SWI/SNF Chromatin Remodeling and Human Malignancies

Julien Masliah-Planchon,[1] Ivan Bièche,[2,3] Jean-Marc Guinebretière,[4] Franck Bourdeaut,[5] and Olivier Delattre[1,6]

[1]Unité de Génétique Somatique, [2]Unité de Pharmacogénomique, [4]Département de Biologie des Tumeurs, [5]Département de Pédiatrie, and [6]Inserm U830, Unité de Génétique et Biologie des Cancers, Institut Curie, 75248 Paris, France; email: julien.masliahplanchon@curie.fr, ivan.bieche@curie.fr, jean-marc.guinebretiere@curie.fr, franck.bourdeaut@curie.fr, olivier.delattre@curie.fr

[3]Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes, Sorbonne Paris Cité, 75006 Paris, France

Annu. Rev. Pathol. Mech. Dis. 2015. 10:145–71

First published online as a Review in Advance on October 27, 2014

The *Annual Review of Pathology: Mechanisms of Disease* is online at pathol.annualreviews.org

This article's doi: 10.1146/annurev-pathol-012414-040445

Keywords

epigenetic, remodeling, transcription, nucleosome, cancer

Abstract

The SWI/SNF complexes, initially identified in yeast 20 years ago, are a family of multi-subunit complexes that use the energy of adenosine triphosphate (ATP) hydrolysis to remodel nucleosomes. Chromatin remodeling processes mediated by the SWI/SNF complexes are critical to the modulation of gene expression across a variety of cellular processes, including stemness, differentiation, and proliferation. The first evidence of the involvement of these complexes in carcinogenesis was provided by the identification of biallelic, truncating mutations of the *SMARCB1* gene in malignant rhabdoid tumors, a highly aggressive childhood cancer. Subsequently, genome-wide sequencing technologies have identified mutations in genes encoding different subunits of the SWI/SNF complexes in a large number of tumors. *SWI/SNF* mutations, and the subsequent abnormal function of SWI/SNF complexes, are among the most frequent gene alterations in cancer. The mechanisms by which perturbation of the SWI/SNF complexes promote oncogenesis are not fully elucidated; however, alterations of *SWI/SNF* genes obviously play a major part in cancer development, progression, and/or resistance to therapy.

INTRODUCTION

The recent genome-wide sequencing approaches that have been applied to human cancers have produced a much more complete catalog of genes that are recurrently mutated in human cancer. Numerous epigenetic processes related to chromatin and DNA modifications are affected by somatic mutations. These include mutations in genes encoding histone-modifying enzymes (such as *CREBBP*, *EP300*, *KDM6A*, *EZH2*, *SUZ12*, and *MLL*), DNA methylation or hydroxylation enzymes (such as *DNMT3A*, *TET1*, and *TET2*), or histones (such as *H3F3A* and *HIST1H3B*). For example, 59% of bladder tumors have mutations in at least one gene encoding enzymes involved in epigenetic gene regulation, including *KDM6A*, *MLL*, *MLL3*, *CREBBP*, *EP300*, *ARID1A*, and *CHD6* (1, 2).

Among epigenetic changes, chromatin remodeling has raised a tremendous level of interest. The family of adenosine triphosphate (ATP) dependent chromatin remodeling complexes can be subdivided into five different classes: SWI/SNF, ISWI, NuRD/Mi2/CHD, INO80, and SWR1. Numerous studies provide substantial evidence that the SWI/SNF complexes are altered in many cancer types, making genes that encode chromatin remodelers probably the most frequently mutated epigenetic regulators. Involvement of the SWI/SNF complexes in tumor formation was first revealed 15 years ago, with the identification of somatic truncating mutations in the *SMARCB1* gene (also known as *hSNF5*, *INI1*, or as the gene encoding the BAF47 subunit) in malignant rhabdoid tumors (MRTs) (3). Subsequently, germline mutations of the *SMARCB1* gene have been implicated in an MRT predisposition syndrome (4). Since these seminal observations, global genomic analyses of several tumor types have revealed high rates of *SWI/SNF* complex gene mutations, which are observed in close to 20% of all human tumors (5). The mutation rate affecting genes encoding SWI/SNF subunits is similar to those of *TP53*, *KRAS*, or *PTEN*, which are the most frequently mutated oncogenes/tumor suppressor genes. Therefore, SWI/SNF complex dysfunction is a major factor in carcinogenesis. We review the genetic and posttranscriptional modifications that affect the SWI/SNF complexes and drive tumor development and progression.

STRUCTURE AND FUNCTIONS OF SWI/SNF COMPLEXES

Snf (sucrose nonfermenting) and *swi* (switch) genes were initially discovered in yeast using genetic screening to identify genes that control, respectively, either the induction of the *suc2* gene that encodes the invertase enzyme or the induction of the HO endonuclease that is required for mating-type switching (6, 7). Subsequently, it became apparent that these two genetic approaches had uncovered a set of genes that encode subunits of large protein complexes, conserved throughout evolution from yeast to human, that play a major role as global regulators of transcription through ATP-dependent chromatin remodeling (8, 9). These complexes were named swi/snf based upon the two phenotypes that led to their discovery.

Human SWI/SNF complexes contain a single ATPase, either BRM (encoded by the *SMARCA2* gene) or BRG1 (*SMARCA4*), and three main core subunits: BAF155 (*SMARCC1*), BAF170 (*SMARCC2*), and BAF47 (*SMARCB1*). These complexes have been traditionally divided into two main types, depending upon their subunit composition: BAF complexes contain either BAF250a (*ARID1A*) or BAF250b (*ARID1B*) subunits; PBAF complexes contain BAF180 (*PBRM1*) and BAF200 (*ARID2*) subunits (**Figure 1**; **Table 1**). In addition to these core subunits, SWI/SNF complexes contain 7 to 15 accessory subunits (**Figure 1**; **Table 1**). Kadoch et al. (5) recently conducted a proteomic analysis and identified several new SWI/SNF subunits, including BCL7A, BCL7B, and BCL7C; BCL11A and BCL11B; and BRD9 and SYT (*SS18*). Data further indicate that the variability of the protein composition of SWI/SNF complexes is much higher than

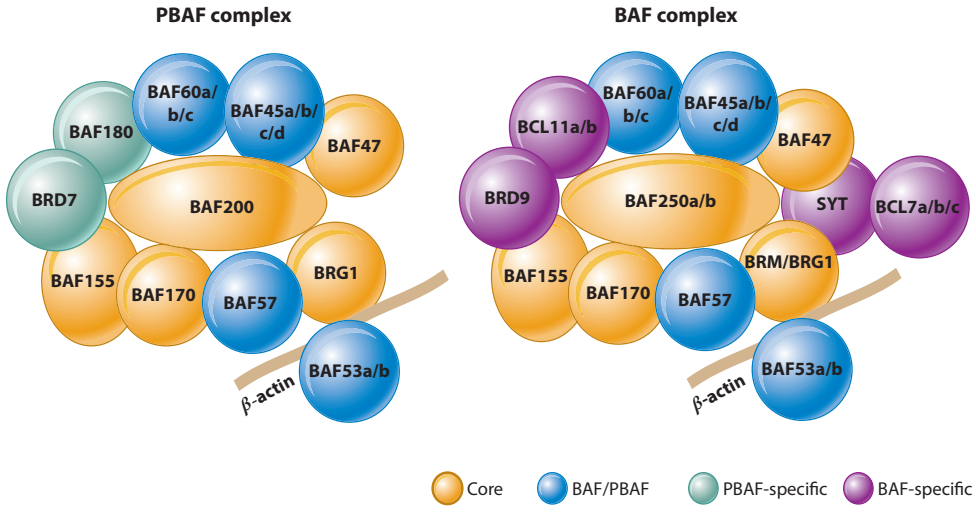

Figure 1

Scheme of the BAF and PBAF SWI/SNF complexes based on the model proposed by Kadoch et al. (5). The different subunits are labeled with their protein names. For correspondence with gene names, see **Table 1**.

envisioned by the traditional view of a limited number of well-defined and stable complexes, which has been replaced by a new concept that takes into account a large number and variety of specialized SWI/SNF complexes. Indeed, different subunits are encoded by sets of paralogs and, therefore, the composition of SWI/SNF complexes is highly variable and depends on cellular and developmental contexts (10, 11).

ATP-dependent remodeling complexes work by directly disrupting histone–DNA contacts using the energy derived from ATP hydrolysis. Mechanisms of remodeling involve nucleosome sliding, dissociation, or replacement (12, 13). Although the precise biochemical mechanisms of the mobilization of nucleosomes remain largely unknown, SWI/SNF proteins contain a number of domains that are known to interact with histones (chromo-, bromo-, and SANT) or DNA (AT-hook, ARID, HMG, zinc finger) and that are expected to play essential roles in the nucleosome targeting and remodeling functions of the complexes.

Yeast *swi/snf* genes and proteins were initially identified based on their ability to activate transcription of the *ho* and *suc2* genes. For these two genes, as well as for many others that are regulated by this complex in yeast, the mechanism of action involves binding in close vicinity to the promoter to assist in the subsequent binding of specific transcription factors. The mechanism of action is less clear in mammals, in which SWI/SNF complexes can bind at a distance from promoters. Recently, the effect of SWI/SNF inactivation on the nucleosome landscape was investigated on a genome-wide scale (14, 15). The detailed mechanisms of action of SWI/SNF complexes have been thoroughly investigated in the context of the activation of the mouse mammary tumor virus (MMTV) promoter by the glucocorticoid receptor (GR) (16). Schematically, the hormone-bound GR first binds the MMTV promoter and then recruits a variety of coactivators, including the SWI/SNF complex, via direct protein interactions with BAF250, BAF60a, BAF57, and BAF53a. The subsequent SWI/SNF chromatin remodeling is critical for the binding of nuclear factor (NF) 1, a transcription factor that is essential for the recruitment of additional transcription factors and, ultimately, activation of transcription (16). Another thoroughly investigated system is the induction of interferon β in response to viral infection (17). The first step consists of the cooperative

