (highly likely in *SMARCA4*-related RTPS), or late onset in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the disease-causing variant identified in the proband.

Sibs of a proband. The risk of the sibs of a proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or known to have the *SMARCB1* or *SMARCA4* disease-causing variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
  - The penetrance of *SMARCB1*-related RTPS may be extremely high (e.g., >90% by age 5 years) in sibs who inherit a *SMARCB1* disease-causing variant. Sibs may develop rhabdoid tumors and should undergo surveillance.
  - Reduced penetrance is observed in *SMARCA4*-related RTPS. Sibs who inherit a *SMARCA4* disease-causing variant may or may not develop rhabdoid tumors and should undergo surveillance.
  - The types of RTPS-related tumors can vary among family members with the same disease-causing variant.
- If the *SMARCB1* or *SMARCA4* disease-causing variant identified in the proband cannot be detected in the constitutional (i.e., leukocyte) DNA of either parent, the recurrence risk to sibs is still greater than that of the general population because of the possibility of parental germline mosaicism [Bruggers et al 2011, Eaton et al 2011, Biegel et al 2014, Gigante et al 2016]. Germline mosaicism may account for up to half of the families with sibs affected by RTPS.

- If the parents have not been tested for the disease-causing variant identified in the proband but are clinically unaffected, sibs are still presumed to be at increased risk for RTPS because of the possibility of reduced penetrance in a heterozygous parent (highly likely in *SMARCA4*-related RTPS) or parental germline mosaicism.

Offspring of a proband. Each child of an individual with a germline *SMARCB1* or *SMARCA4* disease-causing variant has a 50% chance of inheriting the disease-causing variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a germline *SMARCB1* or *SMARCA4* disease-causing variant, members of the parent's family may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – Health Professional Version (part of PDQ®, National Cancer Institute).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies (i.e., those with a family history of RTPS). Once the *SMARCB1* or *SMARCA4* disease-causing variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Note: Rhabdoid tumors associated with RTPS may develop before birth; therefore, if the *SMARCB1* or *SMARCA4* disease-causing variant has been identified in the fetus, high-level ultrasound examination may be used to detect and identify prenatal manifestations of a primary tumor.

Low-risk pregnancies (i.e., those without a known family history of RTPS). If a primary tumor is detected on general prenatal ultrasound screening (and confirmed with high-level ultrasound), prenatal testing for a *SMARCB1* or *SMARCA4* disease-causing variant may be discussed. Note: Specific treatment for this group is currently not available, but interventions may be discussed; long-term survival has been reported in some affected individuals [Seeringer et al 2014b, Nemes et al 2018].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Cancer Society**
  Phone: 800-227-2345
  www.cancer.org
- **American Childhood Cancer Organization**
  Phone: 855-858-2226
  www.acco.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  www.cancercare.org
- **National Brain Tumor Society**
  Phone: 617-924-9997
  Email: info@braintumor.org
  www.braintumor.org
- **European Rhabdoid Registry (EU-RHAB)**
  Stenglingstr. 2.
  Augsburg 86156
  Germany
  Phone: 00498214004342
  Fax: 0049821400174243
  Email: eurhab@klinikum-augsburg.de
  www.rhabdoid.de

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Rhabdoid Tumor Predisposition Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SMARCA4	19p13.2	Transcription activator BRG1	SMARCA4 database	SMARCA4	SMARCA4
SMARCB1	22q11.23	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1	SMARCB1 database UKE Hamburg SMARCB1 database	SMARCB1	SMARCB1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Rhabdoid Tumor Predisposition Syndrome (View All in OMIM)

601607	SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY B, MEMBER 1; SMARCB1
603254	SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY A, MEMBER 4; SMARCA4
609322	RHABDOID TUMOR PREDISPOSITION SYNDROME 1; RTPS1
613325	RHABDOID TUMOR PREDISPOSITION SYNDROME 2; RTPS2

Molecular Pathogenesis

Rhabdoid tumor predisposition syndrome (RTPS) is typically characterized by heterozygous germline disease-causing variants that predict inactivation of *SMARCB1* (more commonly) or *SMARCA4* (very rarely).

SMARCA4 with its ATPase activity is the catalytic subunit and SMARCB1 is a core protein of the SWI/SNF chromatin remodeling complex. SWI/SNF interacts with various pathways (p16-Rb pathway, Wnt/β-catenin pathway, sonic hedgehog signal pathway, polycomb pathway, MYCC, Aurora A) and affects many essential biological functions in developing organs, including cell cycle and cell differentiation, gene expression, and DNA repair [Biegel et al 2014, Kim & Roberts 2014, Kohashi & Oda 2017].

Mechanism of disease causation. Loss of function

Gene-specific laboratory technical considerations

- ***SMARCA4.*** By convention, disease-causing variants are numbered based on the sequence of the transcript encoding the longest isoform, which is transcript NM_001128849.3, comprising 36 exons. Reported disease-causing variants include nonsense and splice site variants and intragenic deletions that predict inactivation.
- ***SMARCB1.*** By convention, disease-causing variants are numbered based on the sequence of the transcript encoding the isoform a, which is transcript NM_003073.5, comprising nine exons. Reported disease-causing variants include nonsense and splice site variants, duplications, intragenic deletions, and exon and whole-gene deletions, which predict inactivation.

