



Germline variants in *SMARCB1* and other members of the BAF chromatin-remodeling complex across human disease entities: a meta-analysis

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Abstract

Germline variants that affect function are found in seven genes of the BAF chromatin-remodeling complex. They are linked to a broad range of diseases that, according to the gene affected, range from non-syndromic or syndromic neurodevelopmental disorders to low-grade tumors and malignancies. In the current meta-analysis, we evaluate genetic and clinical data from more than 400 families and 577 patients affected by *BAF* germline alterations. We focus on *SMARCB1*, including 43 unpublished patients from the EU-RHAB registry and our institution. For this gene, we further demonstrate whole gene as well as exon deletions and truncating variants to be associated with malignancy and early-onset disease. In contrast, non-truncating variants are associated with non-malignant disorders, such as Coffin–Siris syndrome or late-onset tumors like schwannoma or meningioma ($p < 0.0001$). *SMARCB1* germline variants are distributed across the gene with variants in exons 1, 2, 8, and 9 being associated with low-grade entities, and single-nucleotide variants or indels outside of exon 9 that appear in patients with malignancies ($p < 0.001$). We attribute variants in specific *BAF* genes to certain disease entities. Finally, single-nucleotide variants and indels are sometimes detected in the healthy relatives of tumor patients, while Coffin–Siris syndrome and Nicolaides–Baraitser syndrome generally seem to appear de novo. Our findings add further information on the genotype–phenotype association of germline variants detected in genes of the BAF complex. Functional studies are urgently needed for a deeper understanding of *BAF*-related disorders and may take advantage from the comprehensive information gathered in this article.

Introduction

Germline variants in subunits of the BAF (BRG1/BRM-associated factor) or SWItch/sucrose non-fermentable (SWI/SNF) chromatin-remodeling complex have recently been implicated in benign and malignant tumors as well as neurodevelopmental disorders, always depending on the gene affected. *SWI/SNF* is highly conserved from yeast to

its human analog *BAF*, but also displays certain differences in composition and function. These genes encode for a group of proteins that associate to alter the spatial configuration of the DNA in an ATP-dependent manner and hereby regulate its accessibility for transcription factors. BAF functions as an epigenetic modulator of cell differentiation [1], metabolism [2], fate [3], DNA repair [4], and as a tumor suppressor [5]. Latest findings illuminate the role of BAF as a regulator of enhancers associated with developmental processes, an interaction that may be perturbed by loss of its *SMARCB1/BAF47* subunit [6, 7]. In total, the complex is composed of 12–28 subunits and always includes the core units *SMARCB1/BAF47*, *SMARCC1/BAF155*, and the mutually exclusive ATPase *SMARCA4/BAF190A* or *SMARCA2/BAF190* as a catalytic effector molecule. Mammalian BAF complexes divide into Brahma-associated factor (BAF) and Polybromo BAF (PBAF) complexes, defined by the presence of either *ARID1A/B/BAF250A/B* or *ARID2/BAF200* and *PBRM1/BAF180* [8].

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Other defining subunits vary depending on cell type and tissue, enabling the diverse functions of the complex. Considering its versatile regulatory role, it is unsurprising that mutational events in *BAF* genes disturb cellular processes ranging from early development to cell survival and death. Indeed, up to 20% of human cancers harbor somatic gene variants in *BAF* genes, including a large variety of carcinomas, pediatric malignancies, and low-grade tumors [9]. The role of the *BAF* subunit *SMARCB1* as a tumor suppressor is best understood, as it is closely linked to rhabdoid tumors (RT) [5]. Rhabdoid tumors are rare and highly malignant pediatric cancers that may occur in the CNS (Atypical teratoid/rhabdoid tumor: AT/RT), the kidney (Rhabdoid tumor of the kidney: RTK), and soft tissue (Malignant rhabdoid tumor: MRT) predominantly of infants and young children. Their clinical heterogeneity contrasts with a remarkable simple genome, characterized by biallelic *SMARCB1* inactivation as the only recurring feature. This follows a classical two-hit model with germline events in up to 30% of cases (rhabdoid tumor predisposition syndrome type 1, OMIM # 609322) [10]. *SMARCA4* variants may rarely also function in the same manner (rhabdoid tumor predisposition syndrome type 2, OMIM # 613325) [11, 12].

Exomic sequencing of adult and pediatric cancers has discovered somatic gene variants in many units of the *BAF* complex. However, germline variants linked to the development of solid tumors have only been detected in *SMARCA4*, *SMARCB1*, and *SMARCE1* [13]. Constitutional (mostly de novo) variants of *SMARCB1* and *SMARCA4* as a first step followed by somatic loss-of-heterozygosity (LOH) represent a paradigmatic two-hit tumor model of epigenetic regulators. Most prominently they lead to RT, or more rarely (*SMARCB1* only) to cribriform neuroepithelial tumors (CRINET) [14], malignant peripheral nerve sheath tumors (MPNST) [15, 16], epitheloid sarcomas [17], leiomyosarcomas [18], or schwannomas (SWNTS1, OMIM # 162091) [16] (mosaic LOH or haplo-insufficiency in some cases is sufficient regarding the last three entities; in case of schwannoma changes in other genes may be required additionally). *SMARCA4* germline variants may lead to small-cell carcinomas of the ovary, hypercalcaemic type (SCCOHT) [19, 20]. *SMARCE1* variants are restricted to non-NF2-driven clear cell meningioma (OMIM # 607174) [21].

