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SMARCA4: Implications of an altered chromatin-remodeling gene for cancer development and therapy

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Abstract

The SWI/SNF chromatin remodeling complex, via nucleosome topology modulation, regulates transcription. The SMARCA4 (BRG1) subunit codes for the ATPase energy engine of the SWI/SNF complex. *SMARCA4* is a tumor suppressor that is aberrant in ~5–7% of human malignancies. Class I *SMARCA4* alterations (truncating mutations, fusions, and homozygous deletion) lead to loss of function while class II alterations (missense mutations) have a dominant negative/gain-of-function effect and/or loss-of function. S*MARCA4* alterations typify the ultra-rare small cell carcinomas of the ovary hypercalcemic type (SCCOHT) and SMARCA4-deficient thoracic and uterine sarcomas; they are also found in a subset of more common tumors, e.g., lung, colon, bladder, and breast carcinomas. Germline variants in the *SMARCA4* gene lead to various hereditary conditions: rhabdoid tumor predisposition syndrome-2 (RTPS2), characterized by loss-of-function alterations and aggressive rhabdoid tumors presenting in infants and young children; and Coffin-Siris syndrome, characterized by dominant negative/gain-of function alterations and developmental delays, microcephaly, unique facies, and hypoplastic nails of the fifth fingers or toes. A minority of rhabdoid tumors have a germline *SMARCA4* variant as do >40% of women with SCCOHT. Importantly, immune checkpoint blockade has shown remarkable, albeit anecdotal, responses in SCCOHT. Additionally, there is ongoing research into BET, EZH2, HDAC, CDK4/6, and FGFR inhibitors, as well as agents that might induce synthetic lethality via DNA damage repair impairment (ATR inhibitors and platinum chemotherapy), or via the exploitation of mitochondrial oxidative phosphorylation inhibitors or AURKA inhibitors, in *SMARCA4*-aberrant cancers.

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INTRODUCTION

The switch/sucrose-non-fermenting (SWI/SNF) complex is an evolutionarily conserved ATP-dependent chromatin remodeling complex that plays important roles in DNA repair, transcriptional activation of genes normally repressed by chromatin, differentiation, and organ development.(1) The SWI/SNF complex specifically changes chromatin structure by altering DNA-nucleosome topology, with nucleosomes being a structural unit of chromosomes consisting of a length of DNA coiled around a core of histones (Figure 1)(2).

Each SWI/SNF complex is comprised of multiple subunits that have an ATP-dependent catalytic unit, either SMARCA4 (BRG1) or SMARCA2 (BRM), as well as a core regulatory subunit such as SMARCB1 (INI1, BAF47), and variable other subunits including ARID1A (Figure 1)(3,4). Recent studies show important tumor suppressor roles for the SWI/SNF complex, with ~20% of human malignancies bearing pathogenic alterations of its subunits. (5–7)

SMARCA4 is also known as transcriptional activator BRG1. It can activate or repress transcription via its ATPase enzymatic role in the chromatin remodeling complex. This protein can also bind BRCA1 (8), as well as regulate the expression of the tumorigenic protein CD44 (a transmembrane glycoprotein implicated in the growth and metastasis of numerous tumors)(9).

Importantly, *SMARCA4* is one of the most frequently aberrant chromatin remodeling ATPases in cancer; it is altered in approximately 5% to 7% of all human malignancies (Table 1) (7,10–25). Further, mutations of this gene are also the hallmark of certain cancers. For instance, inactivating mutations in *SMARCA4* can be identified in the vast majority of small cell carcinomas of the ovary, hypercalcemic type (SCCOHT), and studies showed high utility of SMARCA4 immunohistochemical (IHC) loss in the diagnosis of this rare tumor that afflicts young women.(20,21,26–30) SMARCA4 deficiency is also a hallmark of thoracic sarcomatoid tumors(22,31) and of malignant rhabdoid cancers of the uterus (undifferentiated uterine sarcoma)(24). Germline *SMARCA4* variants occur and cause Coffin–Siris syndrome (characterized by abnormalities of the craniofacial area, resulting in a coarse facial appearance, microcephaly, and developmental disabilities) and RTPS2 (characterized by young onset of various poorly differentiated tumors) (32) (Table 2)(32–37).

Herein, we review the landscape of SMARCA4 abnormalities, their association with cancer, and the emerging treatment implications of these gene alterations suggesting sensitization to certain therapies, such as immune checkpoint inhibitors (ICIs).

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The SMARC family

The SWI/SNF-related, matrix-associated, actin-dependent regulators of chromatin (SMARC), also called BRG1-associated factors, are components of human SWI/SNF-like chromatin-remodeling protein complexes. *SMARC* family members include *SMARCA4 (BRG1), SMARCA2 (BRM), SMARCB1, SMARCC1, SMARCC2, SMARCD1, SMARCD2, SMARCD3, SMARCE1. SMARCA4* maps to chromosome 19p13.2 (https://www.omim.org/entry/603254)

SMARCA4 structure and function

The *SMARCA4* gene encodes a transcriptional activator protein, which has also been called BRG1 (Figures 2). The SMARCA4 protein features a bromodomain and helicase/ATPase activity (Figure 3). A bromodomain is an approximately 110 amino acid protein domain that recognizes acetylated lysine residues, such as those on the *N*-terminal tails of histones; these domains play a key role in regulating gene transcription. Helicases are enzymes that bind and can remodel nucleic acid or nucleic acid protein complexes. ATPases are enzymes that catalyze the hydrolysis of a phosphate bond in adenosine triphosphate (ATP) to form adenosine diphosphate (ADP); they harness the energy released from the breakdown of the phosphate bond and use it to execute other cellular reactions.