Cancer and Benign Tumors

Sporadic rhabdoid tumors may occur as single tumors in the absence of any other findings of RTPS and harbor somatic (acquired) *SMARCB1* and/or *SMARCA4* variants that are not present in the germline [Schneppenheim et al 2010, Biegel et al 2014]. In these circumstances predisposition to these tumors is not heritable. The routine application of immunohistochemistry to all neural tumors has identified other tumors with loss of SMARCA4 and/or SMARCB1 expression [Biegel et al 2014, Margol & Judkins 2014]. Whether *SMARCB1* or *SMARCA4* plays a role in development of these tumors is not known.

Chapter Notes

Author Notes

The European Rhabdoid Registry (EU-RHAB) was established in 2010 to define a standard of care for affected individuals with malignant rhabdoid tumors, to further the understanding of basic molecular mechanisms by coordinating the collection and analysis of biological materials in order to identify potential targets for pharmaceutical treatment, and eventually to shape the basis for Phase I/II trials.

Research projects

- **SIOPE ATRT01 Study.** An international prospective umbrella trial for children with atypical teratoid/rhabdoid tumors (AT/RT) including a randomized Phase III study evaluating the non-inferiority of three courses of high-dose chemotherapy compared to focal radiotherapy as consolidation therapy
- **RTPS Project.** "Families with rhabdoid tumor predisposition syndromes (RTPS1 and 2) – development of a clinical and human genetic concept"
- **Relapse Project.** "Mechanism of progression in malignant rhabdoid tumors"

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References

Literature Cited

Agaimy A. SWI/SNF complex-deficient soft tissue neoplasms: a pattern-based approach to diagnosis and differential diagnosis. Surg Pathol Clin. 2019;12:149–63. PubMed PMID: 30709441.

Ammerlaan AC, Ararou A, Houben MP, Baas F, Tijssen CC, Teepen JL, Wesseling P, Hulsebos TJ. Long-term survival and transmission of INI1-mutation via nonpenetrant males in a family with rhabdoid tumour predisposition syndrome. Br J Cancer. 2008;98:474–9. PubMed PMID: 18087273.

Andrianteranagna M, Cyrta J, Masliah-Planchon J, Nemes K, Corsia A, Leruste A, Holdhof D, Kordes U, Orbach D, Corradini N, Entz-Werle N, Pierron G, Castex MP, Brouchet A, Weingertner N, Ranchère D, Fréneaux P, Delattre O, Bush J, Leary A, Frühwald MC, Schüller U, Servant N, Bourdeaut F. SMARCA4-deficient rhabdoid tumours show intermediate molecular features between SMARCB1-deficient rhabdoid tumours and small cell carcinomas of the ovary, hypercalcaemic type. J Pathol. 2021;255:1–15. PubMed PMID: 33999421.

Bartelheim K, Nemes K, Seeringer A, Kerl K, Buechner J, Boos J, Graf N, Dürken M, Gerss J, Hasselblatt M, Kortmann RD, Teichert von Luettichau I, Nagel I, Nygaard R, Oyen F, Quiroga E, Schlegel PG, Schmid I, Schneppenheim R, Siebert R, Solano-Paez P, Timmermann B, Warmuth-Metz M, Frühwald MC. Improved 6-year overall survival in AT/RT - results of the registry study Rhabdoid 2007. Cancer Med. 2016;5:1765–75. PubMed PMID: 27228363.

Behnert A, Auber B, Steinemann D, Frühwald MC, Huisinga C, Hussein K, Kratz C, Ripperger T. KBG syndrome patient due to 16q24.3 microdeletion presenting with a paratesticular rhabdoid tumor: coincidence or cancer predisposition? Am J Med Genet A. 2018;176:1449–54. PubMed PMID: 29696793.

Benesch M, Nemes K, Neumayer P, Hasselblatt M, Timmermann B, Bison B, Ebetsberger-Dachs G, Bourdeaut F, Dufour C, Biassoni V, Morales La Madrid A, Entz-Werle N, Laithier V, Quehenberger F, Weis S, Sumerauer D, Siebert R, Bens S, Schneppenheim R, Kool M, Modena P, Fouyssac F. C Frühwald M. Spinal cord atypical teratoid/rhabdoid tumors in children: clinical, genetic, and outcome characteristics in a representative European cohort. Pediatr Blood Cancer. 2020;67:e28022. PubMed PMID: 31571386.

Berchuck A, Witkowski L, Hasselblatt M, Foulkes WD. Prophylactic oophorectomy for hereditary small cell carcinoma of the ovary, hypercalcemic type. Gynecol Oncol Rep. 2015;12:20–2. PubMed PMID: 26076152.

Biegel JA, Busse TM, Weissman BE. SWI/SNF chromatin remodeling complexes and cancer. Am J Med Genet C Semin Med Genet. 2014;166C:350–66. PubMed PMID: 25169151.

Birks DK, Donson AM, Patel PR, Dunham C, Muscat A, Algar EM, Ashley DM, Kleinschmidt-Demasters BK, Vibhakar R, Handler MH, Foreman NK. High expression of BMP pathway genes distinguishes a subset of atypical teratoid/rhabdoid tumors associated with shorter survival. Neuro Oncol. 2011;13:1296–307. PubMed PMID: 21946044.