Variant carriers suffering from intellectual disability or specific neurodevelopmental disorders constitute a second group of patients with currently little evidence for tumor predisposition, although follow-up data from larger groups of patients are lacking. Heterozygous variants in five genes encoding subunits of *BAF* account for the majority of the clinically heterogeneous Coffin–Siris syndrome (CSS, OMIM # 135900), while the clinically more homogenous Nicolaides–Baraitser syndrome (NCBRS, OMIM # 601358)

appears to be due to *SMARCA2* germline variants. Both rely on genetic variants of one copy of the respective genes. Key findings shared in both syndromes include intellectual disability and coarse facial features, distinguishing findings in CSS are thumb/toe hypoplasia and hypertrichosis vs. thickened interphalangeal joints and sparse hair in NCBRS [22]. Penetrance for both syndromes appears to be complete [23, 24]. Interestingly, the co-occurrence of tumors in such patients is restricted to anecdotal reports [25–27].

In the current meta-analysis we link clinical and genetic data from over 400 families with 577 patients carrying *BAF* germline alterations. We include 43 unpublished cases and discuss potential mechanisms causal for pathogenesis in order to decipher genotype–phenotype relations.

Methods

Published cases with *BAF* germline variants

We reviewed the literature, eventually including 534 *BAF* germline variant carriers from more than 60 published manuscripts and from the open source *SMARCB1* database that gathers patients suffering from *SMARCB1*-deficient neoplasia with special regards on tumor genetics (https://www.uke.de/dateien/kliniken/paediatrische-haematologie-und-onkologie/dokumente/smarcb1/smarcb1_data_uke_2009-11-26.html, April 20th 2017). Pubmed-based investigation included the following search items: “*BAF*/SWI/SNF germline mutation/alteration/variant”, or “*BAF*/SWI/SNF constitutional mutation/alteration/variant” supplemented each by the terms “*SMARCA2*”, “*SMARCA4*”, “*SMARCB1*”, “*SMARCC1*”, “*SMARCE1*”, “*ARID1A*”, “*ARID1B*”, “*ARID2*”, “*BRM*”, “*BRG1*”, “*INI1*”, “*BAF190*”, “*BAF190A*”, “*BAF155*”, “*BAF57*”, “*BAF250a*”, *BAF250b*, “*BAF200*”, “tumor”, “neoplasia”, “malignancy”, “rhabdoid tumor”, “*ATRT*”, “*AT/RT*”, “*MRT*”, “*RTK*”, “*CRINET*”, “*SCCOHT*”, “schwannoma”, “schwannomatosis”, “meningioma”, “autism”, “*CSS*”, “Coffin Siris syndrome”, “*NCBRS*”, “*Nicolaides–Baraitser syndrome*”. Patients were included in our study whenever the diagnosis had been verified genetically, and information on the germline status was given.

Novel cases with *BAF* germline variants

Twenty-six patients included in this study are derived from the European rhabdoid registry-cohort (EU-RHAB), another 17 were gathered from our own archives. All individuals are listed in Supplementary Table 1, organized in respect to diagnosis, variant, and relationship to other variant carriers. If already published, the respective literature is cited. Supplementary Table 2 lists families with more than one known

carrier of a *BAF* germline variant separately, while Supplementary Table 3 gives an overview of individuals and families suffering from more than one disease. Unpublished individuals have been submitted to the LOVD-database for public insight: <https://databases.lovd.nl/shared/genes/SMARCB1> (# 00107735-00107756 and # 00107811-00107831).

Statistical analysis

We used χ^2 analysis to determine significance of differences between reference groups. Level of significance was set at <0.05 . If patients suffered from more than one disease, we counted every single entity arising as one separate case: Comparing “cases of low-grade tumor” vs. “cases of malignant tumor”, a patient bearing schwannoma as well as MPNST contributes to both groups. If a patient fell ill with different types of rhabdoid tumor, this was considered as one entity.