Table 1 Subunits of the SWI/SNF complexes

Subunit	Gene (alias)	Predicted molecular weight (kDa)	Type of SWI/SNF complex	Domain	Function
BRG1	*SMARCA4*	184.5	Core subunit	ATPase/bromo	ATPase and helicase catalytic subunit
BRM	*SMARCA2*	181	BAF-specific core subunit	ATPase/bromo	ATPase and helicase catalytic subunit
BAF47	*SMARCB1* (*hSNF5*, *INI1*)	44	Core subunit	SNF5	Unknown
BAF155	*SMARCC1* (*SWI3*)	123	Core subunit	Chromo/SANT/BRCT	Unknown
BAF170	*SMARCC2*	133	Core subunit	Chromo/SANT/BRCT	Unknown
BAF250a	*ARID1A* (*SMARCF1*)	242	BAF-specific core subunit	ARID	DNA binding
BAF250b	*ARID1B*	236	BAF-specific core subunit	ARID	DNA binding
BAF200	*ARID2*	197	PBAF-specific core subunit	ARID	DNA binding
BAF57	*SMARCE1*	47	BAF/PBAF	HMG	Unknown
BAF45a	*PHF10*	56	BAF/PBAF	Zinc finger_RING	Unknown
BAF45b/c/d	*DPF1/3/2*	42.5/43/44	BAF/PBAF	Zinc finger_RING	Unknown
BAF53a/b	*ACTL6A/B*	47.5/47	BAF/PBAF	Actin	Chromatin/nuclear matrix association Enhance ATPase activity
β-actin	*ACTB*	41.5	BAF/PBAF	Actin	Unknown
BAF60a/b/c	*SMARCD1/2/3*	58/59/55	BAF/PBAF	SWIB/MDM2	Unknown
BCL7A/B/C	*BCL7A/B/C*	23/23/23.5	BAF	Unknown	Unknown
BCL11A/B	*BCL11A/B*	91/95.5	BAF	Zinc finger_C2H2	Unknown
BRD9	*BRD9*	67	BAF	Bromo	Bind acetylated H3
SYT	*SS18*	46	BAF	Unknown	Transcriptional coactivator
BAF180	*PBRM1*	193	PBAF	BAH/HMG/Bromo	Unknown
BRD7	*BRD7*	74	PBAF	Bromo	Unknown

binding of transcription activators (NF-κB, activating transcription factor 2/JUN, and interferon regulatory factors) and the HMGA1 architectural chromatin protein to form a stable complex called the enhanceosome. This complex transiently recruits the PCAF acetyltransferase, which acetylates lysines on adjacent histone 3 (H3) and histone 4 (H4) tails. SWI/SNF is then recruited through direct interaction with the CREB binding protein (CREBBP) and acetylated histone tails, and it promotes the twisting of DNA and the removal of histones. This SWI/SNF-mediated chromatin remodeling allows transcription factor II D binding and displacement of the nucleosome located at the transcription start site, an event that permits transcription initiation (17).

Many reports have shown that SWI/SNF complexes may have both transcription activation and repression roles. This dual function of SWI/SNF has recently been dissected in the context of HIV infection (18). During virus latency, the BAF complex represses HIV long terminal repeat (LTR) activity through ATP-dependent active positioning of a nucleosome immediately

downstream of the transcription start site in a thermodynamically unfavorable position. Upon activation, the BAF complex is released from the LTR, which results in a repositioning of nucleosomes in a more favorable position and subsequent derepression of the promoter leading to *tat* gene transcription. Acetylated tat protein finally recruits the PBAF complex, which repositions nucleosomes downstream of the transcription start site to enable efficient initiation of transcription (18). Obviously, it cannot be concluded from this study that BAF has general repressive roles whereas PBAF has activating roles. Rather, insights from this system, as well as from the MMTV and interferon β systems, indicate that the mechanism of action of SWI/SNF complexes is highly dependent on the DNA sequence of the regulated region, the position and posttranslational modifications of occupant nucleosomes, the stoichiometry of general and specific transcription factors, and, ultimately, the precise subunit composition of the complex.

These few examples illustrate how SWI/SNF complexes may play key parts in regulating transcription by remodeling nucleosome occupancy at critical DNA elements, which in turn has major impacts on transcription repression or activation.

STRUCTURE AND FUNCTIONS OF SWI/SNF COMPLEXES IN DIFFERENTIATION AND PROLIFERATION

SWI/SNF complexes are thought to play critical roles in cancer through a broad range of activities. A key role is the general control of the balance between stemness and differentiation (19, 20). As an example, Lessard et al. (21) have recently demonstrated that a switch in the composition of the SWI/SNF complex has an essential role during neurogenesis. Proliferating neural stem cells and progenitor cells express complexes that contain BAF45a and BAF53a. Across neuronal differentiation, these subunits are replaced by BAF45b, BAF45c, and BAF53b, which are predominant in postmitotic neurons (21). This illustrates the role of SWI/SNF complexes in cellular differentiation and indicates that a switch in the composition of SWI/SNF complexes may be a critical component of cell fate choices. The SWI/SNF complexes also contribute to the regulation of a large number of master genes in cancer cells through physical and functional interactions. Indeed, studies have demonstrated that SWI/SNF complexes downregulate the expression of the cyclin-dependent kinase inhibitor $p16^{INK4A}$ (22); repress RB target genes, including *E2F* factors and *CCND1* (23); promote c-MYC oncogene-mediated transactivation (24); induce aberrant activation of Hedgehog signaling by interacting with GLI1 and localizing at GLI1-regulated promoters (25); and participate in the control of genes involved in cellular adhesion and cellular motility (Rho family GTPase), thus contributing to invasion and metastasis (26). These few examples highlight the pleiotropic role that SWI/SNF complexes may have in cancer. Moreover, as initially demonstrated in *Drosophila* and subsequently shown in mammals, SWI/SNF complexes antagonize the action of the Polycomb complex. This has been demonstrated in the context of *SMARCB1*-mediated cancer. Indeed, the development of lymphoma induced by somatic, biallelic inactivation of *Smarcb1* in mouse T cells is prevented by the simultaneous deletion of the *Ezh2* member of the Polycomb-group genes (27). Studies have also suggested that SWI/SNF is a critical component of nuclear-receptor hormone-response programs. The above-mentioned GR-mediated induction of the MMTV promoter has been investigated in particular detail and provides the basis for our understanding of such regulation. Many nuclear receptors—including retinoic acid (28), estrogen, peroxisome proliferator-activated receptor γ (PPARγ) (29), and vitamin D3—recruit SWI/SNF to specific promoters upon hormone binding (28, 30, 31). In addition to nuclear hormone receptors, SWI/SNF complexes cooperate with various transcription factors (32, 33). Taken together, these results indicate that the SWI/SNF complexes have an impact on a broad range of cellular processes through their role in chromatin remodeling.

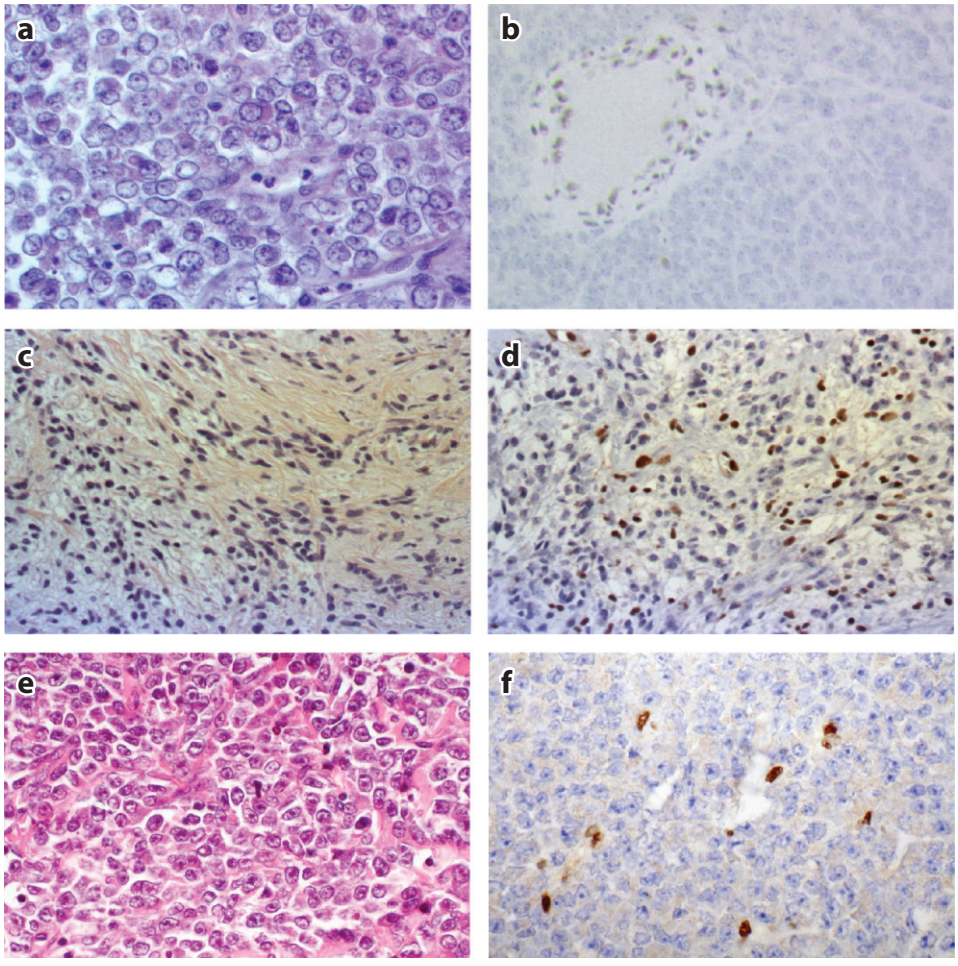

Figure 2

Different types of *SMARCB1*-deficient tumors. (*a*) Rhabdoid tumor of the kidney exhibiting cells with prominent nucleolus in an uncondensed chromatin and typical cytoplasmic eosinophilic inclusions. (*b*) Loss of BAF47 staining in the tumor cells. (*c*) Schwannomas showing the typical biphasic pattern, with both the compact cellular Antoni A area and the loose paucicellular Antoni B areas. (*d*) BAF47 immunostaining in a schwannoma shows a mosaic pattern of loss of BAF47 expression. (*e*) Proximal-type epithelioid sarcoma of left groin showing large epithelioid cells with vesicular nuclei. (*f*) BAF47 immunostaining shows an absence of nuclear staining in tumor cells, whereas inflammatory and endothelial cells are positive.

SMARCB1: A BONA FIDE TUMOR SUPPRESSOR GENE

Somatic Inactivation of *SMARCB1* in Malignant Rhabdoid Tumors

MRTs are rare, aggressive tumors of infancy, characterized by the presence of so-called rhabdoid cells that have a prominent nucleolus, uncondensed chromatin, and characteristic cytoplasmic eosinophilic inclusions consisting of whorls of intermediate filaments (**Figure 2*a***). Although these tumors occur in various anatomical regions—the kidney (34); soft parts (35); the brain, in the atypical teratoid/rhabdoid tumor (ATRT) (36); the liver (37); or peripheral nerves (38)—they are

considered to be a unique entity because of pathological similarities and because of a shared *SMARCB1* loss of function (3, 39, 40). Moreover, recent exome analyses of MRTs have shown remarkably few genomic alterations (41), making MRTs one of the least-mutated tumors among all cancer types sequenced (42). The only gene found to be recurrently mutated is *SMARCB1*, which is biallelically inactivated in almost 95% of MRTs. Biallelic inactivation of *SMARCB1* resulting in a complete loss of function occurs through a variety of events, including whole-gene deletions, large intragenic deletions/duplications, small out-of-frame intragenic deletions/insertions, splice-site mutations, and nonsense mutations (39–41, 43). Missense mutations are rare (39, 40). No mutation hot spot has been found, but exon 1 and exon 8 are almost never altered. In rare MRTs, only one mutated allele is found in the exonic sequence of *SMARCB1*; mutation occurring in the promoter regions or in the intronic sequence (39) of the other allele may explain these exceptional cases. Ultimately, and whatever the mutation, the normal nuclear expression of the protein is consistently abolished, an alteration now shown routinely in clinical practice by immunohistochemistry (**Figure 2*b***) (43, 44).