Birks DK, Donson AM, Patel PR, Sufit A, Algar EM, Dunham C, Kleinschmidt-DeMasters BK, Handler MH, Vibhakar R, Foreman NK. Pediatric rhabdoid tumors of kidney and brain show many differences in gene expression but share dysregulation of cell cycle and epigenetic effector genes. Pediatr Blood Cancer. 2013;60:1095–102. PubMed PMID: 23382118.

Bosse KR, Shukla AR, Pawel B, Chikwava KR, Santi M, Tooke L, Castagna K, Biegel JA, Bagatell R. Malignant rhabdoid tumor of the bladder and ganglioglioma in a 14 year-old male with a germline 22q11.2 deletion. Cancer Genet. 2014;207:415–9. PubMed PMID: 25018128.

Bourdeaut F, Lequin D, Brugières L, Reynaud S, Dufour C, Doz F, André N, Stephan JL, Pérel Y, Oberlin O, Orbach D, Bergeron C, Rialland X, Fréneaux P, Ranchere D, Figarella-Branger D, Audry G, Puget S, Evans DG, Pinas JC, Capra V, Mosseri V, Coupier I, Gauthier-Villars M, Pierron G, Delattre O. Frequent hSNF5/INI1 germline mutations in patients with rhabdoid tumor. Clin Cancer Res. 2011;17:31–8. PubMed PMID: 21208904.

Brennan B, Stiller C, Bourdeaut F. Extracranial rhabdoid tumours: what we have learned so far and future directions. Lancet Oncol. 2013;14:e329–36. PubMed PMID: 23816299.

Brocks D, Schmidt CR, Daskalakis M, Jang HS, Shah NM, Li D, Li J, Zhang B, Hou Y, Laudato S, Lipka DB, Schott J, Bierhoff H, Assenov Y, Helf M, Ressnerova A, Islam MS, Lindroth AM, Haas S, Essers M, Imbusch CD, Brors B, Oehme I, Witt O, Lübbert M, Mallm JP, Rippe K, Will R, Weichenhan D, Stoecklin G, Gerhäuser C, Oakes CC, Wang T, Plass C. DNMT and HDAC inhibitors induce cryptic transcription start sites encoded in long terminal repeats. Nat Genet. 2017;49:1052–60. PubMed PMID: 28604729.

Bruggers CS, Bleyl SB, Pysher T, Barnette P, Afify Z, Walker M, Biegel JA. Clinicopathologic comparison of familial versus sporadic atypical teratoid/rhabdoid tumors (AT/RT) of the central nervous system. Pediatr Blood Cancer. 2011;56:1026–31. PubMed PMID: 20848638.

Chi SN, Zimmerman MA, Yao X, Cohen KJ, Burger P, Biegel JA, Rorke-Adams LB, Fisher MJ, Janss A, Mazewski C, Goldman S, Manley PE, Bowers DC, Bendel A, Rubin J, Turner CD, Marcus KJ, Goumnerova L,

Ullrich NJ, Kieran MW. Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. J Clin Oncol. 2009;27:385–9. PubMed PMID: 19064966.

Chun HE, Johann PD, Milne K, Zapatka M, Buellesbach A, Ishaque N, Iskar M, Erkek S, Wei L, Tessier-Cloutier B, Lever J, Titmuss E, Topham JT, Bowlby R, Chuah E, Mungall KL, Ma Y, Mungall AJ, Moore RA, Taylor MD, Gerhard DS, Jones SJM, Korshunov A, Gessler M, Kerl K, Hasselblatt M, Frühwald MC, Perlman EJ, Nelson BH, Pfister SM, Marra MA, Kool M. Identification and analyses of extra-cranial and cranial rhabdoid tumor molecular subgroups reveal tumors with cytotoxic T cell infiltration. Cell Rep. 2019;29:2338–54.e7. PubMed PMID: 31708418.

Chun HE, Lim EL, Heravi-Moussavi A, Saberi S, Mungall KL, Bilenky M, Carles A, Tse K, Shlafman I, Zhu K, Qian JQ, Palmquist DL, He A, Long W, Goya R, Ng M, LeBlanc VG, Pleasance E, Thiessen N, Wong T, Chuah E, Zhao YJ, Schein JE, Gerhard DS, Taylor MD, Mungall AJ, Moore RA, Ma Y, Jones SJM, Perlman EJ, Hirst M, Marra MA. Genome-wide profiles of extra-cranial malignant rhabdoid tumors reveal heterogeneity and dysregulated developmental pathways. Cancer Cell. 2016;29:394–406. PubMed PMID: 26977886.

Connor YD, Miao D, Lin DI, Hayne C, Howitt BE, Dalrymple JL, DeLeonardis KR, Hacker MR, Esselen KM, Shea M. Germline mutations of SMARCA4 in small cell carcinoma of the ovary, hypercalcemic type and in SMARCA4-deficient undifferentiated uterine sarcoma: clinical features of a single family and comparison of large cohorts. Gynecol Oncol. 2020;157:106–14. PubMed PMID: 31954538.

Coorens THH, Farndon SJ, Mitchell TJ, Jain N, Lee S, Hubank M, Sebire N, Anderson J, Behjati S. Lineage-independent tumors in bilateral neuroblastoma. N Engl J Med. 2020;383:1860–5. PubMed PMID: 33211929.

Dho YS, Kim SK, Cheon JE, Park SH, Wang KC, Lee JY, Phi JH. Investigation of the location of atypical teratoid/rhabdoid tumor. Childs Nerv Syst. 2015;31:1305–11. PubMed PMID: 25953096.