SMARCA4 (BRG1) forms one subunit of several different protein groupings designated SWI/SNF protein complexes. SWI/SNF complexes regulate gene activity/expression by the chromatin remodeling process. Chromatin is the arrangement of protein and DNA that packages DNA into chromosomes. The architecture of chromatin can be remodeled to adjust how tightly DNA is parceled. Chromatin remodeling is one of the critical manners in which gene expression is controlled during development. When DNA is tightly packed, gene expression is dampened as compared to when DNA is loosely packed. SMARCA4 uses ATP to provide energy for chromatin remodeling.

Through their ability to regulate gene activity, SWI/SNF complexes are involved in many cellular functions (Figures 1 and 2): replicating DNA; modulating the growth, division, and differentiation of cells; and repairing damaged DNA. Via these processes, the SMARCA4 protein acts as a tumor suppressor (Figure 2). Having functional SMARCA4 is also important for development past the pre-implantation stage.(38) SMARCA4 plays a role in the growth of smooth muscle of the heart and gastrointestinal tract.(39) Additionally, *SMARCA4* is required for Gli-mediated transcription activation in Sonic hedgehog (Shh) signaling.(40) Mutations of *SMARCA4* correlate with context-dependent expression changes at MYC genes, indicating that the SMARCA4 and MYC proteins are functionally related.(41,42) Cell lines lacking SMARCA4 do not respond to retinoic acid or glucocorticoids, while restoration of SMARCA4 restores sensitivity.(42) Finally, as mentioned earlier, SMARCA4 binds BRCA1(8), and regulates the expression of the tumorigenic transmembrane glycoprotein CD44(9).

SMARCA4 alterations and cancer

The SWI/SNF ATPase SMARCA4 is one of the most frequently mutated chromatin remodeling ATPases in cancer.(43) Mutations are enriched at highly conserved ATPase

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sequences, which reside on important functional surfaces such as the DNA-binding surface or the ATP pocket.(41) Overall, *SMARCA4* is altered in about 5–7% of all malignancies. Table 1 lists some of the tumors best explored in the context of *SMARCA4* genomic alterations or loss of expression. Additional tumors in which *SMARCA4* alterations have been identified include, but are not limited to, lung cancer, colon adenocarcinoma, bladder urothelial carcinoma, and invasive breast ductal carcinoma.(44)

There are two main categories of *SMARCA4* alterations (18)

- → Class 1 mutations – truncating mutations, fusions, and homozygous deletion (loss of function usually associated with protein loss)
- → Class 2 mutations – missense mutations (postulated to have dominant negative or gain of function effects, but some reports suggest loss of function, especially in lung cancer)(25) Dominant-negative activity may be implicated in the context of a wild-type *SMARCA4* allele (when present as heterozygous mutations) or dominant-negative activity with *SMARCA*2. Missense *SMARCA4* mutations can also result in loss of accessibility and loss of chromatin remodeling activity.(41,45)

Rhaboid tumors: Many of the *SMARCA4*-altered tumors have rhabdoid features defined by characteristic large cells with eccentrically located nuclei and abundant eosinophilic cytoplasm. Rhabdoid tumors are rare, highly aggressive cancers that emerge most frequently in the brain or in the kidneys; they affect primarily infants and young children between the ages of 1 and 3 years old, but have also been identified in adults. About one-third of rhabdoid tumors are linked to germline SWI/SNF variants, usually in *SMARCB1* and less commonly in *SMARCA4.*(46)

Small cell carcinoma of the ovary, hypercalcemic type, (SCCOHT): SCCOHT is the most common undifferentiated ovarian cancer that afflicts women aged under 40 years of age. However, it is still very rare. The young women afflicted with SCCOHT usually present with symptoms related to a pelvic mass. The age range at diagnosis is quite wide (7 months to 56 years, with an average age of ~24 years). About 60% of patients with SCCOHT have hypercalcemia. SCCOHT is an aggressive cancer, with long-term survival rates of only~30% in early-stage cases.

SCCOHT is a monogenic illness, harboring somatic and germline *SMARCA4* variants. It has morphological and molecular resemblance to malignant rhabdoid tumors, which are often triggered by variants in a related SWI/SNF gene--*SMARCB1.* Overall, inactivating mutations in the *SMARCA4* gene are seen in 75 to 100% of SCCOHT cases and accompanied by SMARCA4 protein loss. In contrast, only about 0.4% (2/485) of other primary ovarian tumors have similar changes in SMARCA4.(21,47)

The incidence of S*MARCA4* germline variants is high, causing ~43% of SCCOHTs. Women with germline deleterious variants in *SMARCA4* likely have a clinically important risk of SCCOHT up to the age of ~60 years old, particularly in the context of a positive family history. Germline *SMARCA4* genetic testing is recommended for all affected women

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with SCCOHT. Additional cascade testing of at-risk family members upon identification of germline deleterious *SMARCA4* variants should be performed.(48)

In light of the fact that surveillance is of unclear benefit, risk-reducing bilateral salpingo-oophorectomy is indicated in unaffected adult women with germline pathogenic *SMARCA4* variants and a positive family history.(48) Responses to ICIs have been reported.(48,49)

SMARCA4-deficient thoracic sarcoma (SMARCA4-DTS) (22,23): SMARCA4-DTS is a recently described aggressive entity with specific genomic alterations in *SMARCA4.* It represents a distinct subset of thoracic sarcomas with undifferentiated rhabdoid morphology. These sarcomas usually occur in the 30- to 50-year-old age group, with male predominance and a smoking history. Tumors are generally large compressive masses located in the mediastinum, pleura, and/or lung. Median overall survival has been only ~6 months. Pathological diagnosis of this tumor is challenging because of the morphological features with poor differentiation that often mimic undifferentiated carcinoma or carcinoma of unknown primary.