Tumor Predisposition Syndromes Linked to *SMARCB1* Germline Mutations

Although most MRTs appear to be sporadic, some exceptional familial cases as well as multifocal presentations have long suggested the existence of a germline predisposition in some patients. Accordingly, germline mutations and deletions of *SMARCB1* have been identified in pedigrees with several affected siblings [rhabdoid tumor predisposition syndrome (RTPS) 1; Online Mendelian Inheritance in Man database (OMIM) #609322] (4). Broader analyses of apparently sporadic cases have revealed an unexpectedly high (25–30%) frequency of *SMARCB1* germline mutations in infants suffering from MRTs, regardless of the anatomical location (45, 46). The germline mutations cover a spectrum similar to that observed for somatic mutations, with possible contiguous gene syndromes in cases of large germline deletions (47, 48). The penetrance is close to 100% at 18 months (45). In most cases associated with a germline mutation, the germline sequences of the parents are normal. This is consistent with either gonadal mosaicism in one of the parents or with early postzygotic mosaicism in the affected patient. Unaffected carriers have occasionally been reported (45, 46, 49–52). In half of such cases, the alteration is a *SMARCB1* splice-site mutation, which may produce only partial loss of function.

The spectrum of tumors that is observed in the context of a germline *SMARCB1* mutation is not restricted to MRTs. Indeed, Amerlaan (52) and Forest (53) have reported a myoepithelioma and a chondrosarcoma with complete *SMARCB1* inactivation in two patients who survived MRTs in childhood and who harbored, respectively, a germline *SMARCB1* splice-site mutation and a whole-gene deletion. More recently, a case of leiomyoma, a benign smooth muscle tumor, has been described in a patient with a germline splice-site mutation of *SMARCB1* (54). These observations have expanded the spectrum of tumors linked to germline truncating mutations of *SMARCB1*.

SMARCB1 germline mutations are also responsible for about half of the familial cases of multiple schwannomas (55–58). Remarkably, familial schwannomatosis is mostly related to splice-site and missense variants, particularly those affecting exon 1, which is, in contrast, remarkably preserved in MRTs. Nucleotide substitution in the 3′ untranslated region of *SMARCB1* also seems to be frequently associated with familial schwannomatosis (57). In contrast to the full depletion of BAF47 (the product of the *SMARCB1* gene) observed in MRTs, schwannomas usually show a mosaic pattern of BAF47 expression (55), suggesting less deleterious effects of the mutations (**Figure 2*c*,*d***). Smith et al. (59) showed that, unlike mutations found in MRTs, schwannomatosis-related mutants consistently retain a normal ability to control the expression of cell-cycle activators. Hence, schwannomatosis-related mutations are likely hypomorphic variants, whereas

MRT-related mutants have more dramatic effects on protein function. This genotype-to-phenotype correlation may at least partly explain the tremendous difference in the aggressiveness of the two tumor types. Nevertheless, some pedigrees show coassociation of MRTs and schwannomatosis, suggesting that the delineation of the two tumor-predisposition syndromes is not absolute (46, 60).

The frequent association between schwannomatosis and meningiomas in neurofibromatosis type 2 (OMIM #101000) has raised the question of a *SMARCB1*-related predisposition to meningiomas. Supporting this possibility, meningiomas, which are usually associated with multiple schwannomas, have been described in the context of splice-site/missense *SMARCB1* germline mutations (61, 62). Interestingly, both schwannomas and meningiomas are frequently associated with *SMARCB1* and *NF2* gene mutations, together with a 22q loss of heterozygosity encompassing the two genes in the tumors (56, 63). This four-hit/three-steps mechanism suggests a synergistic effect of the alterations in these two genes, which are located in the same chromosome region.

Somatic *SMARCB1* Mutations and Loss of Expression in Non-Rhabdoid Tumors

The variety of tumors observed in *SMARCB1*-related predisposition syndromes indicates that somatic *SMARCB1* mutations may not be restricted to MRTs. Indeed, *SMARCB1* missense mutations have also been reported in approximately 5% of sporadic meningiomas, with a possible hotspot in exon 9 (64, 65). No sporadic case of schwannoma with a somatic mutation of *SMARCB1* has been reported, but complete loss of expression of BAF47 has been observed in half of epithelioid malignant peripheral nerve sheath tumors (66). The underlying genetic alteration has not yet been specified for this tumor. Several studies have also assessed the genetic status of *SMARCB1* and/or the expression profile of BAF47 in various sarcomas (67). Interestingly, complete loss of expression of BAF47 has been observed in 80–90% of distal and proximal epithelioid sarcomas (66, 68) (**Figure 2*e*,*f***). The absence of protein expression seems mostly related to homozygous deletions of the gene (69, 70), whereas point mutations seem to be rare (71, 72). Further study is needed to more fully assess the potential diagnostic utility of *SMARCB1* genetic analysis in adult sarcomas.

Several other types of sarcomas or undifferentiated tumors also show a complete loss of BAF47 expression. Kohashi et al. (73) reported an absence of BAF47 protein expression in 4/24 extraskeletal myxoid chondrosarcomas lacking the *EWS/NR4A3* fusion transcripts. A truncating mutation of both alleles of *SMARCB1* was evident in two cases. Renal medullary carcinomas also show a negative staining for BAF47 protein expression, with loss of heterozygosity at the *SMARCB1* locus in all cases that have been investigated (74, 75). Nevertheless, no point mutation has been observed in these carcinomas. Some pediatric undifferentiated sarcomas (76) or hepatoblastomas (37) that lack rhabdoid morphology may harbor a loss of BAF47 expression. It is unclear at present whether these tumors would be better considered to be MRT variants or new types of *SMARCB1*-deficient tumors. The distinction between aggressive ATRTs and another central nervous system tumor called CRINET (cribriform neuroepithelial tumor) is clearer. CRINET is an indolent choroid plexus tumor with specific morphology and clinical behavior that shows constant loss of BAF47 expression, which is occasionally associated with biallelic nonsense mutations of *SMARCB1* (77). Loss of expression of BAF47 has also been described in undifferentiated chordomas, aggressive tumors with notochordal differentiation that typically arise in the axial spine (78). Finally, BAF47 loss has been described recently in a subset of sinonasal carcinomas (79, 80).

The variety of tumor types that show a loss of BAF47 expression was unknown until a few years ago. The histological heterogeneity of MRTs is a diagnostic challenge for pathologists, especially when the typical rhabdoid morphology is lacking. However, loss of expression of BAF47 can be

observed in tumors other than MRT and, obviously, negative BAF47 staining is not by itself sufficient to firmly establish the diagnosis of MRT (**Figure 2**). The overall genetic landscape of the various *SMARCB1*-deficient tumors remains scarcely known. Further studies are needed to evaluate whether more complete genomic profiling will help in developing diagnostic criteria that more reliably discriminate between MRTs and other BAF47-negative malignancies.

MUTATIONS OF OTHER GENES ENCODING SWI/SNF COMPLEX SUBUNITS

Germline Mutations

Heterozygous nonsense germline mutations of *SMARCA4* have been identified in two pedigrees with familial MRTs. Analysis of the tumors revealed a complete loss of expression of the BRG1 protein (encoded by *SMARCA4*) with somatic inactivation of the wild-type allele by either copy-neutral loss of heterozygosity (81) or acquired somatic mutation (82). Thus, *SMARCA4* is the second member of the SWI/SNF complex involved in the MRT predisposition syndrome (RTPS2; OMIM #613325). More recently, heterozygous mutations in *SMARCE1* have been identified in four individuals with familial multiple spinal meningiomas (OMIM #607174) (83). Again, the four germline mutations described are truncating, and the tumors showed complete loss of BAF57, the *SMARCE1* product, which is consistent with a tumor suppressor mechanism.

Aside from their involvement in tumor predisposition syndromes, germline mutations in *SWI/SNF* genes have also been described in neurodevelopmental disorders. Indeed, heterozygous germline mutations in *ARID1A*, *ARID1B*, *SMARCA2*, *SMARCA4*, *SMARCB1*, and *SMARCE1* have been described in individuals with Coffin–Siris syndrome (CSS; OMIM #135900). CSS is a neurodevelopmental disorder characterized by mental retardation, microcephaly, coarse facial features, agenesis of the corpus callosum, and nail hypoplasia (84). Heterozygous mutations of *SMARCA2*, *ARID1B*, and *SMARCB1* have also been reported in patients with Nicolaides–Baraitser syndrome (OMIM #601358) (85), which is characterized by dysmorphia and mental retardation and shares overlapping clinical features with CSS but also has characteristic facial morphology, hair and digital abnormalities, and epilepsy. CSS and Nicolaides–Baraitser syndrome do not predispose to tumor formation, as none of the CSS patients with *SMARCE1*, *SMARCA4*, or *SMARCB1* mutations has been reported to suffer from meningiomas, schwannomas, or MRTs. Conversely, none of the individuals with a *SWI/SNF* gene-related inherited predisposition to meningiomas, schwannomas, or MRTs showed neurodevelopmental disorders, suggesting that specific types of germline mutations lead to specific disease phenotypes. Indeed, although all *SMARCE1*, *SMARCA4*, and *SMARCB1* mutations described in patients with CSS or Nicolaides–Baraitser syndrome are missense mutations or in-frame deletions, all mutations in the same genes that predispose to tumor formation are clearly truncating.

Somatic Point Mutations

Whole-exome and whole-genome sequencing have enabled mutational profiling of increasing numbers of tumor types. These studies have identified mutations in several genes that encode subunits of the SWI/SNF complex (in addition to *SMARCB1*) (**Figure 3**). These genomic data as well as data from the international Cancer Genome Atlas and the International Cancer Genome Consortium, and the Catalogue of Somatic Mutations in Cancer database, have shown that *SMARCA2*, *SMARCA4*, *ARID1A*, *ARID1B*, *ARID2*, and *PBRM1* are mutated at high frequencies in one or several cancer types.

