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Review Article

Rhabdoid Tumor Predisposition Syndrome (Rtps), Familial Schwannomatosis and Other Conditions Related To *Smarcb1/Ini1* Abnormalities

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Abstract

Rhabdoid tumors are amongst the most aggressive and lethal forms of human cancer. They can arise in any location of the body but are more commonly observed in the brain and in the kidneys. The vast majority of rhabdoid tumors present with recurring loss of function of the *SMARCB1* gene located at 22q11.2. Despite the highly malignant nature of rhabdoid tumors, they were proved to have a "remarkably simple genome" with *SMARCB1* inactivation recognized to be the sole recurrent genetic event involved in tumor development.

Rhabdoid Tumor Predisposition Syndrome (RTPS) presents with a constitutional loss or inactivation of one allele of the *SMARCB1* gene, which results in an increased risk of developing rhabdoid tumors. It has been estimated that up to one third of patients with rhabdoid tumors present *SMARCB1* germline mutations. In familial cases children tend to develop tumors at a younger age, have more extensive disease, and a shorter survival rate than children with sporadic cases. However, there have been cases of long-survivors among RTPS families and presently, the impact of germline mutation on survival remains unclear.

Here we review the literature on RTPS and other conditions related to *SMARCB1* abnormalities. We suggest that genetic counseling should be recommended to the families bearing this condition and facilitated by their clinicians and institutions.

INTRODUCTION

Rhabdoid tumors are amongst the most aggressive and lethal forms of human cancer [1-5]. They are typically diagnosed in infants or children but can occur at any age. Initially, Beckwith and Palmer described rhabdoid tumors in the kidney as an aggressive type of Wilms tumor. Since then, rhabdoid tumors have been described in the spinal cord and brain, as well as soft tissue and liver, among other locations [3,6-9]. When rhabdoid tumors arise in the kidney they are named rhabdoid tumors of the kidney (RTK), and in other locations they receive the generic name of malignant rhabdoid tumors (MRT). When rhabdoid tumors arise in the central nervous system (CNS) they possess an unusual combination of mixed cellular elements similar to what is found in teratomas. Due to this particularity, rhabdoid tumors arising in the CNS are named atypical teratoid/rhabdoid tumors (AT/RT).

The outcome associated with rhabdoid tumorsis dismal with median survival historically being less than 1 year [4,10-14]. Treatment depends on the tumor's location, initial staging and the age of the patient [12,13,15-18]. For AT/RT, patients receive the maximum amount surgical resection possible, while preserving neurologic function, followed by an intensive multimodality regimen. This regimen is divided into five phases: pre-irradiation, chemoradiation, consolidation, maintenance, and continuation therapy. Chemotherapy includes vincristine, cisplatin, cyclosphosphamide, etoposide, actinomycin D and temozolomide with the addition of intrathecal chemotherapy and radiation therapy, which depends on the age and extent of disease at diagnosis [12]. This regimen has improved patients'

survival increasing 2-year overall survival rates up to 70±10%. Despite the progress, the toxic side effects are significant and most patients still rapidly succumb to their disease. The only significant factor that can be associated with the patient's survival is the age of the patient at the time of diagnosis. Younger age is associated with a poor survival rate [19].

GENETICS

The vast majority of rhabdoid tumors present with recurring abnormalities in chromosome 22, regardless of their site of origin [20,21]. These abnormalities are characterized by the loss of function of a gene located at 22q11.2 that is a member of the SWI/SNF chromatin remodeling complex and is known by the names: *hSNF5, INI1, BAF47* and *SMARCB1*.

This gene was name dsucrose non-fermenting gene number 5 (SNF5), because its ortholog was first identified in yeast mutants that were unable to ferment sucrose [22]. The human ortholog (*hSNF5*) was identified for its capacity to bind to DNA and enhance the joining activity of HIV-1 integrase, which was then named integrase interactor 1 (*INI1*) by Kalpana and colleagues [23]. Soon after, the SWI/SNF complex was named BRG1/BRM associated complex (BAF complex), and the gene was then named BRG1-associated factor 47 (*BAF47*) due to its molecular mass of 47kd. Although these names are all widely used, the current recommended nomenclature is *SMARCB1*, which stands for SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member [24]. In this review article we will use the official nomenclature *SMARCB1*.