SMARCA4-DTS has a unique biologic signature: co-loss of SMARCA4 and SMARCA2 with overexpression of SOX2. SMARCA4 loss by IHC varies in studies from 30% to 100% of cases. Durable responses to the ICI pembrolizumab have been documented.(50) Patients do not generally have evidence of germline transmission.(31)

SMARCA4-deficient uterine sarcoma (24): SMARCA4-deficient uterine sarcomas (subset of malignant rhabdoid tumor of the uterus) are rare uterine malignant neoplasms with IHC, morphologic, and genomic similarities to SCCOHT. Sheets of large atypical epithelioid cells with prominent rhabdoid morphology, indistinguishable from the large cell variant of SCCOHT are observed. Median age of onset is about 51 years old. These cancers are aggressive, with a median survival of only ~7 months.

At the molecular level, the tumors have SMARCA4 loss by IHC due to *SMARCA4* gene mutations. Germline SMARCA4 variants have been reported in SMARCA4-deficient uterine sarcomas.(51)

Hereditary Syndromes with *SMARCA4* alterations

Since the SWI/SNF complex plays a central role in gene expression, it is not surprising that there is an association between variants in the SWI/SNF complex, malignant neoplasms and developmental disorders. Germline variants in the SWI/SNF complex have now been shown to be a driving force for several types of cancers and other disorders.(52)

Germline variants in *SMARCA4* have been found in RTPS2, and Coffin-Siris syndrome (Table 2)(32–37). Moreover, ~35% of rhabdoid tumors are associated with germline SWI/SNF variants (mostly in *SMARCB1* and less commonly in *SMARCA4*), and almost half of women with SCCOHT have germline *SMARCA4* variants.(46)

The cancer risk in individuals with germline *SMARCA4* pathogenic variants remains unclear, but it is likely high. For instance, only one publication reports a female with a

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SMARCA4 germline variant who remained cancer-free past her sixth decade(53); however, there is also a publication bias for cancer-positive cases that confounds risk assessment.

Most rhabdoid tumors have been associated with *SMARCB1* loss-of-function mutations, but they can also be caused by *SMARCA4* loss-of-function mutations (leading to non-expression of their respective proteins). In general, prognosis is worse for patients with *SMARCA4*-related malignancies. To differentiate between the two variant types, rhabdoid-neoplasm related hereditary disorders have been separated into two categories:

→ RTPS1, for patients who carry a germline variant in *SMARCB1*;

→ RTPS2, for patients who carry a germline variant in *SMARCA4*.

Germline carriers are more at risk of developing second primary tumors. Females that carry the *SMARCA4* germline variant have a higher risk of developing SCCOHT. This has led to the suggestion that SCOOHT be considered part of the RTPS family of tumors.

Rhabdoid tumor predisposition syndrome 2 (RTPS2)(32,54,55): RTPS's main feature is a high risk of developing rhabdoid tumors, which are lethal cancers presenting mostly in infants and preschool children. The diagnosis of RTPS2 is established by one or more features: (i) a germline heterozygous deleterious variant in *SMARCA4;* (ii) multiple SMARCA4-deficient malignancies; (iii) a proband with a rhabdoid tumor; and/or (iv) a family history of rhabdoid malignant neoplasm.

Rhabdoid tumors most commonly afflict the central nervous system (i.e., atypical teratoid/rhabdoid tumor [AT/RT]), with more than half arising in the cerebellum. These cancers can also arise as extracranial extrarenal malignant rhabdoid tumors, such as rhabdoid tumors of the heart, bladder, liver, retroperitoneum, head and neck, paravertebral muscles, mediastinum, pelvis, rhabdoid tumor of the kidney, and SCCOHT (also known as malignant rhabdoid tumor of the ovary).

Because RTPS2 is ultra-rare, the standard of care for management is not firmly established. However, intensive surveillance from birth is needed. Most patients are treated with aggressive chemotherapy, surgery, and radiotherapy. Preventative bilateral ovary removal may be suggested, perhaps after childbearing or earlier.

Individuals diagnosed with *SMARCA4*-related RTPS2 generally inherited a deleterious variant from an unaffected parent. Since RTPS2 can be passed on in an autosomal dominant fashion, each offspring of an individual with a germline *SMARCA4* pathogenic variant has a 50% chance of inheriting the pathogenic variant.(32) Even so, penetrance appears to be incomplete, and the RTPS-related tumors can differ even within the same family. Pre-implantation genetic testing/prenatal screening are feasible if the deleterious family variant has been identified.

Coffin–Siris syndrome (CSS): Coffin-Siris is an ultra-rare and clinically heterogeneous congenital disorder with the main characteristics being developmental disability, microcephaly, hypoplastic nails of the fifth fingers or toes, and distinct facial features.