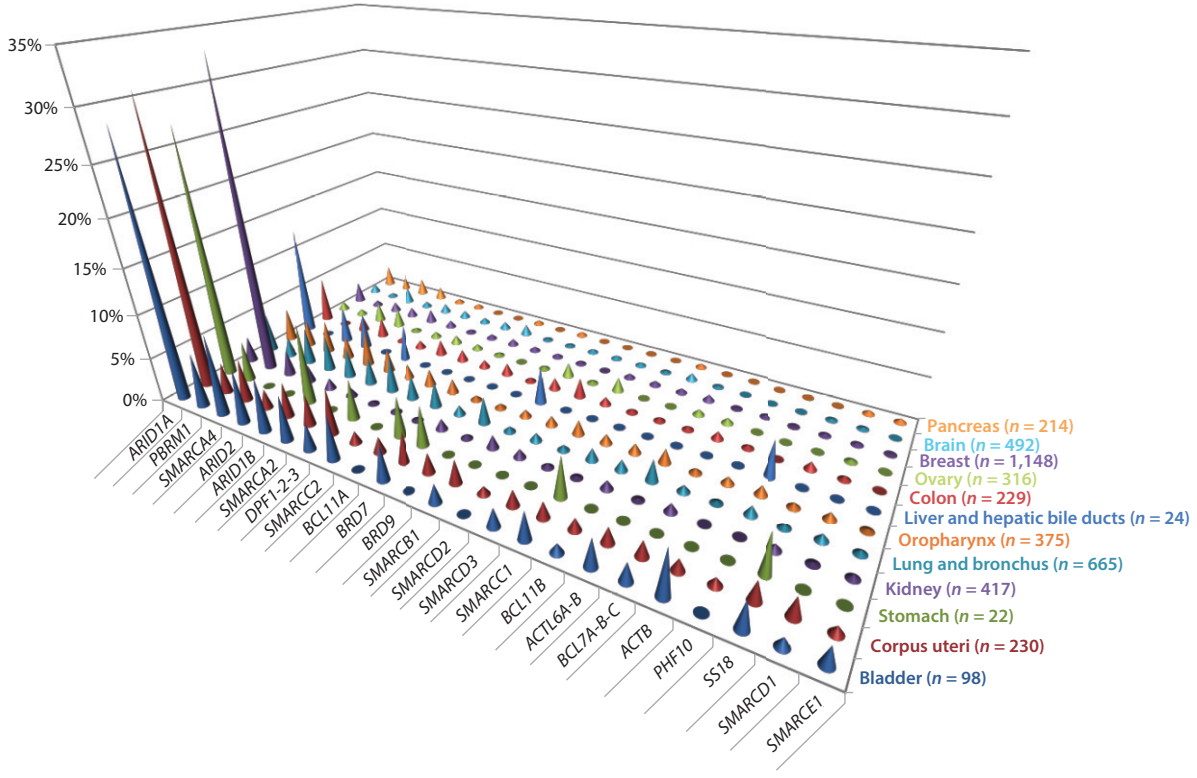

Figure 3

Somatic variations of *SWI/SNF* genes across different tumor types. The frequency of somatic mutations (including neutral mutations) is identified by exome sequencing of 28 genes encoding different SWI/SNF subunits across 12 cancer sites. The different *SWI/SNF* subunit genes are indicated along the x-axis. The y-axis indicates the frequency of mutations. Data were extracted from the Integrative OncoGenomics (IntOGen) platform (**http://www.intogen.org/**), which collects data from the Cancer Genome Atlas, the International Cancer Genome Consortium, and PubMed.

***SMARCA2*, which encodes the BRM ATPase and helicase catalytic subunit of SWI/SNF complexes.** *SMARCA2* is infrequently mutated in primary human tumors, except in adenoid cystic carcinoma (ACC); three missense mutations and two homozygous deletions have been seen in a series of 60 ACCs (86) (**Figure 4**). Thus, this study identified *SMARCA2* as one of the most frequently mutated genes in ACC and also pinpointed mutations in other *SWI/SNF* complex genes, namely, *SMARCE1* and *ARID1A* (86).

***SMARCA4*, which encodes the BRG1 ATPase and helicase catalytic subunit of SWI/SNF complexes.** In addition to the few cases of malignant MRTs mentioned above, *SMARCA4* was found to be mutated in 15.3% (9/59) of patients with Burkitt's lymphoma (87) (**Figure 4**), 10.9% (20/183) of patients with lung adenocarcinoma (88), 7.4% (11/149) of patients with esophageal adenocarcinoma (89), and 4.3% (13/305) of patients with medulloblastoma (90–92).

Interestingly, in medulloblastoma, mutations were exclusively observed in the WNT (5/17, 29.4%) and group 3 (5/50, 10.0%) molecular subtypes, being absent from the sonic Hedgehog and group 4 subtypes.

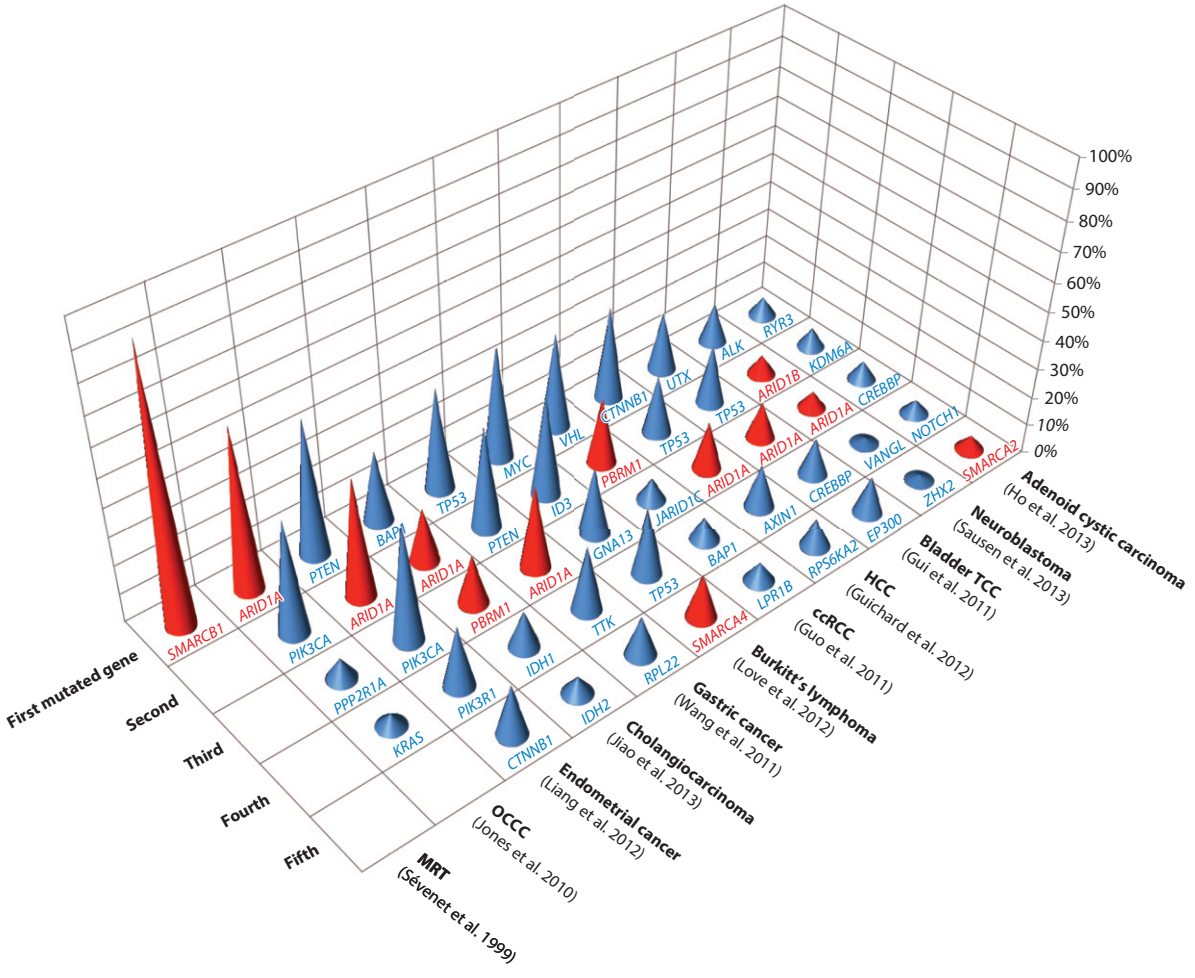

Figure 4

Main tumor types for which *SWI/SNF* genes are among the five most frequently mutated genes. Abbreviations: ccRCC, clear cell renal cell carcinoma; HCC, hepatocellular carcinoma; OCCC, ovarian clear cell carcinoma; MRT, malignant rhabdoid tumors; TCC, transitional cell carcinoma.

Approximately 25% of esophageal adenocarcinomas harbor mutations in genes encoding SWI/SNF complex proteins. In addition to *SMARCA4*, they may affect *ARID1A* (14/149; 9.4%), *ARID2* (9/149; 6.0%), and *PBRM1* (5/145; 3.4%), usually in a mutually exclusive fashion (89).

Most *SMARCA2* and *SMARCA4* mutations are missense or in-frame small deletions (5/5 of the *SMARCA2* mutations in ACC and 9/9 of the *SMARCA4* mutations in Burkitt's lymphoma, 10/20 in lung adenocarcinoma, 8/11 in esophageal adenocarcinoma, and 9/10 in medulloblastoma). Most of these missense mutations cluster within the region encoding the catalytic domains. Recently, Dykhuizen et al. (93) demonstrated that the missense mutations of *SMARCA4* found in medulloblastoma and Burkitt's lymphoma compromise the ATPase activity of SWI/SNF complexes. However, truncating mutations of these two subunits have been observed in some tumors. Indeed,

very recently, germline and somatic truncating mutations in *SMARCA4* have been described as occurring at high frequency (52/57; 91.2%) in ovarian small cell carcinoma of the hypercalcemic type (94–96).

Further investigations are needed to understand the roles of these mutations in tumor formation.

***ARID1A*, alias *SMARCF1*, encodes the BAF250a subunit.** *ARID1A* is the most frequently altered *SWI/SNF* gene in human cancers (**Figure 3**). Indeed, *ARID1A* mutations are present at high frequency in a number of human cancer types including ovarian clear cell carcinomas (OCCCs), an uncommon but aggressive type of ovarian cancer. Roughly half (79/161; 49.1%) of OCCCs carry *ARID1A* mutations, mostly truncating, making it the most frequently mutated gene in this subtype of ovarian cancer (97, 98) (**Figure 4**). These mutations are specific to this subtype of ovarian cancer as serous ovarian carcinomas do not have *ARID1A* mutations. Interestingly, loss of *ARID1A* in OCCCs has been correlated with shorter survival in patients treated with platinum-based chemotherapy (99). Together with *SMARCA4* mutations in ovarian small cell carcinoma of the hypercalcemic type, this suggests a crucial role for SWI/SNF complexes in ovarian tumorigenesis.

In endometrial cancers, two independent studies have shown that *ARID1A* is mutated in 39.0% (155/397) of cases, making it one of the most frequently mutated genes in this type of cancer as well (100, 101) (**Figure 4**). Interestingly, another study compared the rate of *ARID1A* mutation in different histological subtypes and showed that *ARID1A* mutations are enriched in clear cell tumors (3/23; 13%) when compared with serous tumors (3/52; 5.8%) (102).

Hepatocellular carcinoma (HCC) is another tumor in which *ARID1A* mutations are common. Guichard et al. (103) have sequenced a cohort of 125 alcohol-related HCCs and found that *ARID1A* was mutated in 16.8% (21/125) of cases (**Figure 4**). Huang et al. (104) characterized a series of 110 hepatitis B virus–associated HCCs and identified *ARID1A* as the second most frequently mutated gene (14/110; 12.7%) after *TP53*. These results indicate that alteration of *ARID1A* is a major oncogenic event in HCC formation, irrespective of etiology.

In lung adenocarcinoma, in addition to the *SMARCA4* mutations mentioned above, *ARID1A* is mutated in 9.8% (18/183) of cases (88). *ARID1A* and *SMARCA4* mutations tend to be mutually exclusive and together account for 18% (33/183) of lung adenocarcinomas, thus making *SWI/SNF* gene mutations in aggregate the third most frequent type of mutation, just after mutations in *TP53* and *KRAS* (88). Interestingly, no mutation of *SWI/SNF* genes has been described in squamous cell lung cancers (105), indicating that, as in ovarian cancers, tumors arising in the same organ may show highly variable mutation frequency depending on the histological subtype.