Results

BAF-related diseases can be attributed to variants within specific *BAF* genes

Screening by unbiased exomic sequencing in different tumor cohorts and patients with unexplained intellectual disability has revealed an ever expanding relation of various diseases to *BAF* alterations [9]. An overview on diseases related to *BAF* germline variants is given in Table 1. Alterations in *SMARCB1* represent the most common genetic change that predisposes to the development of BAF-related diseases (339 *SMARCB1* variant carriers/577 *BAF* cases in total). *SMARCB1* germline variant carriers also suffer from a broader range of different entities compared to other *BAF* complex gene germline variant carriers. Constitutional variants in *SMARCB1* predispose, for instance, to the rhabdoid tumor predisposition syndrome type 1 ($n = 185$ RTPS1/339 *SMARCB1* variant carriers), resulting in early-onset highly malignant tumors [28]. These patients are affected by rhabdoid tumors at any anatomical site including CNS ($n = 109$ AT/RT/185 *SMARCB1* mutated RT, including 27 unpublished cases), kidney ($n = 12$ RTK/185, including one unpublished case), and soft tissue ($n = 24$ MRT/185, including five unpublished cases). Of note, a significant proportion of patients presented with bi- and multifocal tumors ($n = 39$ multifocal RT/185, including ten unpublished cases). *SMARCB1* germline variants have further been detected in patients with schwannomatosis (89/339 *SMARCB1* variant carriers) or CRINET (3/339) [14]. Except for *SMARCA4*, no other *BAF* complex member encoding gene has been shown to be involved in the

Table 1 Overview on diseases caused by *SMARCB1* germline variants

Affected gene	Atypical teratoid/rhabdoid tumor (AT/RT)	Rhabdoid tumor of the kidney (RTK)	Malignant rhabdoid tumor (MRT)	Multifocal rhabdoid tumor	Schwannoma	Meningioma	SCCOHT	Other tumors	Coffin-Siris syndrome	Nicolaides-Baraitser syndrome	Unaffected carriers	Total
Number of cases	115	13	25	39	89	37	26	12	119	64	38	577
<i>SMARCB1</i>	109	12	24	39	89	23	0	12	14	0	17	339
<i>SMARCA4</i>	6	1	1	0	0	0	26	0	12	0	14	60
<i>SMARCA2</i>	0	0	0	0	0	0	0	0	4	64	0	68
<i>SMARCE1</i>	0	0	0	0	0	14	0	0	6	0	7	27
<i>ARID1A</i>	0	0	0	0	0	0	0	0	8	0	0	8
<i>ARID1B</i>	0	0	0	0	0	0	0	0	69	0	0	69
<i>ARID2</i>	0	0	0	0	0	0	0	0	6	0	0	6

One patient may represent several cases if he developed more than one disease. Other tumors encompass cribriform neuroepithelial tumor (CRINET, $n = 3$), malignant peripheral nerve sheath tumor (MPNST, $n = 2$), conventional chondrosarcoma ($n = 1$), epithelioid sarcoma ($n = 1$), myeloid sarcoma ($n = 1$), myeloid sarcoma ($n = 1$), leiomyosarcoma ($n = 1$), papillary renal cell carcinoma (pRCC1, $n = 1$), leiomyoma ($n = 1$), and myoepithelioma ($n = 1$).

tumorigenesis of these diseases. Very rarely, other neoplasms may arise in the setting of a *SMARCB1* germline variant, i.e., meningioma ($n = 23/339$) [21, 29, 30], malignant peripheral nerve sheath tumor ($n = 2/339$) [15, 16], chondrosarcoma ($n = 1/339$) [31], epitheloid sarcoma ($n = 1/339$) [17], leiomyosarcoma ($n = 1/339$) [18], leiomyoma ($n = 1/339$) [32], and myoepithelioma ($n = 1/339$) [33]. In addition to neoplastic diseases, there are a few cases of patients with CSS, who carry *SMARCB1* germline variants ($n = 14/339$) [22, 34, 35].

The disease spectrum of patients with *SMARCA4* variants partially resembles the *SMARCB1* spectrum of diseases as they are known to cause the RTPS2 ($n = 8/60$ *SMARCA4* variant carriers) [10, 11] and, likewise, may be detected in patients with Coffin–Siris syndrome ($n = 12/60$) [34, 35]. However, *SMARCA4* is the only *BAF* gene that has been mentioned in the context of small cell carcinoma of the ovary hypercalcaemic type (SCCOHT) involving both somatic and germline variants ($n = 26/60$) [20]. So far, 14 unaffected variant carriers ($n = 14/60$) have been published, indicating incomplete penetrance (Table 3 and Supplementary Table 1).

SMARCA2 germline variants ($n = 68$) have not been implicated in tumorigenesis, but they are the only known gene linked to NCBRS [36]. The small number of patients with CSS attributed to *SMARCA2* variants ($n = 4$) have been reclassified as suffering from NCBRS [35].

Constitutional *SMARCE1* variants are less pleiotropic and are seen in association with predominantly spinal clear cell meningioma ($n = 14/27$ *SMARCE1* variant carriers) [21]. Few Coffin–Siris patients ($n = 6/27$) [22, 25, 34, 35] as well as healthy *SMARCE1* variant carriers in families with multiple relatives affected by meningiomas ($n = 7/27$) [37–39] have also been published.