Eaton KW, Tooke LS, Wainwright LM, Judkins AR, Biegel JA. Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. Pediatr Blood Cancer. 2011;56:7–15. PubMed PMID: 21108436.

Errichiello E, Mustafa N, Vetro A, Notarangelo LD, de Jonge H, Rinaldi B, Vergani D, Giglio SR, Morbini P, Zuffardi O. SMARCA4 inactivating mutations cause concomitant Coffin-Siris syndrome, microphthalmia and small-cell carcinoma of the ovary hypercalcaemic type. J Pathol. 2017;243:9–15. PubMed PMID: 28608987.

Evans DG, Bowers NL, Tobi S, Hartley C, Wallace AJ, King AT, Lloyd SKW, Rutherford SA, Hammerbeck-Ward C, Pathmanaban ON, Freeman SR, Ealing J, Kellett M, Laitt R, Thomas O, Halliday D, Ferner R, Taylor A, Duff C, Harkness EF, Smith MJ. Schwannomatosis: a genetic and epidemiological study. J Neurol Neurosurg Psychiatry. 2018;89:1215–19. PubMed PMID: 29909380.

Fischer-Valuck BW, Chen I, Srivastava AJ, Floberg JM, Rao YJ, King AA, Shinohara ET, Perkins SM. Assessment of the treatment approach and survival outcomes in a modern cohort of patients with atypical teratoid rhabdoid tumors using the National Cancer Database. Cancer. 2017;123:682–7. PubMed PMID: 27861763.

Forest F, David A, Arrufat S, Pierron G, Ranchere-Vince D, Stephan JL, Clemenson A, Delattre O, Bourdeaut F. Conventional chondrosarcoma in a survivor of rhabdoid tumor: enlarging the spectrum of tumors associated with SMARCB1 germline mutations. Am J Surg Pathol. 2012;36:1892–6. PubMed PMID: 23154773.

Fossey M, Li H, Afzal S, Carret AS, Eisenstat DD, Fleming A, Hukin J, Hawkins C, Jabado N, Johnston D, Brown T, Larouche V, Scheinemann K, Strother D, Wilson B, Zelcer S, Huang A, Bouffet E, Lafay-Cousin L. Atypical teratoid rhabdoid tumor in the first year of life: the Canadian ATRT registry experience and review of the literature. J Neurooncol. 2017;132:155–62. PubMed PMID: 28102486.

Foulkes WD, Kamihara J, Evans DGR, Brugières L, Bourdeaut F, Molenaar JJ, Walsh MF, Brodeur GM, Diller L. Cancer surveillance in Gorlin syndrome and rhabdoid tumor predisposition syndrome. Clin Cancer Res. 2017;23:e62–e67. PubMed PMID: 28620006.

Frühwald MC, Hasselblatt M, Nemes K, Bens S, Steinbügl M, Johann PD, Kerl K, Hauser P, Quiroga E, Solano-Paez P, Biassoni V, Gil-da-Costa MJ, Perek-Polnik M, van de Wetering M, Sumerauer D, Pears J, Stabell N, Holm S, Hengartner H, Gerber NU, Grotzer M, Boos J, Ebinger M, Tippelt S, Paulus W, Furtwängler R. Hernáiz- Driever P, Reinhard H, Rutkowski S, Schlegel PG, Schmid I, Kortmann RD,Timmermann B, Warmuth-Metz M, Kordes U, Gerss J, Nysom K, Schneppenheim R, Siebert R, Kool M, Graf N. Age and DNA methylation subgroup as potential independent risk factors for treatment stratification in children with atypical teratoid/rhabdoid tumors. Neuro Oncol. 2020;22:1006–17. PubMed PMID: 31883020.

Frühwald MC, Nemes K, Boztug H, Cornips MCA, Evans DG, Farah R, Glentis S, Jorgensen M, Katsibardi K, Hirsch S, Jahnukainen K, Kventsel I, Kerl K, Kratz CP, Pajtler KW, Kordes U, Ridola V, Stutz E, Bourdeaut F. Current recommendations for clinical surveillance and genetic testing in rhabdoid tumor predisposition: a report from the SIOPE Host Genome Working Group. Fam Cancer. 2021;20:305–16. PubMed PMID: 33532948.

Furtwängler R, Kager L, Melchior P, Rübe C, Ebinger M, Nourkami-Tutdibi N, Niggli F, Warmann S, Hubertus J, Amman G, Leuschner I, Vokuhl C, Graf N, Frühwald MC. High-dose treatment for malignant rhabdoid tumor of the kidney: no evidence for improved survival-The Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) experience. Pediatr Blood Cancer. 2018.:65. PubMed PMID: 28843054.

German Childhood Cancer Registry. Annual report. 2019. Available online. Accessed 5-25-22.

Gigante L, Paganini I, Frontali M, Ciabattoni S, Sangiuolo FC, Papi L. Rhabdoid tumor predisposition syndrome caused by SMARCB1 constitutional deletion: prenatal detection of new case of recurrence in siblings due to gonadal mosaicism. Fam Cancer. 2016;15:123–6. PubMed PMID: 26342593.

Gossai N, Biegel JA, Messiaen L, Berry SA, Moertel CL. Report of a patient with a constitutional missense mutation in SMARCB1, Coffin-Siris phenotype, and schwannomatosis. Am J Med Genet A. 2015;167A:3186–91. PubMed PMID: 26364901.