ARID1A is also frequently mutated in other cancer types, including 18.7% (41/219) of gastric cancers (106, 107), 14.3% (28/196) of bladder cancers (1, 2), 9.7% (19/195) of colorectal cancers (108), 4.9% (6/122) of pancreatic cancers (109, 110), 13.6% (8/59) of Burkitt's lymphomas (87), 18.8% (6/32) of cholangiocarcinomas (111), and 16.7% (5/30) of lymphoplasmacytic lymphomas (also known as Waldenström's macroglobulinemia) (112) (**Figure 4**).

Most *ARID1A* somatic mutations are truncating, with nonsense or frameshift mutations detected throughout the gene, thus strongly supporting a loss-of-function mechanism. However, both alleles are affected in only 30% of OCCCs, and a similar situation prevails in other tumors, such as gastric cancer and HCC. The observation that only one allele of *ARID1A* is mutated while the other allele is expressed suggests that *ARID1A* haploinsufficiency is being selected for in cancer cells.

Finally, comparison of *ARID1A* mutation types in gastric (106) and colorectal cancers (108) has revealed similar patterns, with most mutations consisting of indels within G or C homopolymer

repeats in coding regions. This suggests that *ARID1A* mutations, like those involving *TGFBRII* or *BAX* in these tumors, result from microsatellite instability (MSI) stemming from mismatch repair defects. Supporting this hypothesis, studies on gastric cancer have revealed that *ARID1A* mutations are significantly associated with MSI (106, 107). Similarly, the Cancer Genome Atlas Research Network has reported that *ARID1A* mutations in colorectal tumors were enriched in MSI tumors (37% versus 5%) (108).

***ARID1B*, which encodes the BAF250b subunit.** When compared with *ARID1A*, *ARID1B* is rarely mutated in human cancers except in childhood neuroblastoma, where mutations of both genes occur at similar rates: 7.0% (5/71) and 5.6% (4/71), respectively (113) (**Figure 4**). *ARID1B* somatic alterations described in neuroblastoma are mostly hemizygous intragenic deletions, or splice-site or missense mutations. Alterations in *ARID1A/B* correlate with a more aggressive neuroblastoma, as the median survival in mutated cases is lower than that observed for any other genetic alteration, including *MYCN* amplification. Thus, *ARID1A/B* mutational status is a potential biomarker for identifying patients at risk for early therapy failure and disease progression (113).

***ARID2*, which encodes the BAF200 subunit.** *ARID2* is mutated in some primary human cancers, in particular in 5-8% of HCCs, particularly HCCs that are related to hepatitis C virus (HCV) (14% of HCV-related cases compared with 2% of hepatitis B virus–related cases) (103, 114, 115), non–small cell lung cancer (15/183; 8.2%) (116), melanoma (9/121; 7.4%) (117), oral squamous cell carcinoma (5/50; 10.0%) (118), and esophageal adenocarcinoma (9/149; 6.0%) (89). Homozygous deletions or somatic mutations associated with a loss of heterozygosity, responsible for a complete loss of function of *ARID2*, have been identified in these cancer types.

In melanoma, *ARID2* alterations were exclusive from *ARID1A/B* mutations, and most frequently resulted from UVB-related C → T transitions (117). Similarly, *ARID2* mutations observed in non–small cell lung cancer may be related to tobacco exposure (116).

***PBRM1*, which encodes the BAF180 subunit.** *PBRM1* is mutated in 20–40% of clear cell renal cell carcinomas (ccRCCs), making *PBRM1* the second most frequently mutated gene after *VHL* in the most common histological type of renal cancer (119–122) (**Figure 4**). *PBRM1* and the three other most commonly mutated genes in ccRCC (i.e., *VHL*, *BAP1*, and *SETD2*) are all two-hit tumor suppressor genes and are all located in a 43-Mb region on chromosome 3p that is deleted in 90% of ccRCCs. Interestingly, *SMARCC1*, which encodes another member of the SWI/SNF complex, is also located in this region but has not been reported to be mutated in ccRCC.

PBRM1 mutations and *BAP1* mutations are mutually exclusive (but *PBRM1* mutations are not exclusive of *VHL* or *SETD2* mutations), suggesting either a functional redundancy or a synthetic lethality. The *BAP1* tumor suppressor gene encodes the BRCA1 associated protein-1 (BAP1) deubiquitinase involved in double-strand break repair. In addition to ccRCC, it is frequently mutated in uveal melanoma, mesothelioma, and cholangiocarcinoma. Expression profiles of *PBRM1*-mutated tumors are enriched for expression of a hypoxia signature gene set, whereas *BAP1*-mutated cases are associated with decreased expression of Polycomb repressive complex 2 (PRC2) target genes (120). Interestingly, *PBRM1* and *BAP1* mutation status identified subtypes of ccRCC with distinct clinical outcomes—i.e., a high-risk *BAP1*-mutated group and a favorable *PBRM1*-mutated group (123). This case exemplifies how next-generation sequencing can be used to integrate genomics with clinical prognostication.

Apart from ccRCC, *PBRM1* has been found to be mutated in 17% of cholangiocarcinomas (111) (**Figure 4**). *PBRM1* mutations seem to be infrequent in other human cancers.

The other genes encoding SWI/SNF subunits—including *ACTB*, *ACTL6A*, *ACTL6B*, *BRD7*, *BRD9*, *PHF10*, *DPF1*, *DPF2*, *DPF3*, *SMARCC1*, *SMARCC2*, *SMARCD1*, *SMARCD2*, *SMARCD3*, and *SMARCE1* (**Figure 1**; **Table 1**)—exhibit rare point mutations in solid tumors (**Figure 3**). Their mutation rates are in the range of those observed for passenger mutations that are not expected to confer any significant selective growth advantage.

Other Types of Alterations in the SWI/SNF Complex

The newly identified SWI/SNF subunits (i.e., *BCL7A*, *BCL7B*, *BCL7C*, *BCL11A*, *BCL11B*, *BRD9*, and *SS18*) (5) (**Figure 1**; **Table 1**) may be mutated in hematological malignancies. For example, *BCL11B* truncating, missense mutations and heterozygous deletions are identified in 16% of human T cell acute lymphoblastic leukemias (124). Satterwhite et al. (125) have described a subtype of aggressive chronic lymphocytic leukemia harboring a t(2;14)(p13;q32.3) translocation involving the *IGH* locus and *BCL11A* that results in strong upregulation of this gene. Altogether, these results indicate a clear involvement of the *BCL11* gene family in lymphoid malignancies. *BCL7A* is also involved in lymphoid malignancies, either by translocation in Burkitt's lymphoma (126) or by promoter hypermethylation in primary cutaneous T cell lymphoma (127). Further studies are necessary to validate the involvement of these new *SWI/SNF* genes in the dysregulation of the SWI/SNF complexes in human cancers and, particularly, in hematological malignancies.

The t(X;18) chromosomal translocation involving the *SS18* gene (which encodes the SYT subunit of the SWI/SNF complex) is the hallmark of synovial sarcoma (128). A reduced expression of *SMARCB1* has been noted in about two-thirds of synovial sarcomas with SS18-SSX fusion transcripts (44, 129). Interestingly, Kadoch et al. (130) recently demonstrated that the SYT-SSX fusion protein competes for assembly with wild type SYT, leading to an altered SWI/SNF complex from which the BAF47/*SMARCB1* protein is evicted; the subsequent degradation of the BAF47 protein accounts for the weak staining observed in these tumors. Therefore, functional inactivation of *SMARCB1* and subsequent alteration of the SWI/SNF complex may constitute key elements in the development of synovial sarcomas.

LINK BETWEEN ALTERATIONS IN SWI/SNF COMPLEXES AND CLEAR CELL HISTOLOGICAL SUBTYPE

Although abnormalities in SWI/SNF complexes have been observed in a large number of tumors of various histological types, it is striking that a significant number of tumors exhibit a peculiar clear cell morphology. Indeed, mutations in *ARID1A* and *PBRM1* are frequently found in, respectively, OCCCs (97, 98) (**Figure 5*a*,*b***) and ccRCCs (119–122) (**Figure 5*c*,*d***). In addition, *ARID1A* mutations in endometrial tumors are enriched in the clear cell histological subtype compared with the serous subtype (102). Moreover, spinal meningiomas associated with germinal mutation of *SMARCE1* are of the clear cell histological subtype. Thus, the association between clear cell histological subtype and SWI/SNF complex mutations extends across tumors with diverse cellular origins.

These data suggest that the clear cell phenotype results from a common physiopathological mechanism related to functional alteration of the SWI/SNF complexes. Different causes have been proposed to explain the lack of cytoplasmic staining in clear cell tumors, including a paucity of intracytoplasmic organelles; dilated, swollen, or enlarged mitochondria or cisternae; and excessive cytoplasmic accumulation of substances such as glycogen, lipid droplets, mucosubstances, or mucin vacuoles. Histochemical and ultrastructural studies of clear cell meningioma (131), ccRCC

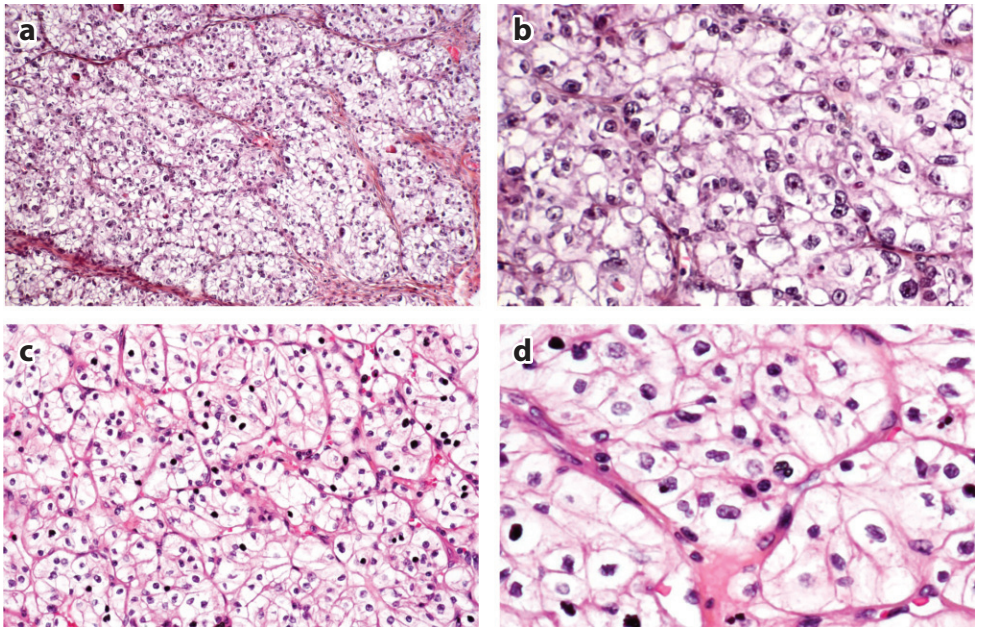

Figure 5

Different types of clear cell carcinomas associated with *SWI/SNF* mutations. (*a*) Hematoxylin and eosin (H+E) staining (×100) of an ovarian clear cell carcinoma in a 63-year-old woman; the tumor shows diffuse growth with large polygonal cells. (*b*). H+E staining (×400) of the same tumor showing cells with irregular nuclei, prominent eosinophilic nucleoli, and large clear cytoplasm. (*c*) H+E staining (×200) of a clear cell renal cell carcinoma with typical solid sheet and alveoli in a 58-year-old man. (*d*) H+E staining (×400) showing cells with a large clear cell vegetal cytoplasm and central nuclei surrounded by delicate capillaries.