Germline alterations of *ARID1/2* genes (*ARID1A*, *ARID1B*, *ARID2*) have only been linked to Coffin–Siris syndrome with *ARID1B* variants (69/83 *ARID1/2* variant carriers) as the most common genetic change for this neurodevelopmental disorder so far [22, 34, 35]. Intriguingly, truncating *ARID1/2* variants seem to have different impact on the phenotype depending on whether they occur in the germline, causing CSS, or as somatic events with an association to tumor development [40–42]. The preponderance of *ARID1B* variations could be explained by the hypothesis that full *ARID1A* deletions are lethal, a fact that is underlined by the circumstance that most *ARID1A* variations in CSS patients occur as a mosaic [22, 35].

Surpassing all *BAF* genes, *SMARCB1* germline variants have the highest pleiotropy. This includes malignant as well as low-grade tumors and neurodevelopmental disorders, most prominently CSS, but also individuals with *EHMT1*-negative Kleefstra syndrome [43]. In contrast, variants in

SMARCA4, *SMARCA2*, *SMARCE1*, *ARID1A*, *ARID1B*, and *ARID2* each are clinically more distinct.

Type of *SMARCB1* variant determines type of disease

We next took a closer look on the type of variants occurring within *SMARCB1*, correlating them with resulting phenotypes (Table 2). We focussed on *SMARCB1* as the most pleiotropic gene of the *BAF* family members.

Truncating *SMARCB1* variants (whole gene deletions, partial deletions, nonsense, and frameshift variants) are much more likely to be associated with malignancies ($p < 0.001$, χ^2 analysis). While partial and whole gene deletions of *SMARCB1* only appear in the setting of rhabdoid tumors, this entity rarely arises due to *SMARCB1* missense or in-frame variants. We identified one single patient with a *SMARCB1* missense variant (c.1142 C > G p.Thr381Arg) suffering from a CRINET [14]. Instead, *SMARCB1* missense variants display a clear association with low-grade tumor entities and non-oncologic illnesses (benign: $n = 34/42$, malignant: $n = 1/42$, non-oncologic: $n = 4/42$, unaffected carriers 3/42). Indeed, in all 13 Coffin–Siris *SMARCB1* variant carriers in our study an in-frame or missense variant provides the genetic basis for the disease (Supplementary Table 1). These variants cluster closely at exon 8 and 9, indicating for a specific position effect in the pathogenesis of *SMARCB1*-related CSS. Development of schwannoma and meningioma is more complex and involves other co-operating genes such as *NF2* and *LZTR1* [21, 44]. *SMARCB1*-Schwannomatosis (SWNTS1) is characterized by spinal and often painful peripheral schwannomas excluding acoustic neurinoma, that appear in the setting of *SMARCB1* nonsense- and frameshift variants, but not exon-spanning deletions, which carry a high risk for malignancy. Splice-site variants are detectable in several tumor entities of both benign and malignant clinical behavior.

The most frequent combination of entities arising simultaneously is schwannoma plus meningioma. So far four families and two further patients have been published. The families include 16 patients, who developed both schwannoma and meningioma, while four individuals exclusively suffered from meningioma, four others from schwannoma, and three healthy carriers were observed (Supplementary Table 2).

SWNTS1 may also encompass RT, however. Of note, one patient additionally developed an MPNST within a schwannoma (Family 5: AT/RT $n = 2$, schwannoma $n = 3$, no evidence of disease (NEoD) $n = 1$ [45]; Family 6: AT/RT $n = 2$, schwannoma + MPNST $n = 1$, NEoD $n = 1$ [15]), and there is one further report of a *SMARCB1* germline variant carrier with schwannoma and MPNST

Table 2 Age of disease onset and type of tumor caused by different *SMARCB1* germline variants

	Atypical teratoid/rhabdoid tumor	Rhabdoid tumor of the kidney	Malignant rhabdoid tumor	Multifocal rhabdoid tumor (soft tissue)	Schwannoma	Meningioma	Other tumors
Whole gene deletion	17	3	11	15	0	0	2
Partial deletion	15	0	4	3	0	0	0
Nonsense	28	4	3	15	10	1	0
Frameshift	28	4	3	4	12	1	4
Splice-site	14	0	3	0	24	2	3
Missense	0	0	0	0	30	18	1
Duplication	4	0	0	1	0	0	1
Indel	1	0	0	0	1	0	0
Complex	1	0	0	0	1	0	1

Dots indicate single patients. Numbers count for cases of disease, so that patients with more than one disease may contribute to more than one category. Other tumors encompass cribriform neuroepithelial tumor (CRINET, $n = 3$), malignant peripheral nerve sheath tumor (MPNST, $n = 2$), myeloid sarcoma ($n = 1$), epithelioid sarcoma ($n = 1$), conventional chondrosarcoma ($n = 1$), leiomyosarcoma ($n = 1$), leiomyoma ($n = 1$), papillary renal cell carcinoma type 1 (pRCC1, $n = 1$) and myoepithelioma ($n = 1$).