The SWI/SNF chromatin remodeling complex consists of 8-11 proteins and uses the energy of ATP hydrolysis to remodel nucleosomes and modulate gene transcription. *SMARCB1* encodes for a member of this complex that is recruited to gene promoters that regulate cell cycle, growth and differentiation [25-27].

The *SMARCB1*abnormalities in rhabdoid tumors are characterized as somatically acquired biallelic inactivating truncating mutations within tumors, with or without germline mutations that would predispose to cancer [1,5,23,28,29]. This somatic inactivation implicates *SMARCB1*as a tumor suppressor gene as defined by Knudson in the "two-hit model" [30,31].

Interestingly, despite the highly malignant nature of rhabdoid tumors, extensive genetic evaluation of newly diagnosed specimens has shown that rhabdoid tumors have a "remarkably simple genome." This was found through whole-exome sequencing and SNP array analysis that identified an extremely low rate of mutations. As a result, *SMARCB1* inactivation was recognized to be the sole recurrent genetic event involved in tumor development [32-34].

HISTOLOGY

The histology of rhabdoid tumors can be fairly variable. The classic rhabdoid phenotype is characterized by cells with large eccentric nuclei, a prominent nucleolus, and eosinophilic cytoplasm with pale cytoplamatic inclusion body. Although most of these tumors contain at least focal areas of rhabdoid cells, most rhabdoid tumors are primarily composed of undifferentiated cells and the rhabdoid component can be absent or not detected. AT/RTs may contain a variety of primitive neuroectodermal epidermal or mesenchymal cells, which stresses the importance of differential diagnosis with primitive neuroectodermal tumors (PNET) and choroid plexus carcinomas [35]. Immunohistochemical markers are essential for the diagnosis. Rhabdoid tumors have a classic immune profile that shows diffuse expression of smooth muscle actin (SMA), epithelial membrane antigen (EMA) and vimentin associated with variable expression of neuron-specific enolase (NSE), Leu7 and S100 and absence of expression of SMARCB1, desmin and myogenin [36,37]. It has been shown that rhabdoid tumors exhibit loss of SMARCB1 protein expression, [37] and this can be useful when reclassifying pediatric CNS tumors that were initially misdiagnosed as medulloblastomas, supretentorial primitive neuroectodermal tumors (PNET) or choroid plexus carcinomas [38,39]. However, the loss of SMARCB1 protein expression is not exclusive to rhabdoid tumors. Some extracranial non rhabdoid tumors, including epithelioid sarcomas and hereditary types of schwannomas, may present with total or partial loss of SMARCB1 expression [40,41]. This phenomenon has also been observed in nearly all medullary carcinomas of the kidney, most of epithelial sarcomas and half of epithelioid malignant peripheral nerve sheath tumors [40,42,43].

RHABDOID TUMOR PREDISPOSITION SYNDROME-RTPS

Rhabdoid Tumor Predisposition Syndrome (RTPS) presents with a constitutional loss or inactivation of one allele of the *SMARCB1* gene, which results in an increased risk of developing rhabdoid tumors. This syndrome is characterized by a pedigree in which at least two individuals carry germline mutations of the *SMARCB1* tumor suppressor gene. It has been estimated that up to one third of patients with rhabdoid tumors present *SMARCB1*germline mutations [19,44-46]. Although most of these mutations occur *de novo*, familial cases have been reported in which an inherited constitutional *SMARCB1* mutation of 1 allele predisposes a patient to rhabdoid tumor development. Typically, in these families, there is more than one affected child and carrier of *SMARCB1* mutant alleles that do not develop the disease [47-53]. However, if a child presents a *de novo* germline *SMARCB1* mutation and endure till adulthood, he/she will be the first individual in the family to carry and potentially transmit the mutation.

When comparing familial versus sporadic AT/RT, it has been found that in familial cases children tend to develop tumors at a younger age, have more extensive disease, and a shorter survival rate than children with sporadic cases [19,46,47]. However, there have been cases of long-survivors among RTPS families [54-56]. Presently, the impact of germline mutation on survival remains unclear.

A recent genetic study that utilized matched tumor and blood samples from 100 patients with rhabdoid tumors originating from different locations, detected underlying genetic predisposition due to a germline *SMARCB1* alteration in one third of newly diagnosed tumors. The authors also found 9 cases that demonstrated a parent to child transmission of a mutated copy of the gene, with at least one family member possessing

either a rhabdoid tumor or schwannomas. Two of these families presented multiple affected children in a manner consistent with gonadal mosaicism [45].