Harisiadis L, Chang CH. Medulloblastoma in children: a correlation between staging and results of treatment. Int J Radiat Oncol Biol Phys. 1977;2:833–41. PubMed PMID: 597384.

Hasselblatt M, Nagel I, Oyen F, Bartelheim K, Russell RB, Schüller U, Junckerstorff R, Rosenblum M, Alassiri AH, Rossi S, Schmid I, Gottardo NG, Toledano H, Viscardi E, Balbin M, Witkowski L, Lu Q, Betts MJ, Foulkes WD, Siebert R, Frühwald MC, Schneppenheim R. SMARCA4-mutated atypical teratoid/rhabdoid tumors are associated with inherited germline alterations and poor prognosis. Acta Neuropathol. 2014;128:453–6. PubMed PMID: 25060813.

Hasselblatt M, Thomas C, Federico A, Nemes K, Johann PD, Bison B, Bens S, Dahlum S, Kordes U, Redlich A, Lessel L, Pajtler KW, Mawrin C, Schüller U, Nolte K, Kramm CM, Hinz F, Sahm F, Giannini C, Penkert J, Kratz CP, Pfister SM, Siebert R, Paulus W, Kool M, Frühwald MC. SMARCB1-deficient and SMARCA4-deficient malignant brain tumors with complex copy number alterations and TP53 mutations may represent the first clinical manifestation of Li-Fraumeni syndrome. Am J Surg Pathol. 2022. Epub ahead of print. PubMed PMID: 35446794.

Heck JE, Lombardi CA, Cockburn M, Meyers TJ, Wilhelm M, Ritz B. Epidemiology of rhabdoid tumors of early childhood. Pediatr Blood Cancer. 2013;60:77–81. PubMed PMID: 22434719.

Ho B, Johann PD, Grabovska Y, De Dieu Andrianteranagna MJ, Yao F, Frühwald M, Hasselblatt M, Bourdeaut F, Williamson D, Huang A, Kool M. Molecular subgrouping of atypical teratoid/rhabdoid tumors-a reinvestigation and current consensus. Neuro Oncol. 2020;22:613–24. PubMed PMID: 31889194.

Holdhof D, Johann PD, Spohn M, Bockmayr M, Safaei S, Joshi P, Masliah-Planchon J, Ho B, Andrianteranagna M, Bourdeaut F, Huang A, Kool M, Upadhyaya SA, Bendel AE, Indenbirken D, Foulkes WD, Bush JW, Creytens D, Kordes U, Frühwald MC, Hasselblatt M, Schüller U. Atypical teratoid/rhabdoid tumors (ATRTs) with SMARCA4 mutation are molecularly distinct from SMARCB1-deficient cases. Acta Neuropathol. 2021;141:291–301. PubMed PMID: 33331994.

Holsten T, Bens S, Oyen F, Nemes K, Hasselblatt M, Kordes U, Siebert R, Frühwald MC, Schneppenheim R, Schüller U. Germline variants in SMARCB1 and other members of the BAF chromatin-remodeling complex across human disease entities: a meta-analysis. Eur J Hum Genet. 2018;26:1083–93. PubMed PMID: 29706634.

Johann PD, Erkek S, Zapatka M, Kerl K, Buchhalter I, Hovestadt V, Jones DT, Sturm D, Hermann C, Segura Wang M, Korshunov A, Rhyzova M, Gröbner S, Brabetz S, Chavez L, Bens S, Gröschel S, Kratochwil F, Wittmann A, Sieber L, Geörg C, Wolf S, Beck K, Oyen F, Capper D, van Sluis P, Volckmann R, Koster J, Versteeg R, von Deimling A, Milde T, Witt O, Kulozik AE, Ebinger M, Shalaby T, Grotzer M, Sumerauer D, Zamecnik J, Mora J, Jabado N, Taylor MD, Huang A, Aronica E, Bertoni A, Radlwimmer B, Pietsch T, Schüller U, Schneppenheim R, Northcott PA, Korbel JO, Siebert R, Frühwald MC, Lichter P, Eils R, Gajjar A, Hasselblatt M, Pfister SM, Kool M. Atypical teratoid/rhabdoid tumors are comprised of three epigenetic subgroups with distinct enhancer landscapes. Cancer Cell. 2016;29:379–93. PubMed PMID: 26923874.

Kehrer-Sawatzki H, Kordes U, Seiffert S, Summerer A, Hagel C, Schüller U, Farschtschi S, Schneppenheim R, Bendszus M, Godel T, Mautner VF. Co-occurrence of schwannomatosis and rhabdoid tumor predisposition syndrome 1. Mol Genet Genomic Med. 2018;6:627–37. PubMed PMID: 29779243.

Kim KH, Roberts CW. Mechanisms by which SMARCB1 loss drives rhabdoid tumor growth. Cancer Genet. 2014;207:365–72. PubMed PMID: 24853101.

Kohashi K, Oda Y. Oncogenic roles of SMARCB1/INI1 and its deficient tumors. Cancer Sci. 2017;108:547–52. PubMed PMID: 28109176.