[16]. A *SMARCB1*-negative leiomyoma as well as a leiomyosarcoma both affected schwannoma patients [18, 32]. Furthermore, Gossai et al. published a Coffin–Siris patient, diagnosed with schwannomatosis-induced cord compression at 33 years of age [25]. Another interesting case is a former MRT patient reported by Forest et al., who subsequently developed chondrosarcoma [31]. A further family of six individuals had two healthy variant carriers, while three members were diagnosed with AT/RT in childhood. Of the latter, one developed a *SMARCB1*-negative myoepithelioma later in life. The sixth member died at age of 0.6 years from a posterior fossa mass not further analyzed [33].

Categorizing variant carriers with regard to their specific germline event reveals clear differences, but also some overlaps. Exon-spanning deletions are solely linked to the generation of RT, whereas non-truncating variants only rarely predispose to malignancies. Nonsense, frameshift, and splice-site variants exhibit varying effects concerning development of malignant or non-malignant disease.

***SMARCB1* variant determines age of disease onset**

In order to evaluate genetic and clinical variables, we plotted age of disease onset and type of variant of 160 *SMARCB1* germline variant carriers with tumor disease. We found that the distribution across time depends on the type of the underlying variant: Truncating variants are associated with early-onset disease, non-truncating variants with late-onset disease (average age 45 months vs. 519.5 months, $p < 0.0001$; median age of onset 7 months vs. 474 months, Table 2). Missense variants in *SMARCB1* are detected in

individuals not diagnosed with tumors before their 10th year of age. Disregarding two exceptional patients with constitutional whole gene deletion and diagnosis of RT at age 14 and 24.5 years [10, 46], there is a strong correlation between functional impact of a *SMARCB1* germline variant and age of disease onset. This rule applies also to low-grade *SMARCB1* tumors with truncating (median age at onset: 294 months) vs. non-truncating germline variants (median age at onset: 474 months, average age 308 vs. 519 months, $p < 0.0005$).

***SMARCB1*-associated tumor entities show characteristic variation patterns**

To gain a detailed overview of the genomic landscape of *SMARCB1* germline events we arranged the variants along the gene, sorting them by malignant or benign clinical behavior (Fig. 1). While single-nucleotide variants associated with malignancies tend to be located in the center of the gene (61/98, on exons 3–7; 37/98, 38% on exons 1, 2, 8, 9), such that appear in the context of schwannoma, meningioma, or Coffin–Siris syndrome are predominantly found on its ends (52/63, 82.5% on exons 1, 2, 8, 9; 11/63, 17.5% on exons 3–7; $p < 0.001$). Strikingly, variants in the MYC binding, the HIV integrase binding, and the PPP1R15A interacting domain are exclusively associated with development of rhabdoid tumors. While variants in the DNA binding site or the SNF5 domain may also predispose to schwannoma or meningioma, those leading to CRINET or CSS reside outside specific domains known so far.