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It is caused by germline variants in different subunits of the ATP-dependent SWI/SNF chromatin remodeling complex--*ARID1A, ARID1B, SMARCA4, SMARCA2, SMARCB1* or *SMARCE1* as well as *SOX11*.(33–36) *SMARCA4* is mutated in ~7–11% of patients. Most *SMARCA4* germline alterations that have been reported in Coffin-Siris syndrome patients are non-truncating (either missense or small in-frame deletions) clustered within the highly conserved ATPase/helicase domain, thus suggesting dominant-negative or gain-of-function effects. In contrast, most SCCOHTs are due to biallelic germline and/or somatic inactivating (nonsense or frameshift) alterations causing complete loss of SMARCA4 expression. A case report of a patient with mild Coffin-Siris syndrome who developed SCCOHT as a teenager showed an inactivating *SMARCA4* variant, which is, as mentioned, non-traditional for this syndrome.(33)

Coffin-Siris syndrome appears to follow an autosomal dominant pattern of inheritance. However, the condition is not usually inherited from an affected parent, but rather occurs from *de novo* mutations that likely take place during the embryonic period.

Potential Therapeutic Targeting

Because tumor suppressor loss is not directly druggable, investigators have pursued therapeutic vulnerabilities that exploit concomitant changes in gene expression and signaling pathways. In the case of *SMARCA4*-altered cancers, immunotherapy with ICIs has emerged as a promising treatment modality (Table 3)(18,48–50,56–61). *SMARCA4* alterations result in abnormal SWI/SNF complexes; such aberrant chromatin remodeling complexes can influence the transcription of interferon-stimulated genes important for immune responsiveness, as well as the differentiation, activation and recruitment of several immune cell types.(62) Multiple other signals have also been investigated for potential pharmacologic intervention.

Immunotherapy: Although the low mutation burden of SCCOHT would not predict responsiveness to ICI responsiveness, programmed cell death protein [ligand] 1 (PD-[L]1) inhibitors such as pembrolizumab have shown exceptional and durable responses in patients with relapsed SCCOHT.(48,49) Case reports of remarkable responses in aggressive SMARCA4-deficient thoracic sarcoma and in *SMARCA4*-altered NSCLC have also been published.(50,56,57) Although the number of patients reported above is small, it should be noted that the hallmark of the above cancers is *SMARCA4* alterations. Furthermore, ICI treatment correlated with significantly improved outcomes overall in *SMARCA4*-aberrant NSCLC.(18) Some of these ICI responses were seen in patients with high tumor mutation burden (TMB) and/or high PDL1 expression by IHC, each of which are markers for immunotherapy response, but other patients had low TMB and were PD-L1 negative and still responded (Table 3)(63–67). Unfortunately, SMARCA4-deficient small-cell lung carcinoma has been reported to have had a negative outcome on ICI, as reflected by hyperprogressive disease (accelerated progression, which is sometimes observed in patients treated with immunotherapy).(58–61)

Bromodomain/BET inhibitors: BET inhibitors are a class of drugs that reversibly bind the bromodomains of Bromodomain and Extra-Terminal motif (BET) proteins BRD2–4,

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and thwart protein-protein interaction between BET proteins and acetylated histones and transcription factors. BET inhibitors have been investigated in SCCOHT models, based on the reliance of *SMARCA4*-mutant esophageal cancer models for BET protein BRD4 and the co-regulation of an oncogenic network by BRD4 and SMARCA4. SCCOHT cells in orthotopic xenograft models showed sensitivity to BET inhibitors.(68)

EZH2 inhibitors: A potential therapeutic target for *SMARCA4* aberrations comes from studies demonstrating that SWI/SNF loss leads to elevated PRC2.(48) Indeed, SMARCA4-deficient cancer cells display sensitivity to suppression of the methyltransferase known as enhancer of zeste homolog 2 (EZH2), which serves as the catalytic subunit of PRC2. In SCCOHT cells, EZH2 inhibitors potently suppress growth of SCCOHT cell line xenografts. The only trial (NCT02601950) to include patients with SCCOHT investigated the EZH2 inhibitor tazemetostat, and early results were reported for 10 patients with SCCOHT, one of whom achieved a partial response (PR).(69)

Histone deacetylase inhibitors (HDAC): Targeting histone modification complexes has also shown promise for treatment of patients with SCCOHT. HDAC inhibitors in SCCOHT result in re-expression of SMARCA2, which strongly suppresses proliferation of SCCOHT cells including in *in vivo* xenograft models of SCCOHT cells, which were responsive to the HDAC inhibitor, quisinostat.(70) However, a single clinical case report did not find efficacy with this approach.(71)

Cyclin inhibitors: SCCOHT cells are also sensitive to cyclin-dependent kinase 4/6 (CDK4/6) inhibition. SMARCA4 loss causes downregulation of cyclin D1, limiting CDK4/6 kinase activity in SCCOHT cells and leading to *in vitro* and *in viv*o susceptibility to CDK4/6 inhibitors.(72) A similar synthetic lethal interaction between SMARCA4-loss and CDK4/6 inhibition was noted in SMARCA4-deficient NSCLC. (73)

Kinase inhibitors: Exploiting an arrayed kinome-focused siRNA screen, Lang and colleagues showed sensitivity of SCCOHT cell lines in culture and in xenograft models to the multi-targeted tyrosine kinase inhibitor ponatinib (approved in the USA for *BCR-ABL*-positive leukemia treatment).(74) A reliance upon FGFR signaling as the primary mechanism for this sensitivity was implicated (keeping in mind that ponatinib is a potent FGFR inhibitor (in addition to a BCR-ABL kinase inhibitor)). These results are in agreement with observations in rhabdoid tumors where re-expression of SMARCB1 resulted in decreased expression of FGFR1 and FGFR2, as well as the relative *in vitro* and *in vivo* sensitivity of rhabdoid tumor cell lines ponatinib.(75,76) Ponatinib warrants further investigation in SCCOHT and other rhabdoid tumors.