Kordes U, Bartelheim K, Modena P, Massimino M, Biassoni V, Reinhard H, Hasselblatt M, Schneppenheim R, Frühwald MC. Favorable outcome of patients affected by rhabdoid tumors due to rhabdoid tumor predisposition syndrome (RTPS). Pediatr Blood Cancer. 2014;61:919–21. PubMed PMID: 24123847.

Lafay-Cousin L, Hawkins C, Carret AS, Johnston D, Zelcer S, Wilson B, Jabado N, Scheinemann K, Eisenstat D, Fryer C, Fleming A, Mpofu C, Larouche V, Strother D, Bouffet E, Huang A. Central nervous system atypical teratoid rhabdoid tumours: the Canadian Paediatric Brain Tumour Consortium experience. Eur J Cancer. 2012;48:353–9. PubMed PMID: 22023887.

Lavrut PM, Le Loarer F, Normand C, Grosos C, Dubois R, Buenerd A, Conter C, Dijoud F, Blay JY, Collardeau-Frachon S. Small cell carcinoma of the ovary, hypercalcemic type: report of a bilateral case in a teenager associated with SMARCA4 germline mutation. Pediatr Dev Pathol. 2016;19:56–60. PubMed PMID: 26230154.

Le Loarer F, Zhang L, Fletcher CD, Ribeiro A, Singer S, Italiano A, Neuville A, Houlier A, Chibon F, Coindre JM, Antonescu CR. Consistent SMARCB1 homozygous deletions in epithelioid sarcoma and in a subset of myoepithelial carcinomas can be reliably detected by FISH in archival material. Genes Chromosomes Cancer. 2014;53:475–86. PubMed PMID: 24585572.

Li D, Ahrens-Nicklas RC, Baker J, Bhambhani V, Calhoun A, Cohen JS, Deardorff MA, Fernández-Jaén A, Kamien B, Jain M, Mckenzie F, Mintz M, Motter C, Niles K, Ritter A, Rogers C, Roifman M, Townshend S, Ward-Melver C, Schrier Vergano SA. The variability of SMARCA4-related Coffin-Siris syndrome: Do nonsense candidate variants add to milder phenotypes? Am J Med Genet A. 2020;182:2058–67. PubMed PMID: 32686290.

Lin DI, Allen JM, Hecht JL, Killian JK, Ngo NT, Edgerly C, Severson EA, Ali SM, Erlich RL, Ramkissoon SH, Vergilio JA, Ross JS, Elvin JA. SMARCA4 inactivation defines a subset of undifferentiated uterine sarcomas with rhabdoid and small cell features and germline mutation association. Mod Pathol. 2019;32:1675–87. PubMed PMID: 31190001.

Margol AS, Judkins AR. Pathology and diagnosis of SMARCB1-deficient tumors. Cancer Genet. 2014;207:358–64. PubMed PMID: 25246033.

Metts JL, Park SI, Soares BP, Fong C, Biegel JA, Goldsmith KC. Concurrent myeloid sarcoma, atypical teratoid/rhabdoid tumor, and hypereosinophilia in an infant with a germline SMARCB1 mutation. Pediatr Blood Cancer. 2017.:64. PubMed PMID: 27555087.

Moes-Sosnowska J, Szafron L, Nowakowska D, Dansonka-Mieszkowska A, Budzilowska A, Konopka B, Plisiecka-Halasa J, Podgorska A, Rzepecka IK, Kupryjanczyk J. Germline SMARCA4 mutations in patients with ovarian small cell carcinoma of hypercalcemic type. Orphanet J Rare Dis. 2015;10:32. PubMed PMID: 25886974.

Nakata K, Colombet M, Stiller CA, Pritchard-Jones K, Steliarova-Foucher E. Incidence of childhood renal tumours: an international population-based study. Int J Cancer. 2020;147:3313–27. PubMed PMID: 32902866.

Negahban S, Ahmadi N, Oryan A, Khojasteh HN, Aledavood A, Soleimanpour H, Mohammadianpanah M, Oschlies I, Gesk S, Siebert R, Daneshbod K, Daneshbod Y. Primary bilateral Burkitt lymphoma of the lactating breast: a case report and review of the literature. Mol Diagn Ther. 2010;14:243–50. PubMed PMID: 20799767.

Nemes K, Bens S, Kachanov D, Teleshova M, Hauser P, Simon T, Tippelt S, Woessmann W, Beck O, Flotho C, Grigull L, Driever PH, Schlegel PG, Khurana C, Hering K, Kolb R, Leipold A, Abbink F, Gil-Da-Costa MJ, Benesch M, Kerl K, Lowis S, Marques CH, Graf N, Nysom K, Vokuhl C, Melchior P, Kröncke T, Schneppenheim R, Kordes U, Gerss J, Siebert R, Furtwängler R, Frühwald MC. Clinical and genetic risk factors define two risk groups of extracranial malignant rhabdoid tumours (eMRT/RTK). Eur J Cancer. 2021;142:112–22. PubMed PMID: 33249395.

Nemes K, Clément N, Kachanov D, Bens S, Hasselblatt M, Timmermann B, Schneppenheim R, Gerss J, Siebert R, Furtwängler R, Bourdeaut F, Frühwald MC, et al. The extraordinary challenge of treating patients with congenital rhabdoid tumors--a collaborative European effort. Pediatr Blood Cancer. 2018;65:e26999. PubMed PMID: 29418059.