(132), OCCC (133, 134), and clear cell endometrial cancer (135, 136) reveal mainly glycogen excess with lipid droplets. Steinberg et al. (137) evaluated glucose metabolism in different histological types of renal carcinoma and noted that ccRCC was distinct in having increased levels of glycogen, greater glycolytic activity, and reduced gluconeogenesis. Interestingly, it has been demonstrated that CARM1, the arginine methyltransferase recently found to methylate BAF155 (138), is necessary for the expression of genes directly involved in glycogen metabolism (139). Although further investigations are necessary to explore the mechanistic links between alterations in SWI/SNF complexes and the clear cell phenotype, one attractive hypothesis is that they induce excessive glycogen accumulation as a consequence of abnormal carbohydrate metabolism. It will be interesting to know whether other rare tumors with clear cell histotypes that have not yet been investigated in large genome-scale studies also harbor *SWI/SNF* gene mutations. Possible examples of such tumors include clear cell adenocarcinoma of the vagina, clear cell sugar tumor of the lung, perivascular epithelioid cell tumor, clear cell sarcoma (formerly known as malignant melanoma of the soft parts), clear cell chondrosarcoma, clear cell squamous cell carcinoma, or the extremely rare glycogen-rich clear cell carcinoma of the breast. Finally, regarding a possible link between SWI/SNF complexes and carbohydrate metabolism, it is important to recall that *snf* mutants in yeast were characterized by deficient carbohydrate metabolism, suggesting that SWI/SNF complexes have a conserved role in carbohydrate metabolism throughout evolution. In support of such a hypothesis, mice with liver-specific conditional inactivation of *Smarcb1* die during the neonatal period due to severe hypoglycemia and impaired energy metabolism (140).

IMPACT AND ROLE OF MUTATIONS OF SWI/SNF COMPLEXES ON TUMOR DEVELOPMENT

Although *SWI/SNF* genes are frequently altered in human cancers, making these complexes a major target in oncogenesis, the pattern of mutations varies from one tumor type to another. Mutations in *SMARCB1* and *PBRM1* are observed with a high frequency, and quite specifically in MRTs and ccRCC, respectively, which may suggest that those subunits have cell- or tissue-type-specific functions. These mutations are mostly biallelic and clearly truncating, thus supporting a complete loss-of-function mechanism (**Figure 6*a***).

Most other cancer subtypes exhibit a broader spectrum of SWI/SNF mutations across the different subunit-encoding genes. The preponderance of mutations in the enzymatic subunits (BRM/*SMARCA2* and BRG1/*SMARCA4*) and DNA-targeting subunits (BAF250a/*ARID1A*, BAF250b/*ARID1B*, BAF200/*ARID2*, and BAF180/*PBRM1*) suggests that these subunits have the most critical role in oncogenesis. For other subunit genes, the types of changes are highly variable. Some cancer types harbor truncating mutations of a single allele of *SWI/SNF* genes—for instance, mutations of *ARID1A* in OCCC—suggesting that haploinsufficiency and reduced levels of the wild-type protein are critical (**Figure 6*b***). In other cancers, missense mutations are predominantly observed, which in most cases leaves open several possible functional consequences, including loss-of-function, dominant negative, and gain-of-function effects. Such missense mutations are mostly observed in *SMARCA2* and *SMARCA4*, which encode mutually exclusive catalytic subunits of the SWI/SNF complex (**Figure 6*b***). Interestingly, most of the *SMARCA2/4* missense mutations cluster within the region encoding the helicase domains of BRM and BRG1 proteins. Recently, some *SMARCA4* mutants were shown to have compromised ATPase activity and to act dominantly over the wild-type allele to increase the percentage of cells in G2/M and anaphase (93).

BAF250a/*ARID1A* and BAF250b/*ARID1B* are mutually exclusive, BAF-specific subunits occupying the same position in the complex. Although mutations in both genes can occur in the same tumors (120), a recent study demonstrated that *ARID1B* has synthetic lethality with *ARID1A* in cancer cells (141). Thus, partial loss of *ARID1A* and *ARID1B* alleles may cooperate to promote tumor formation, but one persisting functional allele is required for the growth of cancer cells. Similarly, two studies have recently reported that the silencing of *SMARCA2* in tumors with *SMARCA4* mutations induces cell cycle arrest (142, 143), further demonstrating that, although hypomorphic SWI/SNF complexes may promote tumor formation, complete inactivation of the complexes may suppress cell growth. Taken together, these results help clarify the role of mutations in different *SWI/SNF* genes in the same tumor type and even in the same tumor (**Figure 7**).

Another mechanism of alteration of SWI/SNF subunits is through chromosome translocation. The SYT-SSX chimera invades the SWI/SNF complex and evicts the BAF47 subunit (**Figure 6*c***) (130). Other mechanisms that may alter the functions of the SWI/SNF complexes have been proposed. For example, CARM1, an arginine methyltransferase, specifically methylates Arg1064 of the BAF155/*SMARCC1* subunit of SWI/SNF complexes and, hence, may contribute to breast cancer progression and metastasis (138) (**Figure 6*d***). Consequently, methylated BAF155 could serve as a sensitive biomarker for human breast cancer progression. Finally, in 2011, Prensner et al. (144) characterized a long noncoding RNA, termed SChLAP1, that is overexpressed in 71% of prostate cancers and is involved in aggressiveness and disease progression. SChLAP1 binds directly to BAF47/*SMARCB1* and thus antagonizes SWI/SNF complexes, leading to increased cancer cell invasiveness and metastasis (145) (**Figure 6*e***). These results suggest that SChLAP1-mediated alteration in SWI/SNF complexes contributes to the development of prostate cancer and can potentially serve as a novel marker of aggressive behavior.

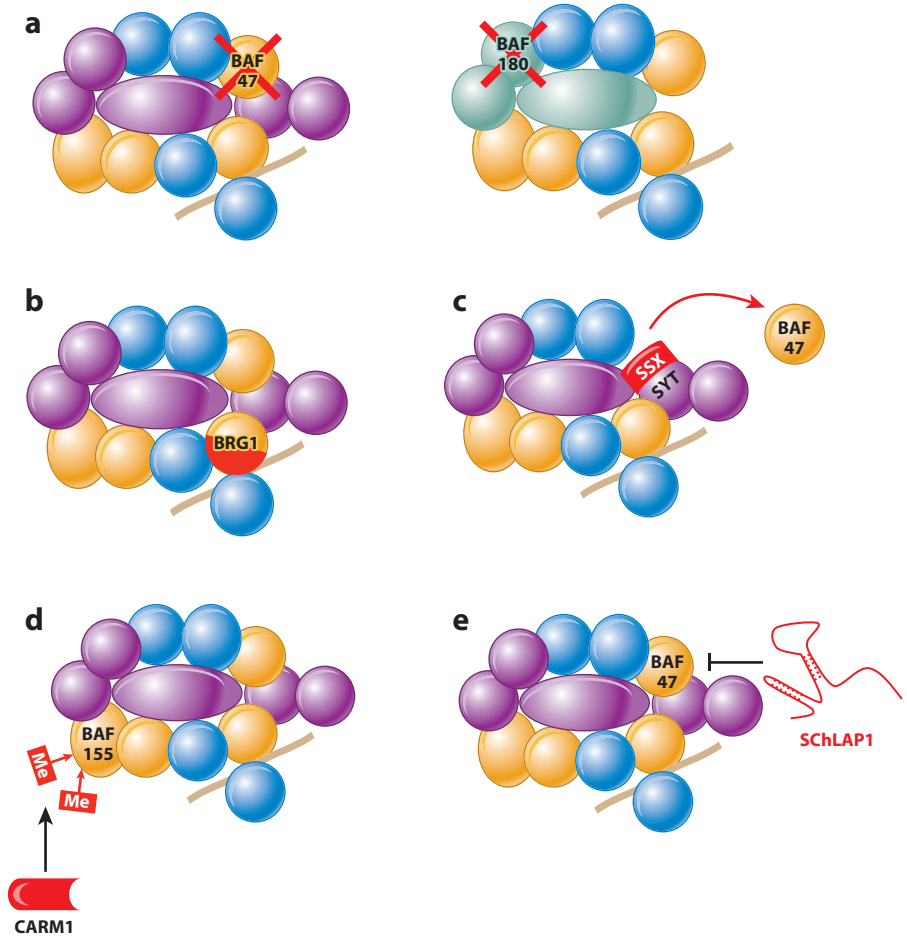

Figure 6

Different mechanisms of somatic alteration in SWI/SNF complexes. (*a*) Biallelic inactivation of one SWI/SNF subunit, for example, as occurs in *SMARCB1* in malignant rhabdoid tumors and in *PBRM1* in clear cell renal cell carcinomas. (*b*) Monoallelic mutation of one SWI/SNF subunit and an example of mutation in *SMARCA4* occurring in medulloblastoma. In some cases, several different SWI/SNF subunits can be mutated in the same tumor. (*c*) Chromosomal translocation. The example shown is the t(X; 18) in synovial sarcoma that leads to an SYT-SSX oncogenic fusion protein, which disrupts the SWI/SNF complex by ejecting the BAF47 subunit. (*d*) Posttranslational modification. The example shows CARM1-mediated methylation (Me) of arginine residue 1064 of BAF155, which regulates metastasis of breast cancer cells. (*e*) Long noncoding RNA-mediated SWI/SNF alteration. An example is the SChLAP1 overexpression in prostate cancer that contributes to aggressive behavior by impairing BAF47-mediated regulation of gene expression.