DNA repair: SMARCA4 binds BRCA1(8), a gene product key to DNA damage repair. Furthermore, preclinical data suggests that SMARCA4-deficient lung cancer cells showed enhanced replication stress. Exposure to ATR inhibitors (which impair DNA repair) resulted in replication catastrophe in these cells.(77) Similarly, low expression of SMARCA4 is significantly associated with platinum-based chemotherapy responsiveness in NSCLC, probably because platinum induces extensive DNA damage.(78)

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Other therapeutic targets: In the preclinical setting, Wang et al(79) have demonstrated killing of SMARCA4-deficient tumors of gynecologic origin with mitochondrial oxidative phosphorylation inhibitors. These agents may be effective because SMARCA4 loss attenuates glucose transport leading to decreased glycolysis and increased dependence on mitochondria respiration. This type of synthetic lethality has also been reported for lung cancer cell lines.(80)

AURKA activity has also been identified as essential for survival and proliferation in NSCLC cells lacking SMARCA4. In these cells, RNAi-mediated depletion or chemical inhibition of AURKA using VX-680 induces cell death *in vitro* and in xenograft murine models. This effect may be because AURKA-dependent, centrosome-independent mitotic spindle assembly, is vital for the survival of *SMARCA4*-mutant but not of *SMARCA4* wild-type cells. Therefore, AURKA inhibitors may exploit a synthetic lethal vulnerability for NSCLCs carrying *SMARCA4*-inactivating alterations.(81)

CONCLUSIONS

The protein encoded by *SMARCA4* is an ATPase member of the SWI/SNF chromatin remodeling protein family. It provides the energy machinery for remodeling nucleosomes and thereby regulating the transcriptional activation of genes normally repressed by chromatin. Approximately 5–7% of cancers have aberrations in *SMARCA4. SMARCA4* anomalies are the molecular hallmark of several ultra-rare aggressive cancers (Table 1): SCCOHT and SMARCA4-deficient thoracic and uterine sarcomas. *SMARCA4* abnormalities are also discerned in a small subgroup of more common tumors including, but not limited to lung, colon, bladder, and breast carcinomas. Germline variants in the *SMARCA4* gene lead to various hereditary conditions (Table 2): RTPS2 due to loss-of-function *SMARCA4* abnormalities, and presenting with lethal rhabdoid tumors in infants and young children; and Coffin-Siris syndrome, a subset of which is due to dominant negative/gain-of function *SMARCA4* alterations, and presenting with craniofacial differences, short fifth fingers and toes with underdeveloped or absent nails, feeding difficulties, hypotonia, and intellectual disability.

A small subset of patients with rhabdoid tumors and ~43% of women with SCCOHT have a germline *SMARCA4* alteration. Emerging literature suggests that, despite its role as a tumor suppressor, *SMARCA4* alterations, especially those that result in loss of function, are actionable, with immune checkpoint blockade demonstrating responses in a small number of published patients with SCCOHT or SMARCA-4 deficient thoracic or uterine sarcomas, as well as in *SMARCA4*-altered NSCLC (Table 3). Targeted therapies with BET, EZH2, HDAC, CDK4/6, FGFR inhibitors, and inhibitors of DNA damage repair are mechanistically sound as they have shown activity in preclinical models and/or have reasonable biologic rationale. Whether or not some of these compounds could also alleviate the congenital manifestations of disease (aside from the cancer itself) may merit investigation.(82) More trials with a biomarker-driven approach are needed for patients whose malignancies harbor *SMARCA4*-alterations.(83,84)

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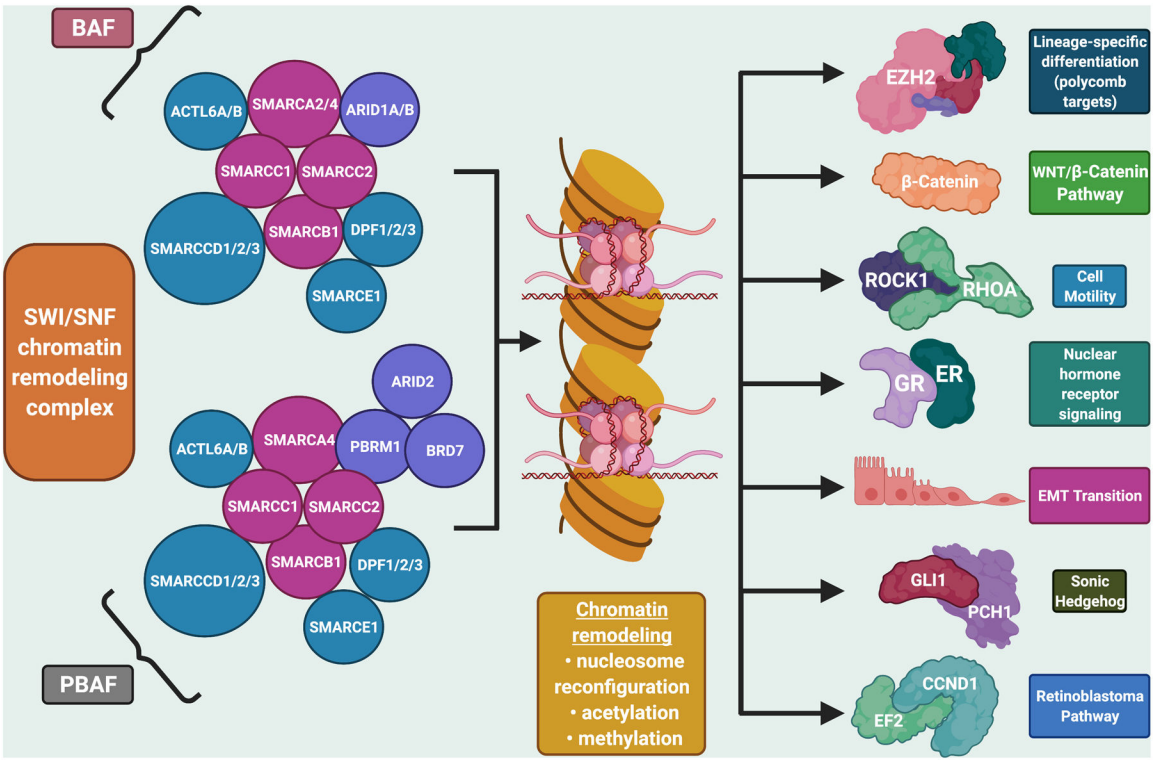