Nemes K, Frühwald MC. Emerging therapeutic targets for the treatment of malignant rhabdoid tumors. Expert Opin Ther Targets. 2018;22:365–79. PubMed PMID: 29528755.

Nemes K, Johann PD, Tüchert S, Melchior P, Vokuhl C, Siebert R, Furtwängler R, Frühwald MC. Current and emerging therapeutic approaches for extracranial malignant rhabdoid tumors. Cancer Manag Res. 2022;14:479–98. PubMed PMID: 35173482.

Pejovic T, McCluggage WG, Krieg AJ, Xu F, Lee DM, Witkowski L, Foulkes WD. The dilemma of early preventive oophorectomy in familial small cell carcinoma of the ovary of hypercalcemic type. Gynecol Oncol Rep. 2019;28:47–49. PubMed PMID: 30886884.

Prasad RN, Gardner UG, Yaney A, Prevedello DM, Koboldt DC, Thomas DL, Mardis ER, Palmer JD. Germline BAP1 mutation in a family with multi-generational meningioma with rhabdoid features: a case series and literature review. Front Oncol. 2021;11:721712. PubMed PMID: 34504799.

Reddy AT, Strother DR, Judkins AR, Burger PC, Pollack IF, Krailo MD, Buxton AB, Williams-Hughes C, Fouladi M, Mahajan A, Merchant TE, Ho B, Mazewski CM, Lewis VA, Gajjar A, Vezina LG, Booth TN, Parsons KW, Poss VL, Zhou T, Biegel JA, Huang A. Efficacy of high-dose chemotherapy and three-dimensional conformal radiation for atypical teratoid/rhabdoid tumor: a report from the Children's Oncology Group Trial ACNS0333. J Clin Oncol. 2020;38:1175–85. PubMed PMID: 32105509.

Schenone CV, King A, Castro E, Ketwaroo P, Donepudi R, Sanz-Cortes M. Prenatal detection of disseminated extrarenal malignant rhabdoid tumor with placental metastases. Ultrasound Obstet Gynecol. 2021;57:1008–10. PubMed PMID: 32621313.

Schneppenheim R, Frühwald MC, Gesk S, Hasselblatt M, Jeibmann A, Kordes U, Kreuz M, Leuschner I, Martin Subero JI, Obser T, Oyen F, Vater I, Siebert R. Germline nonsense mutation and somatic inactivation of

SMARCA4/BRG1 in a family with rhabdoid tumor predisposition syndrome. Am J Hum Genet. 2010;86:279–84. PubMed PMID: 20137775.

Schrey D, Carceller Lechón F, Malietzis G, Moreno L, Dufour C, Chi S, Lafay-Cousin L, von Hoff K, Athanasiou T, Marshall LV, Zacharoulis S. Multimodal therapy in children and adolescents with newly diagnosed atypical teratoid rhabdoid tumor: individual pooled data analysis and review of the literature. J Neurooncol. 2016;126:81–90. PubMed PMID: 26608522.

Seeringer A, Bartelheim K, Kerl K, Hasselblatt M, Leuschner I, Rutkowski S, Timmermann B, Kortmann RD, Koscielniak E, Schneppenheim R, Warmuth-Metz M, Gerss J, Siebert R, Graf N, Boos J, Frühwald MC. Feasibility of intensive multimodal therapy in infants affected by rhabdoid tumors - experience of the EU-RHAB registry. Klin Padiatr. 2014a;226:143–8. PubMed PMID: 24633978.

Seeringer A, Reinhard H, Hasselblatt M, Schneppenheim R, Siebert R, Bartelheim K, Leuschner I, Frühwald MC. Synchronous congenital malignant rhabdoid tumor of the orbit and atypical teratoid/rhabdoid tumor--feasibility and efficacy of multimodal therapy in a long-term survivor. Cancer Genet. 2014b;207:429–33. PubMed PMID: 25262118.

Smith MJ, Wallace AJ, Bowers NL, Eaton H, Evans DG. SMARCB1 mutations in schwannomatosis and genotype correlations with rhabdoid tumors. Cancer Genet. 2014;207:373–8. PubMed PMID: 24933152.

Sredni ST, Tomita T. Rhabdoid tumor predisposition syndrome. Pediatr Dev Pathol. 2015;18:49–58. PubMed PMID: 25494491.

Teplick A, Kowalski M, Biegel JA, Nichols KE. Educational paper: screening in cancer predisposition syndromes: guidelines for the general pediatrician. Eur J Pediatr. 2011;170:285–94. PubMed PMID: 21210147.