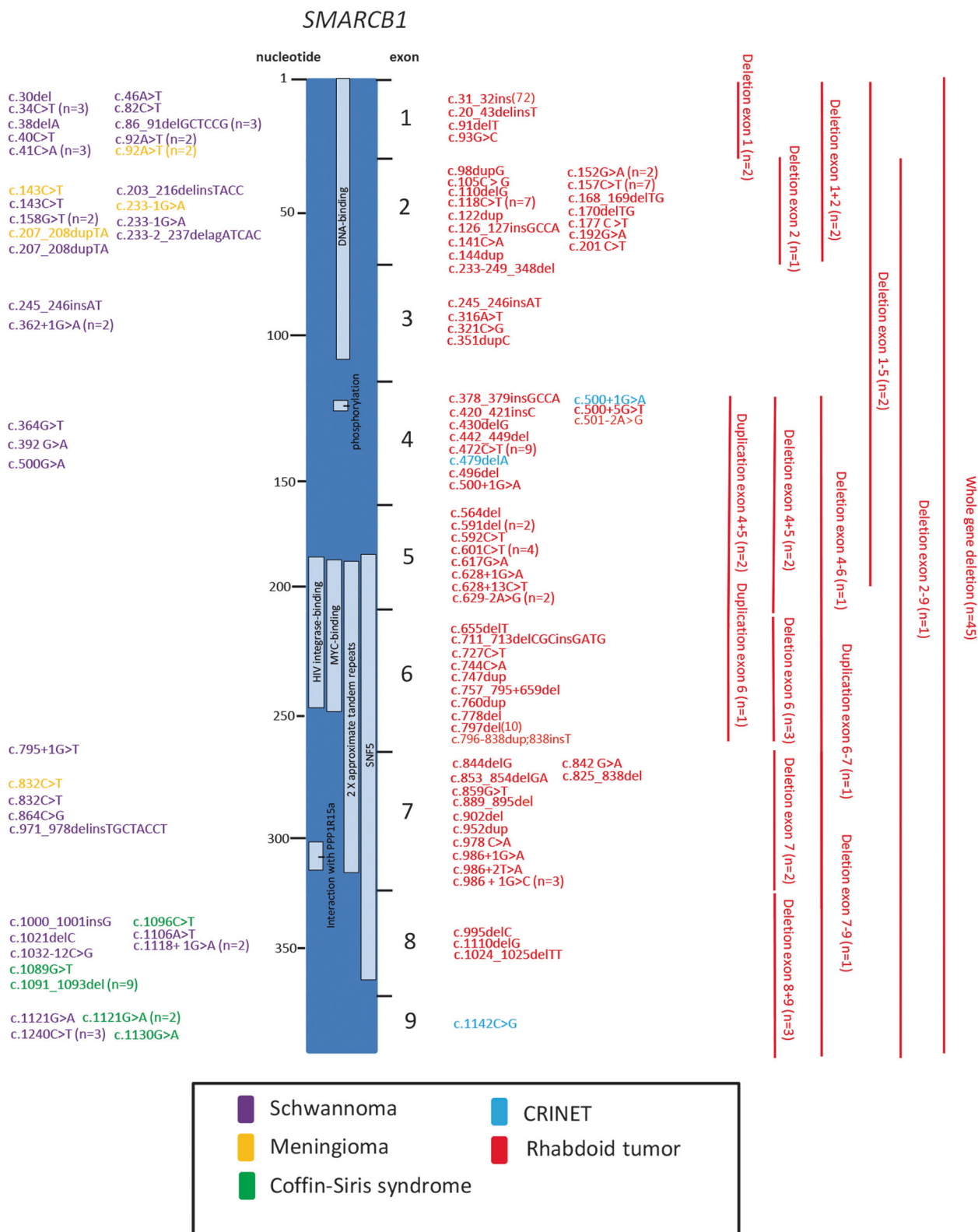


Fig. 1 Distribution and type of germline variants occurring along the *SMARCB1* gene. On the left side, variants causing benign entities are indicated in violet (schwannoma), yellow (meningioma), and green (Coffin–Siris syndrome), while the right side shows malignancies in red (rhabdoid tumor) and light blue (CRINET). Red bars show extent

of deletions and duplications. Note that variants in benign disorders are mainly present in 1, 2, 8, and 9, while malignant tumors are frequently caused by variants within exons 2–7. Light blue bars indicate for known domains

Table 3 Distribution of BAF germline alterations in families with unaffected variant carriers

		Whole gene deletion	Partial deletion	Nonsense	Missense	Frameshift	In-frame	Splice-site	Duplication	Indel	Total number of families
Affected	SMARCB1	0	2	1	1	3	0	4	1	0	12
Gene	SMARCA4	0	0	3	1	1	0	0	0	0	5
	SMARCE1	0	1	0	0	2	0	0	0	1	4

Healthy individuals with germline mutations in *SMARCA2*, *ARID1A*, *ARID1B*, and *ARID2* are not known.

Unaffected BAF germline variant carriers harbor diverse types of variants excluding whole gene deletions and in-frame variants

Table 3 summarizes family screening results depicting the prevalence of healthy carriers related to index tumor patients with constitutional BAF-related disease. This involves individuals with variants in *SMARCB1* (17/38 unaffected variant carriers in total) [10, 14, 15, 29, 33, 45, 47–51], *SMARCA4* (14/38) [11, 12, 52, 53], and *SMARCE1* (7/38) [37–39], but no healthy carriers of *ARID1A/B* or *ARID2* variants (0/38). Referred to all variant carriers of a particular gene, the incidence of unaffected individuals is by far higher among *SMARCE1* and *SMARCA4* variant carriers (7/27 and 14/60) than in carriers of *SMARCB1* variants (17/339), suggesting incomplete penetrance for variant carriers with *SMARCB1* variants, that is even further reduced regarding the *SMARCA4* and *SMARCE1* situation. Truncating as well as non-truncating variants were found. Of interest, neither whole gene deletions nor in-frame variants appear in this context (0/38). The largest group is represented by splice-site variants in *SMARCB1* (6/38).

Discussion

Reviewing and extending the number of *BAF* germline variant carriers known so far provides insight into a wide landscape of various genetic events with diverging impact on a carrier's phenotype.

Considering the phenotypic range from aggressive tumors to asymptomatic individuals, the intriguing question concerns the underlying modifying effectors. Though up to 20% of human cancers harbor *BAF* variants [9], research focussing exclusively on germline variants usually is restricted to very small cohorts of patients. Thus, meta-analyses are required to gain an overview.