Figure 1: The SWI/SNF chromatin remodeling complex:

The SWI/SNF complex is a multi-subunit chromatin-remodeling complex that has been implicated in cancer development. The complex interacts with transcription factors to modulate gene expression that contributes to cell differentiation and development. It includes the subunit SMARCA4, which has been shown to function as a tumor suppressor (2). Figure created with biorender.com

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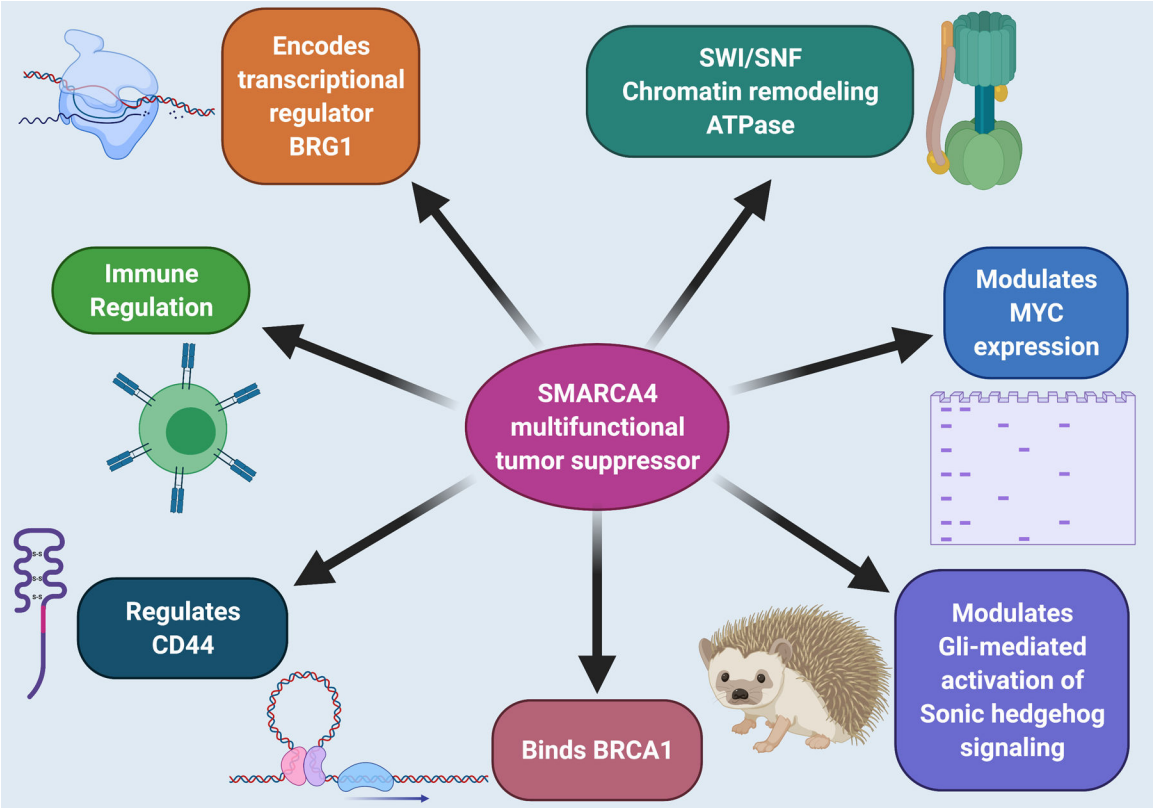

Figure 2: SMARCA4 is a multifunctional tumor suppressor.

Its cancer-relevant functions include, but are not limited to, binding BRCA1, modulating MYC and sonic hedgehog expression, and regulating transcription via its role in the SWI/SNF chromatin remodeling complex. However, SMARCA4 has pleiotropic functional effects and regulates multiple additional transcriptional pathways and biologies. Figure created with biorender.com