Torchia J, Golbourn B, Feng S, Ho KC, Sin-Chan P, Vasiljevic A, Norman JD, Guilhamon P, Garzia L, Agamez NR, Lu M, Chan TS, Picard D, de Antonellis P, Khuong-Quang DA, Planello AC, Zeller C, Barsyte-Lovejoy D, Lafay-Cousin L, Letourneau L, Bourgey M, Yu M, Gendoo DM, Dzamba M, Barszczyk M, Medina T, Riemenschneider AN, Morrissy AS, Ra YS, Ramaswamy V, Remke M, Dunham CP, Yip S, Ng HK, Lu JQ, Mehta V, Albrecht S, Pimentel J, Chan JA, Somers GR, Faria CC, Roque L, Fouladi M, Hoffman LM, Moore AS, Wang Y, Choi SA, Hansford JR, Catchpoole D, Birks DK, Foreman NK, Strother D, Klekner A, Bognár L, Garami M, Hauser P, Hortobágyi T, Wilson B, Hukin J, Carret AS, Van Meter TE, Hwang EI, Gajjar A, Chiou SH, Nakamura H, Toledano H, Fried I, Fults D, Wataya T, Fryer C, Eisenstat DD, Scheinemann K, Fleming AJ, Johnston DL, Michaud J, Zelcer S, Hammond R, Afzal S, Ramsay DA, Sirachainan N, Hongeng S, Larbcharoensub N, Grundy RG, Lulla RR, Fangusaro JR, Druker H, Bartels U, Grant R, Malkin D, McGlade CJ, Nicolaides T, Tihan T, Phillips J, Majewski J, Montpetit A, Bourque G, Bader GD, Reddy AT, Gillespie GY, Warmuth-Metz M, Rutkowski S, Tabori U, Lupien M, Brudno M, Schüller U, Pietsch T, Judkins AR, Hawkins CE, Bouffet E, Kim SK, Dirks PB, Taylor MD, Erdreich-Epstein A, Arrowsmith CH, De Carvalho DD, Rutka JT, Jabado N, Huang A. Integrated (epi)-genomic analyses identify subgroup-specific therapeutic targets in CNS rhabdoid tumors. Cancer Cell. 2016;30:891–908. PubMed PMID: 27960086.

Torchia J, Picard D, Lafay-Cousin L, Hawkins CE, Kim SK, Letourneau L, Ra YS, Ho KC, Chan TS, Sin-Chan P, Dunham CP, Yip S, Ng HK, Lu JQ, Albrecht S, Pimentel J, Chan JA, Somers GR, Zielenska M, Faria CC, Roque L, Baskin B, Birks D, Foreman N, Strother D, Klekner A, Garami M, Hauser P, Hortobágyi T, Bognár L, Wilson B, Hukin J, Carret AS, Van Meter TE, Nakamura H, Toledano H, Fried I, Fults D, Wataya T, Fryer C, Eisenstat DD, Scheineman K, Johnston D, Michaud J, Zelcer S, Hammond R, Ramsay DA, Fleming AJ, Lulla RR, Fangusaro JR, Sirachainan N, Larbcharoensub N, Hongeng S, Barakzai MA, Montpetit A, Stephens D, Grundy RG, Schüller U, Nicolaides T, Tihan T, Phillips J, Taylor MD, Rutka JT, Dirks P, Bader GD, Warmuth-Metz M, Rutkowski S, Pietsch T, Judkins AR, Jabado N, Bouffet E, Huang A. Molecular subgroups of atypical teratoid rhabdoid tumours in children: an integrated genomic and clinicopathological analysis. Lancet Oncol. 2015;16:569–82. PubMed PMID: 25882982.

van den Munckhof P, Christiaans I, Kenter SB, Baas F, Hulsebos TJ. Germline SMARCB1 mutation predisposes to multiple meningiomas and schwannomas with preferential location of cranial meningiomas at the falx cerebri. Neurogenetics. 2012;13:1–7. PubMed PMID: 22038540.

Voisin MR, Ovenden C, Tsang DS, Gupta AA, Huang A, Gao AF, Diamandis P, Almeida JP, Gentili F. Atypical teratoid/rhabdoid sellar tumor in an adult with a familial history of a germline SMARCB1 mutation: case report and review of the literature. World Neurosurg. 2019;127:336–45. PubMed PMID: 31004861.

Witkowski L, Donini N, Byler-Dann R, Knost JA, Albrecht S, Berchuck A, McCluggage WG, Hasselblatt M, Foulkes WD. The hereditary nature of small cell carcinoma of the ovary, hypercalcemic type: two new familial cases. Fam Cancer. 2017;16:395–9. PubMed PMID: 27866340.

Witkowski L, Goudie C, Ramos P, Boshari T, Brunet JS, Karnezis AN, Longy M, Knost JA, Saloustros E, McCluggage WG, Stewart CJR, Hendricks WPD, Cunliffe H, Huntsman DG, Pautier P, Levine DA, Trent JM, Berchuck A, Hasselblatt M, Foulkes WD. The influence of clinical and genetic factors on patient outcome in small cell carcinoma of the ovary, hypercalcemic type. Gynecol Oncol. 2016;141:454–60. PubMed PMID: 26975901.

Witkowski L, Lalonde E, Zhang J, Albrecht S, Hamel N, Cavallone L, May ST, Nicholson JC, Coleman N, Murray MJ, Tauber PF, Huntsman DG, Schönberger S, Yandell D, Hasselblatt M, Tischkowitz MD, Majewski J, Foulkes WD. Familial rhabdoid tumour "avant la letter"--from pathology review to exome sequencing and back again. J Pathol. 2013;231:35–43. PubMed PMID: 23775540.

Zaky W, Dhall G, Ji L, Haley K, Allen J, Atlas M, Bertolone S, Cornelius A, Gardner S, Patel R, Pradhan K, Shen V, Thompson S, Torkildson J, Sposto R, Finlay JL. Intensive induction chemotherapy followed by myeloablative chemotherapy with autologous hematopoietic progenitor cell rescue for young children newly-diagnosed with central nervous system atypical teratoid/rhabdoid tumors: the Head Start III experience. Pediatr Blood Cancer. 2014;61:95–101. PubMed PMID: 23934933.

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