Hence, the scope of our work was to broaden the perspective on *BAF* genetics by integrating new and existing data with regard to disease spectrum, possible pathomechanisms, and clinical data. Affecting a core *BAF* member, germline alterations in *SMARCB1* have first been related to the development of rhabdoid tumors in the late

nineties [54]. While this finding has been confirmed in numerous studies, further research suggested other entities to be involved as well. Among others, schwannoma, meningioma, and CSS were ascertained to arise in the setting of *SMARCB1* germline variants. Detailed consideration of the specific genetic events reveals that *SMARCB1*-related rhabdoid tumors are exclusively associated with truncating variants. It is noteworthy that variants occurring in more benign tumor entities or CSS tend to affect the first and last exons, whereas such causing RT either represent as exon-spanning or complete *SMARCB1* deletions or single-nucleotide variants and indels that widely spare out exon 1. For exon 9, it is known that variants do not lead to nonsense-mediated decay, which might explain the apparent lack of changes associated with malignancy here. Variants within the center of the gene (*MYC* binding, HIV integrase binding, and interaction with PPP1R15A) may predispose to rhabdoid tumors, while those at the beginning of *SMARCB1* (*DNA* binding) may additionally lead to schwannoma or meningioma. A series of variants cannot be directly linked to any known domain, including all single-nucleotide variants resulting in CRINET and CSS. Future 3D modeling of the protein structure and its interfaces with other proteins of the complex along with functional analyses might help to understand this peculiar pattern. However, investigating the functional impact of selected variants may be of high value for a deeper understanding of *BAF* genetics.

Our data strengthens the results Smith et al. demonstrated in a smaller study regarding schwannoma and RT. The overview (Fig. 1) points out that this phenomenon may also hold true for other diseases, emphasizing the role of the first and last exons of *SMARCB1* especially in the generation of non-malignant disease [16]. Nevertheless, a few truncating variants in exon 1, 2, and 8, predispose to malignant tumors. Presuming a consistent frequency of variation along the gene, these observations might indicate a particular susceptibility for its first and last exons, as non-truncating variants in its center may indeed exist, but obviously do not become apparent in a clinical setting. To date, deletions of every *SMARCB1* exon have been detected. Independent of their extent (ranging from one exon up to whole gene deletion) they categorically lead to formation of RT.

The effectors modifying the very discordant outcome of variations probably affecting function in the BAF complex remain largely unknown (It is obvious that severity of a disease depends on the functional alterations of the protein a mutated gene encodes; still it remains unclear, why the same type of variant or, in rare cases, the very same variant might be related to both, a benign tumor and a malignancy.). In our cohort, three types of variants—nonsense, frameshift, and splice-site variants—predispose to RT and schwannoma as well. Santen et al. further state that germline variants in *ARID1A/B* and *SMARCB1* causing mental retardation syndromes can also be found as somatic variants in tumor patients [55]. Moreover, one patient with both CSS and schwannoma and a *SMARCB1* germline variant has been reported [25]. The combination of intellectual disability and malignancy due to germline alterations interestingly seems uncommon. While the impact of splice-site variants generally is hard to predict, nonsense and frameshift variants can result in protein truncation. However, the different outcome of affected individuals suggests that in some cases there might be residual protein activity, potentially in form of a variant leaving at least parts of the protein functional. This assumption is supported by data derived from Hulsebos et al., who expressed four schwannomatosis-associated *SMARCB1* exon 1 variants in rhabdoid tumor cells lacking endogenous *SMARCB1*. This resulted in the synthesis of a shortened *SMARCB1* protein due to reinitiation of translation at an AUG-codon downstream of the nonsense variant [56]. When analyzing samples one should also keep in mind the possible presence of cells containing unaffected DNA in the sense of a parental germline mosaicism, as it is typical for familial schwannomatosis [57]. Gonadal mosaicism of the parents appears to be regularly involved in hereditary RT [10, 47, 58–60].

It further appears useful not only to involve location and specific type of a variant, but also its time point during development and to further have a look at additional genes that may be required for tumorigenesis. Information about temporal distribution of variants is only given in an experimental setting. According to Han et al., tamoxifen-mediated inactivation of *SMARCB1* in mice results in different phenotypes depending on time of injection. Mice develop RT, when *SMARCB1* is inactivated in a short timeframe between E6 and E10, while injection at earlier and later stages of development leads to embryonic lethality, hepatotoxicity, or T-cell lymphoma [61], suggesting a cellular period of vulnerability to truncating variants that result in RT. Human variant carriers not receiving a second hit in the critical timeframe might accumulate additional variants later in life, which is in line with the 3-step/4-hit model of pathogenesis for schwannoma. Here, an adjacent gene, *NF2*, contributes to tumorigenesis: Initially, a constitutional variant inactivates one copy of *SMARCB1*,

followed by a loss of its second copy together with the adjacent *NF2* and an inactivating variant of the remaining wild-type *NF2* as somatic events [62]. Comparable mechanisms of pathogenesis have been assumed for meningioma [50]. These considerations match well the clinical data: Patients suffering from schwannoma and meningioma fall ill significantly later in life, as do carriers of non-truncating *SMARCB1* variants. This also holds true for the three families suffering from schwannoma as well as RT. Interestingly, the effect may also be observed within a group of patients suffering from low-grade *SMARCB1*-mutated tumors. Comparing variant carriers with or without truncating variants, the median age of tumor onset is considerably lower for the former (24.5 vs. 39.5 years), possibly indicating a residual protein activity in the case of a missense variant. Individuals, who are diagnosed with an RT in adolescence or adulthood, are exceedingly rare. One may thus hypothesize the persistence of stem cells that have retained their vulnerability for a critical second hit. Indeed, RT cells exhibit common features of embryonic stem cells [63], although the cell of origin of RT yet remains to be elucidated.