Over 15 years before the description of the syndrome [52], Lynch and collaborators published a report of two female siblings that presented paravertebral tumors within their first year of life. These tumors possessed identical pathological features that were characteristic of rhabdoid tumors and rapidly progressed to death [57]. Occurring almost simultaneously with the identification of *SMARCB1* as a tumor suppressor gene, another case report described two sisters of consanguineous parents that were diagnosed with AT/RT and treated within 15 days of each other. Despite treatment, these sisters died shortly after the time of diagnosis at 14 and 16 months, respectively [51].

In Sévenet [52] analyzed three pedigrees of cancer-prone families demonstrating loss-of-function mutations in the *SMARCB1* gene in the constitutional DNA of affected members, but not in healthy relatives. This indicates the *de novo* occurrence of the mutations. Based on this data, the authors describe, for the first time, a hereditary syndrome where constitutional mutations of the *SMARCB1* gene could predispose patients to rhabdoid tumors. These findings further strengthened the role of *SMARCB1* as a tumor-suppressor gene. In this report, the presence of multiple siblings developing tumors and carrying the same somatic mutations, not shared by the parents, suggests that families may demonstrate incomplete penetrance and gonadal mosaicism [52].

In the literature, reported cases of familial associated rhabdoid tumors are scarce but growing [19,45,47,48,49,50-54,57-60].

Germline mutations can be associated with multiple tumors [45]. Cases of siblings that developed either AT/RTs or RTKs with identical mutations of the *SMARCB1* gene that were also detected at the germline level of the patients, but not found in the parents or the other siblings have been communicated [50]. A report described two infants with rhabdoid tumors primary of the kidney (RTK) and *SMARCB1* germline mutations, who then developed second primary rhabdoid tumors of the CNS (AT/RT) [61]. Almost simultaneously, a report a four-month-old child that presented with an AT/RT and subsequently developed an RTK with identical mutations of the *SMARCB1* gene was published [28].

Reported cases of familial associated rhabdoid tumors are still uncommon but are increasing in frequency suggesting that this condition might not be as rare as previously considered [19,45,47-54,57-60].

A SECOND LOCUS FOR RHABDOID TUMOR PREDISPOSITION SYNDROME

In 2006, for the first time, evidence of an alternative tumor suppressor locus for RTPS was demonstrated. The authors describe a family with RTPS without linkage to *SMARCB1*. Among 3 children studied, one child was affected by AT/RT and another by RTK. This study included rigorous and extensive analyses to confirm the diagnoses and exclude *SMARCB1* involvement [58]. The family was further evaluated and in 2010 the authors published their findings showing germline nonsense mutations and somatic inactivation of another member of the SWI/SNF chromatin-remodeling complex, the subunit SMARCA4 (or BRG1) [62]. This syndrome was defined as rhabdoid tumor predisposition syndrome type 2 (RTPS2), and RTPS with *SMARCB1* alterations was then named rhabdoid tumor predisposition syndrome type 1 (RTPS1).Very recently, a second case of RTPS2 was published in a family where tumors were reclassified after entire exome sequencing of genomic DNA from its members [60].

SCHWANNOMATOSIS

Schwannomas are benign nerve sheath tumors that most frequently occur as solitary, encapsulated subcutaneous masses. Several syndromes are associated with an increased frequency of schwannomas, of these syndromes the most widely known are the neurofibromatoses. The characteristic tumors of neurofibromatosis 2 (NF2) are vestibular schwannomas, and of neurofibromatosis 1 (NFl) are neurofibromas. Schwannomatosis is a third major form of neurofibromatosis characterized by the development of multiple spinal, peripheral and cranial nerve schwannomas in the absence of vestibular schwannomas [63,64]. Tumors of patients with schwannomatosis have been reported to present somatic mutations in the *NF2* gene but linkage studies excluded *NF2* as the transmissible germline schwannomatosis gene [65-67].

Recently, the tumor suppressor gene *SMARCB1* has been found to harbor alterations in both familial and sporadic schwannomatosis patients [68-72]. Hulsebos and colleagues identified two family members with a *SMARCB1* inactivating germline mutation in exon 1, along with a second mutation in exon 5 of the other *SMARCB1* allele and partial loss of the SMARCB1protein expression within the tumors. These findings pointed to *SMARCB1*as a candidate predisposing gene in familial schwannomatosis [73].