RELATIONSHIP BETWEEN ALTERATIONS IN THE SWI/SNF COMPLEX AND OTHER MUTATIONS IN CANCER

In addition to identifying frequent alterations in SWI/SNF complex genes, exome sequencing studies have unraveled several associations with other mutations in oncogenes and tumor suppressor genes. In gastric cancer (107) and OCCCs (97, 98), *ARID1A* mutations have been positively

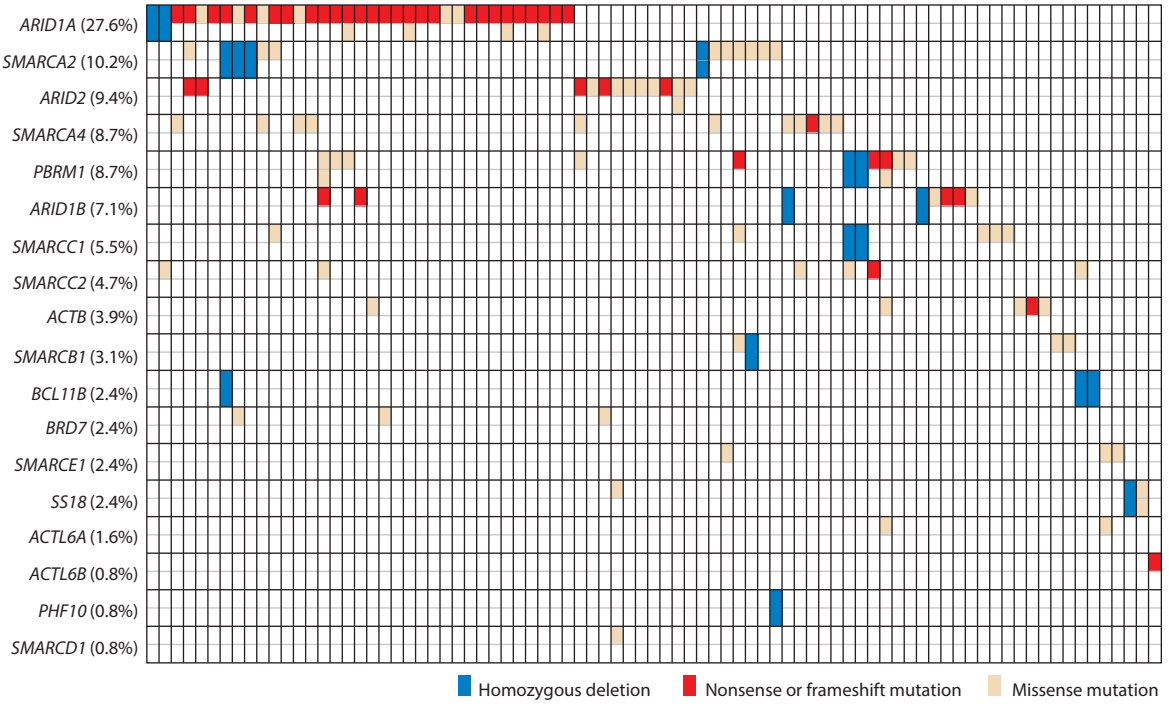

Figure 7

An example of the variety of *SWI/SNF* gene mutations in bladder urothelial carcinoma. *SWI/SNF* mutations in bladder urothelial carcinomas were extracted from The Cancer Genome Atlas network and visualized using the cBioPortal for Cancer Genomics (**http://www.cbioportal.org**) (146, 147). A total of 83 of 127 (65.4%) bladder urothelial carcinomas were mutated in at least one *SWI/SNF* gene. For each gene, the two lines schematize the two alleles. This figure highlights three points: (*a*) that several *SWI/SNF* genes can be mutated in a single tumor type, (*b*) that several *SWI/SNF* genes can be mutated in the same tumor, and (*c*) that concomitant loss of functionally redundant subunits (such as *ARID1A* and *ARID1B*, or *SMARCA2* and *SMARCA4*) is not observed.

correlated with the presence of *PIK3CA*-activating mutations, suggesting potential cooperating effects between these two genes. Furthermore, *ARID1A* mutations in gastric or OCC cancers, as well as *ARID1B* mutations in HCCs (114), show a significant negative correlation with *TP53*-inactivating mutations. Thus, the mutation of genes encoding chromatin-remodeling complexes may substitute for *TP53* mutations during the process of carcinogenesis. Taken together, these data reveal potential cooperating interactions between alterations in SWI/SNF complex genes and other tumor-promoting pathways. However, these data should be considered carefully because human cancers are both histologically and genetically diverse diseases, and observed statistical correlations may be due to an association with the molecular context rather than a mechanistic relationship. For example, in gastric and colorectal cancers, gene mutations in SWI/SNF complexes tend to occur in MSI tumors, whereas *TP53* mutations generally occur in tumors in which microsatellite DNA is stable (108).

TARGETING ALTERATIONS IN SWI/SNF COMPLEX FOR CANCER TREATMENT

Some hypotheses are emerging describing how these insights might be translated to novel therapies. One interesting option came from the evidence of functional antagonism between SWI/SNF

and PRC2 complexes (22, 27). Inhibition of EZH2 in SMARCB1-deficient rhabdoid cells dramatically affects H3K27 trimethylation, leads to a rapid arrest in G1 phase, and induces late cytotoxicity (148). These antiproliferative effects have been confirmed in vivo in xenograft models (148). Whether this approach could be applied to other SWI/SNF-dependent cancers remains to be investigated; however, it is tempting to speculate that the broad antagonism of SWI/SNF and PRC2 should not depend only on *SMARCB1* and, thus, that EZH2 inhibition could target various cancer types with diverse SWI/SNF mutations. Another approach would be to target the signaling pathways downstream of SWI/SNF. Several detailed mechanistic studies have proposed avenues for treating cancers that have alterations in the SWI/SNF complex. The most promising results have been obtained with Aurora kinase A inhibitors in MRT. The overexpression of Aurora kinase A observed in malignant rhabdoid cell lines depends on *SMARCB1* inactivation and enhances cell proliferation (149). Targeting this kinase in vitro and in vivo dramatically reduces tumor proliferation. These results have led to an ongoing clinical trial with alisertib (MLN8237) in children with ATRT. *SMARCB1* inactivation also leads to hyperactivation of GLI1 in ATRTs (25). Because SMO inhibitors act upstream of GLI1, they show no activity on ATRT cell lines. However, targeting the sonic hedgehog pathway remains of interest because it has been demonstrated that arsenic trioxide inhibits GLI1 signaling and has promising antiproliferative effects on rhabdoid cell lines (150). Although blocking a single pathway is worth trying, the broad synchronous dysregulation of many oncogenic pathways induced by SWI/SNF alterations suggests that monotherapy may be suboptimal. The specific inhibition of an active protein domain might also open novel therapeutic perspectives. For example, BRG1 and BRM helicase subunits as well as BAF180, BRD7, and BRD9 SWI/SNF subunits have bromodomains (**Table 1**) that recognize the acetylated lysine of the histone necessary for nucleosome remodeling activity. Hence, the use of selective bromodomain inhibitors such as JQ1, which has recently proven efficient against some tumor types (151, 152), could be an effective targeted therapeutic approach for SWI/SNF-related malignancies. Interestingly, it has been demonstrated that JQ1 induced a marked decrease of cell viability in patient-derived primary ATRT cells with loss of *SMARCB1* (153). Finally, the synthetic lethal interactions between *SMARCA4* and *SMARCB1* (154), between *SMARCA2* and *SMARCA4*, and between *ARID1B* and *ARID1A* may constitute extremely powerful strategies, provided that specific inhibitors can be identified.

CONCLUSIONS

Evidence has emerged about the central position of the SWI/SNF complexes in human tumorigenesis. Alterations of the SWI/SNF complex in cancer cells are now used as relevant diagnostic biomarkers and possible prognostic biomarkers in several tumor types. Some questions remain to be addressed to fully appreciate these functions, but after more than 20 years of research, it has become apparent that SWI/SNF complexes are critical epigenetic regulators of tumorigenesis through their pleiotropic roles in the regulation of the cell cycle, oncogenic pathways, and metabolism. In the future, pharmacological manipulation of the SWI/SNF complex may be a promising approach that will enable therapeutic strategies for cancer to be optimized.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors acknowledge Paul Fréneaux for the pictures of *SMARCB1*-deficient tumors. This work was supported by grants from the Institut Curie, Inserm, the Ligue Contre le Cancer (le programme Equipes Labellisées), the European Union [Kid Cancer Kinome (KCK) and European Embryonal Tumors (EET) pipeline programs], the Société Française de Lutte Contre les Cancers et Leucemies de l'Enfant et de l'Adolescent, the Annenberg Foundation, and the following associations: Association Abigaël, Marabout de Ficelles, Courir pour Mathieu, ADAM, les Torocinelles, Couleur Jade, Franck, Un Rayon de Soleil, APAESIC, Dans les pas du Géant, Association Olivier Chappe, Les Bagouz à Manon, Enfants et Santé, and Les Amis de Claire.

LITERATURE CITED

1. Gui Y, Guo G, Huang Y, Hu X, Tang A, et al. 2011. Frequent mutations of chromatin remodeling genes in transitional cell carcinoma of the bladder. *Nat. Genet.* 43(9):875–78
2. Guo G, Sun X, Chen C, Wu S, Huang P, et al. 2013. Whole-genome and whole-exome sequencing of bladder cancer identifies frequent alterations in genes involved in sister chromatid cohesion and segregation. *Nat. Genet.* 45(12):1459–63
3. Versteege I, Sévenet N, Lange J, Rousseau-Merck MF, Ambros P, et al. 1998. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. *Nature* 394(6689):203–6
4. Sévenet N, Sheridan E, Amram D, Schneider P, Handgretinger R, Delattre O. 1999. Constitutional mutations of the *hSNF5/INI1* gene predispose to a variety of cancers. *Am. J. Hum. Genet.* 65(5):1342–48
5. Kadoch C, Hargreaves DC, Hodges C, Elias L, Ho L, et al. 2013. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat. Genet.* 45(6):592–601
6. Neigeborn L, Carlson M. 1984. Genes affecting the regulation of *suc2* gene expression by glucose repression in *Saccharomyces cerevisiae*. *Genetics* 108(4):845–58
7. Haber JE, Garvik B. 1977. A new gene affecting the efficiency of mating-type interconversions in homothallic strains of *Saccharomyces cerevisiae*. *Genetics* 87(1):33–50
8. Peterson CL, Herskowitz I. 1992. Characterization of the yeast *SWI1*, *SWI2*, and *SWI3* genes, which encode a global activator of transcription. *Cell* 68(3):573–83
9. Khavari PA, Peterson CL, Tamkun JW, Mendel DB, Crabtree GR. 1993. BRG1 contains a conserved domain of the SWI2/SNF2 family necessary for normal mitotic growth and transcription. *Nature* 366(6451):170–74
10. Mohrmann L, Verrijzer CP. 2005. Composition and functional specificity of SWI2/SNF2 class chromatin remodeling complexes. *Biochim. Biophys. Acta* 1681(2–3):59–73
11. Wang W, Côté J, Xue Y, Zhou S, Khavari PA, et al. 1996. Purification and biochemical heterogeneity of the mammalian SWI/SNF complex. *EMBO J.* 15(19):5370–82
12. Gutiérrez J, Paredes R, Cruzat F, Hill DA, van Wijnen AJ, et al. 2007. Chromatin remodeling by SWI/SNF results in nucleosome mobilization to preferential positions in the rat osteocalcin gene promoter. *J. Biol. Chem.* 282(13):9445–57
13. Whitehouse I, Flaus A, Cairns BR, White MF, Workman JL, Owen-Hughes T. 1999. Nucleosome mobilization catalysed by the yeast SWI/SNF complex. *Nature* 400(6746):784–87
14. Lu P, Roberts CWM. 2013. The SWI/SNF tumor suppressor complex: regulation of promoter nucleosomes and beyond. *Nucleus* 4(5):374–78
15. Tolstorukov MY, Sansam CG, Lu P, Koellhoffer EC, Helming KC, et al. 2013. SWI/SNF chromatin remodeling/tumor suppressor complex establishes nucleosome occupancy at target promoters. *PNAS* 110(25):10165–70
16. King HA, Trotter KW, Archer TK. 2012. Chromatin remodeling during glucocorticoid receptor regulated transactivation. *Biochim. Biophys. Acta* 1819(7):716–26