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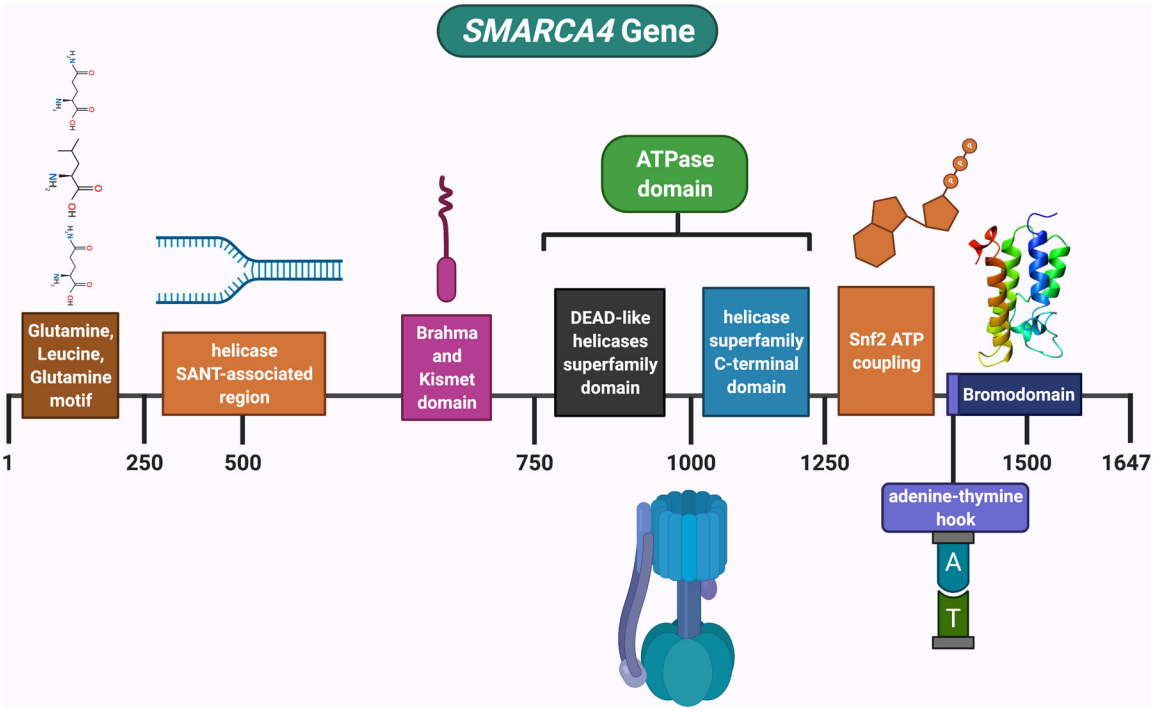

Figure 3: SMARCA4 is the core catalytic subunit (ATPase) of the SWI/SNF chromatin remodeling complex.

The ATPase utilizes ATP to generate energy that is critical for the nucleosome remodeling function of the complex. SMARCA4 has a bromodomain, which is a domain that recognizes acetylated lysine residues, such as those on the *N*-terminal tails of histones; these domains regulate gene transcription. It also has a helicase, which is an enzyme that binds and can remodel nucleic acid or nucleic acid protein complexes. Figure created with biorender.com

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Table 1.

Examples of tumors with somatic *SMARCA4* alterations and/or loss of SMARCA4 expression by IHC*

		Tumors with Altered *SMARCA4*			
Tumor Type	**Total, N**	**N**	**%**	**Comments**	**References**
Undifferentiated/rhabdoid gastrointestinal tract carcinomas	13	2	15.4%	12/13 cases (92%) showed loss of at least one SWI/SNF component Loss of SMARCB1 (5/13), SMARCA2 (10/13), SMARCA4 (2/13), and ARID1A (2/13) by IHC was observed either in combination or isolated.	(10)
Gastric cancer	1199	27	2%	Exhibited complete loss (N=6 of 27 patients), reduced (N=9), and heterogeneous (N=12) SMARCA4 patterns by IHC; SMARCA4-altered gastric cancer had divergent, often undifferentiated histomorphology	(11)
Lung Cancer	146	8	5.5%	Lung adenocarcinoma (SMARCA4 loss by IHC)	(12)
	115	6	5.2%	Lung SCCs (SMARCA4 loss by IHC)	
	122	46	37%	Primary lung tumors: SMARCA4 negative by IHC (confirmed to be due to inactivating and biallelic mutations by ultra-deep sequencing)	(13)
	60	6	10%	SMARCA4 loss of protein expression (60 tumors includes 41 adenocarcinomas and 19 squamous cancers	(14)
	37	13	35%	SMARCA4 mutations in NSCLC cell lines	(15)
	19	1	5%	SMARCA4 mutations in SCLC cell lines	
	103	16	15.5%	SMARCA4 loss by IHC in NSCLC	(16)
	93	11	12%	SMARCA4 loss by IHC in lung adenocarcinomas	(17)
	4813	407	8%	Two types of *SMARCA4* mutations in NSCLC: class 1 (truncating mutations, fusions, and homozygous deletion) and class 2 (missense mutations). Protein loss in class 1 mutations (81% vs. 0%, $P < 0.001$). *SMARCA4* alterations correlated with shorter OS, with class 1 alterations associated with shortest OS ($P<0.001$). ICIs correlated with better outcomes in patients with *SMARCA4*-mutant tumors ($P = 0.01$); class 1 mutations had the best response ($P = 0.027$).	(18)
Ovarian Cancer	360	15	4%	Clear cell carcinoma (SMARCA4 loss by IHC)	(19)
				SCCOHT	(19–21)
	46 12 17	42 12 14	91% 100% 82%	Primary tumors, SMARCA4 loss by IHC *SMARCA4* biallelic inactivating mutations 14/17 (82%), SMARCA4 loss (IHC); 9/12, *SMARCA4* inactivating mutation	
	285	2	0.4%	Primary ovarian cancers other than SCCOHT	(21)
SMARCA4-deficient thoracic sarcoma (SMARCA4-DTS)	30	30	100%	SMARCA4 and SMARCA2 loss with overexpression of SOX2 by IHC; poorly differentiated tumors with rhabdoid features	(22)
	12	40	30%	Rhabdoid thoracic sarcomas had SMARCA4 loss by IHC	(23)
Endometrial stromal sarcomas (uterine)	52	4	8%	Endometrial stromal sarcomas (SMARCA4 loss by IHC)	(19)
SMARCA4-deficient undifferentiated uterine sarcoma (malignant uterine rhabdoid tumor)	4	4	100%	SMARCA4 loss by IHC. Uterine tumors with morphologic, IHC, and genetic similarities to SCCOHT	(24)