Shortly after this finding, based on a study of 21 patients with schwannomatosis and 8 schwannomatosis-associated tumors, Sestini and collaborators suggested that a four-hit mechanism involving two distinct linked tumor suppressor genes, the *SMARCB1* and the *NF2*, trigger schwannomatosis-related tumorigenesis [72]. Almost simultaneously, Boyd and collaborators evaluated 19 schwannomatosis kind reds and found that over two-thirds (13/19) segregated constitutional alterations in the *SMARCB1* transcript. These findings supported the four-hit mechanism with co-mutation of *SMARCB1*and *NF2* tumor suppressor genes [68,72]. Constitutional mutations in *SMARCB1*were demonstrated in 40-50% of familial cases and in 8-10% of sporadic cases of schwannomatosis [69,71,72,74-76]. Germline mosaicism may also occur in schwannomatosis [73].

At this point, it is accepted that tumorigenesis may occur through a four-hit, three-step model, which starts with a germline mutation in *SMARCB1* (hit 1), followed by a loss of a portion of chromosome 22 that contains the second *SMARCB1* allele and one *NF2* allele (hits 2 and 3), followed by a mutation in the remaining wild-type *NF2* allele (hit 4) [75]. *SMARCB1* is located fairly close (approximately six mega bases centromeric) to *NF2* on chromosome 22. Therefore, a single event, which is the loss of a region of chromosome 22 containing wild-type

alleles of *SMARCB1* and *NF2* can, in some cases, account for 2 of 4 inactivating events.

Schwannomatosis and Rhabdoid Tumors

Although somatic and germline *SMARCB1* mutations have been identified in rhabdoid tumors and schwannomatosis, their co-occurrence within families that carry these mutations has only been reported a few times [77-79].

Due to the presence of adult carriers of the *SMARCB1* mutation in RTPS families, it has been suggested that the risk of developing a rhabdoid tumor or schwannomatosis secondary to these mutations could be time dependent [49,68].

Recently, exon analysis of 23 patients with familial schwannomatosis identified 61% of probands with *SMARCB1*germline point mutations. These findings also confirmed the previous finding that the majority of the constitutional alterations of *SMARCB1* in familial schwannomatosis are predicted to be non-truncating and therefore, they do not inactivate SMARCB1 protein expression, in contrast to mutations found in RTPS that did lead to a complete loss of protein expression [5,29,41,80]. Interestingly, schwannomatosis-related mutant SMARCB1 proteins seem to be biologically functional and retain the ability to repress cyclinD1 transcription [80] . This might be of fundamental significance for the pathway that defines the tumor type developed.

Schwannomatosis and other Tumors

As previously mentioned, schwannomatosis is characterized by multiple non-intradermal, non-vestibular schawannomas [63]. Although infrequently, other tumors such as meningiomas and ependymmomas, besides rhabdoid tumors, have been described in schwannomatosis patients [77-79,81-84].

Cribriform neuroepithelial tumors (CRINET)

Recently, Hasselblat and colleagues reported two cases of unusual intracranial non rhabdoid neuroectodermal tumors with in and around the third and fourth ventricle presenting a cribri form and trabecular histology with well-defined epithelial membrane antigen (EMA) immune positive expression within the membrane of tumor cells and loss of SMARCB1 protein expression [85]. The children with these tumors responded well to conventional therapy and they were in complete remission longer than 5 years after diagnosis. These unusual neuroectodermal tumors with "distinct cribriform non rhabdoid histological features and loss of SMARCB1 protein expression, lack of rhabdoid differentiation and a relatively favorable prognosis" were named cribri form neuroepithelial tumors (CRINET) [85]. To date, about four years after the initial description of this entity, only 3 additional cases have been described [86-88]. These 3 additional cases were all intraventricular and occurred in pediatric patients between 10-26 months of age [86,88].

Ibrahim and collaborators described a *SMARCB1* germline mutation associated with CRINET in which the patient harbored two heterozygous mutations, one of which was constitutionally expressed in the blood, suggesting a two-hit mechanism for tumor development [30,87]. However, the most recent published case, although *SMARCB1* mutation was detected in the tumor, no mutation was identified in the genomic DNA. Genetic testing for both somatic and germline mutations may help further characterization of this entity.

CONCLUSION

Germline mutations of the *SMARCB1* gene predispose patients to rhabdoid tumors, schwannomatosis and other neoplasms. Families may demonstrate incomplete penetrance and gonadal mosaicism. Genetic counseling should be recommended to the families and facilitated by their clinicians and institutions.

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