For investigating possible pathomechanisms, asymptomatic carriers of *SMARCB1* germline variants are of particular interest. All unaffected carriers involved in our study are related to diseased persons. Of note, only oncogenic variants appear in healthy variant carriers, and we do not know of the latter kindred with CSS or NCBRS patients. The oncogenic variants do not show any preference of gender, age, or degree of kinship, confirming an accidental second hit that might hit or not hit an individual as the underlying cause for disease pathogenesis. Interestingly, all types of variants except in-frame variants or deletions larger than two exons are represented in this group. This is in sharp contrast to the large number of RT patients with extended *SMARCB1* deletions (38%) and might indicate full penetrance for this kind of variant, whereas single-nucleotide variants are characterized by incomplete penetrance as well as variable expression. Nevertheless, one should keep in mind the possibility of parental germ cell mosaicism in these cases [60], which is why relatives should be screened thoroughly for such events. Remarkably, the amount of unaffected variant carriers differs among genes and it is much more likely to find a patient with healthy, variant-bearing relatives in families affected by *SMARCA4* (23% of all *SMARCA4* variant carriers reviewed in this article) or *SMARCE1* variants (25%) than it is in those with *SMARCB1* driven disease (5%). This is in line with the assumption that the 22q.11.2 locus is a highly unstable region susceptible to variants, deletions and translocations, and numerous diseases emerging from genomic alterations at this site reflect this observation (DiGeorge-syndrome, OMIM # 188400; Shprintzen-syndrome, OMIM

192430; 22q11.2 duplication syndrome, OMIM # 608363; Emanuel-syndrome, OMIM # 609029; Supernumerary der(22)t(8;22)-syndrome, OMIM # 613700; CSS3, OMIM # 614608; RTPS1, OMIM # 609322; SWNTS1, OMIM # 162091).

Certain entities can be attributed to germline variants in specific genes. Having a closer look on their distribution, it becomes clear that for every single gene other principles for tumorigenesis may be valid and that they differ from what is known about somatic alterations. Somatic variants in *ARID1/2* genes are widely known to occur in a broad variety of cancers [64]. In contrast, truncating germline variants in *ARID1A*, *ARID1B*, or *ARID2* predispose to CSS [22, 34, 35, 65] and hardly ever lead to tumor formation. On the other hand, both, truncating and non-truncating germline variants in *SMARCB1* [10, 51], regularly result in tumor development. Of note, the latter can also be associated with a CSS phenotype without tumor predisposition, when the 3' end of the gene is affected [22, 34, 35]. Variants in *SMARCE1* seem to be restricted to generation of meningioma or CSS [38], whereas *SCCOHT* only appears in the context of *SMARCA4* variants [20]. Heterozygous missense variants involving *SMARCA4* regularly lead to CSS [34, 35], indicating for a dominant negative effect for this type of germline alteration. Only one case of RT emerging from *SMARCA4* missense variant is known so far [12]. Regarding *SMARCB1* and *SMARCA4*, malignancy usually seems to be associated with loss of protein function due to truncating variants or complete deletions; however, the question arises how far splice-site and, rarely, missense variants detected in malignant tumors may exert a functional impact.

In the light of these obvious and largely regular patterns of disease expression one must assume substantial functional differences for the core units the complex is composed of. The BAF complex is expressed ubiquitously in all cells, with changes in subunit composition depending on the tissue. Its core units, although expressed consistently, may also exhibit different levels of activity or manners of function in their role as a chromatin remodeler, depending on cell type, stage of cell development and outside influences, finally cellular necessities of transcriptional action. This could explain differing impact of comparable variants at least in parts. Recent findings have underlined the importance of the BAF complex in terms of lineage specification and cell differentiation, and for particular subunits functional effects can be hypothesized. *SMARCB1* seems to play a crucial role for the functional integrity of the whole complex, as its loss leads to reduced binding to promoters and enhancers, thereby perturbing cell differentiation, while its level at super-enhancers and, of note, cell survival is barely affected [7]. However, further investigation with focus on the relevance and function of specific *BAF* subunits is needed to get a deeper

understanding of how *BAF*-related diseases emerge and, finally, can be cured.

In conclusion, we have reviewed a large series of *BAF* germline variant carriers, matching clinical with genetic data, and discussing possible mechanisms of pathogenesis. We have gathered information of 577 patients of over 400 families and include 43 individuals that have not been published so far.

Our data highlight the impact of truncating germline variants and their influence on disease development. We provide a broad overview of what is known so far and give useful impulses for further investigation in terms of understanding the complex *BAF* genetics.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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