*A complete list of tumor types with altered SMARCA4 can be found in work by Fernando and colleagues(25)

Abbreviations: ICI = immune checkpoint inhibitor; IHC = immunohistochemistry; NSCLC = non-small cell lung cancer; OS = overall survival; SCC = squamous cell carcinoma; SCCOHT=small cell carcinoma of the ovary hypercalcemic type; SCLC=small cell lung cancer; SMARCA4-DTS = SMARCA4-deficient thoracic sarcoma

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Table 2:

Germline S*MARCA4* alterations

Name of disorder	Features	% with *SMARCA4* versus *other* alterations	Associated cancers	Comments	References
Rhabdoid tumor predisposition syndrome (RTPS)	Significantly increased risk of rhabdoid tumors before the age of 3.	*SMARCA4* variants: ~5% to 15% (RTPS2) *SMARCB1* variants: ~85%–95% (RTPS1)	Rhabdoid tumors can occur in almost any location, most commonly in the central nervous system; >50% in the cerebellum. Other common locations: extracranial extrarenal malignant rhabdoid tumors (eMRT)--heart, bladder, liver, retroperitoneum, head and neck, paravertebral muscles, mediastinum, pelvis; rhabdoid tumor of the kidney (RTK); and SCCOHT (seen only in RTPS2, which is due to germline *SMARCA4* alterations (and not in RTPS1 (with germline *SMARCB1* alterations)	These highly aggressive cancers are designated rhabdoid because their cells look like rhabdomyoblasts, which are cells that are normally seen in embryos and develop into muscles. ~35% of pediatric malignant rhabdoid tumors are linked to germline SWI/SNF alterations SMARCA4 mutation type Mostly loss-of-function *SMARCA4* alterations	(32)
Coffin-Siris syndrome	Rare and clinically heterogeneous congenital disorder Hallmarks include developmental disability, microcephaly, abnormalities of the fifth fingers or toes, and characteristic facial features.	~7–11%	Case report with SCCOHT (patient had mild Coffin-Siris syndrome with inactivating SMARCA4 alteration (non-traditional for Coffin-Siris syndrome since most SMARCA4 alterations in this syndrome are dominant negative/gain-of function).)	Associated with mutations in *ARID1A, ARID1B, SMARCA4, SMARCA2, SMARCB1* or *SMARCE1* or *de novo SOX11* mutations SMARCA4 mutation type Mostly non-truncating (either missense or small in-frame deletions) within the highly conserved ATPase/helicase domain, thus suggesting dominant-negative or gain-of-function effects (though some of these mutations may also show loss of function).	(33–36)
SCCOHT	Rare and very aggressive type of undifferentiated ovarian cancer	Most patients have *SMARCA4* alterations; ~43% germline		Mostly affects young women (mean age at diagnosis = 24 years). Morphologically similar to rhabdoid tumors. Ultra-rare, aggressive cancer. Also known as malignant rhabdoid tumor of the ovary SMARCA4 mutation type: Generally, loss-of-function *SMARCA4* mutations.	(37)

Abbreviations: SCOOHT = small cell carcinoma of the ovary, hypercalcemic type; RTPS = rhabdoid tumor predisposition syndrome type 2

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Table 3:

Examples of *SMARCA4* alterations in cancer treated with immunotherapy (immune checkpoint inhibitors)

Disease	Report type	Immunotherapy	Outcome	Comment	References
POSITIVE OUTCOME					
SMARCA4-deficient thoracic sarcoma	Case report	Pembrolizumab	PR after first dose	PD-L1 positive on tumor cells = 60%	(56)
SMARCA4-deficient thoracic sarcoma	Case report	Pembrolizumab	PR, ongoing at 11+ months	PD-L1 negative, TMB low	(50)
SMARCA4-altered NSCLC	Retrospective review of patients treated at Sloan Kettering	ICIs	ICI treatment correlated with improved outcomes ($P = 0.01$) Class 1 mutations (truncating mutations, fusions, and homozygous deletion—associated with protein loss) had the best response	SMARCA4 alterations found in ~10% of NSCLC and associated with poor prognosis	(18)
SMARCA4-mutated NSCLC (lung adenocarcinoma)	Case report	Nivolumab	PR for 14+ months	TMB very high at 396 mutations/mb; PD-L1 negative by IHC Patient's tumor had failed to respond to three prior lines of therapy	(57)
SCCOHT	Case series of four patients	ICIs	All patients responded to ICI →1 patient with PR for 6+ months →3 patients with CR, each ongoing for ≥1.5+ years	8 of 11 cases demonstrated PD-L1 expression (IHC) with strong associated T-cell infiltration	(48,49)
NEGATIVE OUTCOME					
SMARCA4-deficient small-cell lung carcinoma	Case report	Nivolumab	Hyperprogressive disease		(58–61)

Abbreviations: CR = complete remission; ICI= immune checkpoint inhibitor; NSCLC = non-small cell lung cancer; PR = partial response; SCCOHT = small cell carcinoma ovary hypercalcemic type; TMB = tumor mutation burden

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