17. Ford E, Thanos D. 2010. The transcriptional code of human IFN-β gene expression. *Biochim. Biophys. Acta* 1799(3–4):328–36
18. Rafati H, Parra M, Hakre S, Moshkin Y, Verdin E, Mahmoudi T. 2011. Repressive LTR nucleosome positioning by the BAF complex is required for HIV latency. *PLOS Biol.* 9(11):e1001206
19. De la Serna IL, Carlson KA, Imbalzano AN. 2001. Mammalian SWI/SNF complexes promote MyoD-mediated muscle differentiation. *Nat. Genet.* 27(2):187–90
20. Gresh L, Bourachot B, Reimann A, Guigas B, Fiette L, et al. 2005. The SWI/SNF chromatin-remodeling complex subunit SNF5 is essential for hepatocyte differentiation. *EMBO J.* 24(18):3313–24
21. Lessard J, Wu JI, Ranish JA, Wan M, Winslow MM, et al. 2007. An essential switch in subunit composition of a chromatin remodeling complex during neural development. *Neuron* 55(2):201–15
22. Kia SK, Gorski MM, Giannakopoulos S, Verrijzer CP. 2008. SWI/SNF mediates polycomb eviction and epigenetic reprogramming of the *INK4B-ARF-INK4A* locus. *Mol. Cell. Biol.* 28(10):3457–64
23. Versteege I, Medjkane S, Rouillard D, Delattre O. 2002. A key role of the hSNF5/INI1 tumour suppressor in the control of the G1-S transition of the cell cycle. *Oncogene* 21(42):6403–12
24. Cheng SW, Davies KP, Yung E, Beltran RJ, Yu J, Kalpana GV. 1999. C-MYC interacts with hSNF5/INI1 and requires the SWI/SNF complex for transactivation function. *Nat. Genet.* 22(1):102–5
25. Jagani Z, Mora-Blanco EL, Sansam CG, McKenna ES, Wilson B, et al. 2010. Loss of the tumor suppressor SNF5 leads to aberrant activation of the hedgehog-GLI pathway. *Nat. Med.* 16(12):1429–33
26. Caramel J, Quignon F, Delattre O. 2008. RhoA-dependent regulation of cell migration by the tumor suppressor hSNF5/INI1. *Cancer Res.* 68(15):6154–61
27. Wilson BG, Wang X, Shen X, McKenna ES, Lemieux ME, et al. 2010. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Cancer Cell* 18(4):316–28
28. Flajollet S, Lefebvre B, Cudejko C, Staels B, Lefebvre P. 2007. The core component of the mammalian SWI/SNF complex SMARCD3/BAF60c is a coactivator for the nuclear retinoic acid receptor. *Mol. Cell Endocrinol.* 270(1–2):23–32
29. Salma N, Xiao H, Mueller E, Imbalzano AN. 2004. Temporal recruitment of transcription factors and SWI/SNF chromatin-remodeling enzymes during adipogenic induction of the peroxisome proliferator-activated receptor gamma nuclear hormone receptor. *Mol. Cell. Biol.* 24(11):4651–63
30. Chiba H, Muramatsu M, Nomoto A, Kato H. 1994. Two human homologues of *Saccharomyces cerevisiae* SWI2/SNF2 and *Drosophila brahma* are transcriptional coactivators cooperating with the estrogen receptor and the retinoic acid receptor. *Nucleic Acids Res.* 22(10):1815–20
31. Debril M-B, Gelman L, Fayard E, Annicotte J-S, Rocchi S, Auwerx J. 2004. Transcription factors and nuclear receptors interact with the SWI/SNF complex through the BAF60C subunit. *J. Biol. Chem.* 279(16):16677–86
32. Pedersen TA, Kowenz-Leutz E, Leutz A, Nerlov C. 2001. Cooperation between C/EBPα TBP/TFIIB and SWI/SNF recruiting domains is required for adipocyte differentiation. *Genes Dev.* 15(23):3208–16
33. Young DW, Pratap J, Javed A, Weiner B, Ohkawa Y, et al. 2005. SWI/SNF chromatin remodeling complex is obligatory for BMP2-induced, RUNX2-dependent skeletal gene expression that controls osteoblast differentiation. *J. Cell. Biochem.* 94(4):720–30
34. Haas JE, Palmer NF, Weinberg AG, Beckwith JB. 1981. Ultrastructure of malignant rhabdoid tumor of the kidney. A distinctive renal tumor of children. *Hum. Pathol.* 12(7):646–57
35. Tsuneyoshi M, Daimaru Y, Hashimoto H, Enjoji M. 1985. Malignant soft tissue neoplasms with the histologic features of renal rhabdoid tumors: an ultrastructural and immunohistochemical study. *Hum. Pathol.* 16(12):1235–42
36. Rorke LB, Packer RJ, Biegel JA. 1996. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. *J. Neurosurg.* 85(1):56–65
37. Trobaugh-Lotrario AD, Tomlinson GE, Finegold MJ, Gore L, Feusner JH. 2009. Small cell undifferentiated variant of hepatoblastoma: adverse clinical and molecular features similar to rhabdoid tumors. *Pediatr. Blood Cancer* 52(3):328–34
38. Rizzo D, Fréneaux P, Brisse H, Louvrier C, Lequin D, et al. 2012. SMARCB1 deficiency in tumors from the peripheral nervous system: a link between schwannomas and rhabdoid tumors? *Am. J. Surg. Pathol.* 36(7):964–72

39. Sévenet N, Lellouch-Tubiana A, Schofield D, Hoang-Xuan K, Gessler M, et al. 1999. Spectrum of hSNF5/INI1 somatic mutations in human cancer and genotype-phenotype correlations. *Hum. Mol. Genet.* 8(13):2359–68
40. Biegel JA, Zhou JY, Rorke LB, Stenstrom C, Wainwright LM, Fogelgren B. 1999. Germ-line and acquired mutations of *INI1* in atypical teratoid and rhabdoid tumors. *Cancer Res.* 59(1):74–79
41. Lee RS, Stewart C, Carter SL, Ambrogio L, Cibulskis K, et al. 2012. A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. *J. Clin. Investig.* 122(8):2983–88
42. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. 2013. Cancer genome landscapes. *Science* 339(6127):1546–58
43. Bourdeaut F, Fréneaux P, Thuille B, Lellouch-Tubiana A, Nicolas A, et al. 2007. hSNF5/INI1-deficient tumours and rhabdoid tumours are convergent but not fully overlapping entities. *J. Pathol.* 211(3):323–30
44. Hoot AC, Russo P, Judkins AR, Perlman EJ, Biegel JA. 2004. Immunohistochemical analysis of hSNF5/INI1 distinguishes renal and extra-renal malignant rhabdoid tumors from other pediatric soft tissue tumors. *Am. J. Surg. Pathol.* 28(11):1485–91
45. Bourdeaut F, Lequin D, Brugières L, Reynaud S, Dufour C, et al. 2011. Frequent *hSNF5/INI1* germline mutations in patients with rhabdoid tumor. *Clin. Cancer Res.* 17(1):31–38
46. Eaton KW, Tooke LS, Wainwright LM, Judkins AR, Biegel JA. 2011. Spectrum of *SMARCB1/INI1* mutations in familial and sporadic rhabdoid tumors. *Pediatr. Blood Cancer* 56(1):7–15
47. Lafay-Cousin L, Payne E, Strother D, Chernos J, Chan M, Bernier FP. 2009. Goldenhar phenotype in a child with distal 22q11.2 deletion and intracranial atypical teratoid rhabdoid tumor. *Am. J. Med. Genet. A* 149A(12):2855–59
48. Jackson EM, Shaikh TH, Gururangan S, Jones MC, Malkin D, et al. 2007. High-density single nucleotide polymorphism array analysis in patients with germline deletions of 22q11.2 and malignant rhabdoid tumor. *Hum. Genet.* 122(2):117–27
49. Taylor MD, Gokgoz N, Andrulis IL, Mainprize TG, Drake JM, Rutka JT. 2000. Familial posterior fossa brain tumors of infancy secondary to germline mutation of the *hSNF5* gene. *Am. J. Hum. Genet.* 66(4):1403–6
50. Janson K, Nedzi LA, David O, Schorin M, Walsh JW, et al. 2006. Predisposition to atypical teratoid/rhabdoid tumor due to an inherited *INI1* mutation. *Pediatr. Blood Cancer* 47(3):279–84
51. Bruggers CS, Bleyl SB, Pysher T, Barnette P, Afify Z, et al. 2011. Clinicopathologic comparison of familial versus sporadic atypical teratoid/rhabdoid tumors (AT/RT) of the central nervous system. *Pediatr. Blood Cancer* 56(7):1026–31
52. Ammerlaan ACJ, Ararou A, Houben MPWA, Baas F, Tijssen CC, et al. 2008. Long-term survival and transmission of *INI1*-mutation via nonpenetrant males in a family with rhabdoid tumour predisposition syndrome. *Br. J. Cancer* 98(2):474–79
53. Forest F, David A, Arrufat S, Pierron G, Ranchere-Vince D, et al. 2012. Conventional chondrosarcoma in a survivor of rhabdoid tumor: enlarging the spectrum of tumors associated with SMARCB1 germline mutations. *Am. J. Surg. Pathol.* 36(12):1892–96
54. Hulsebos TJM, Kenter S, Siebers-Renelt U, Hans V, Wesseling P, Flucke U. 2014. SMARCB1 involvement in the development of leiomyoma in a patient with schwannomatosis. *Am. J. Surg. Pathol.* 38(3):421–25
55. Hulsebos TJM, Plomp AS, Wolterman RA, Robanus-Maandag EC, Baas F, Wesseling P. 2007. Germline mutation of *INI1/SMARCB1* in familial schwannomatosis. *Am. J. Hum. Genet.* 80(4):805–10
56. Sestini R, Bacci C, Provenzano A, Genuardi M, Papi L. 2008. Evidence of a four-hit mechanism involving SMARCB1 and NF2 in schwannomatosis-associated Schwannomas. *Hum. Mutat.* 29(2):227–31
57. Smith MJ, Wallace AJ, Bowers NL, Rustad CF, Woods CG, et al. 2012. Frequency of *SMARCB1* mutations in familial and sporadic schwannomatosis. *Neurogenetics* 13(2):141–45
58. Rousseau G, Noguchi T, Bourdon V, Sobol H, Olschwang S. 2011. SMARCB1/INI1 germline mutations contribute to 10% of sporadic schwannomatosis. *BMC Neurol.* 11:9
59. Smith MJ, Walker JA, Shen Y, Stemmer-Rachamimov A, Gusella JF, Plotkin SR. 2012. Expression of *SMARCB1* (*INI1*) mutations in familial schwannomatosis. *Hum. Mol. Genet.* 21(24):5239–45

60. Swensen JJ, Keyser J, Coffin CM, Biegel JA, Viskochil DH, Williams MS. 2009. Familial occurrence of schwannomas and malignant rhabdoid tumour associated with a duplication in *SMARCB1*. *J. Med. Genet.* 46(1):68–72
61. Bacci C, Sestini R, Provenzano A, Paganini I, Mancini I, et al. 2010. Schwannomatosis associated with multiple meningiomas due to a familial *SMARCB1* mutation. *Neurogenetics* 11(1):73–80
62. Christiaans I, Kenter SB, Brink HC, van Os TAM, Baas F, et al. 2011. Germline *SMARCB1* mutation and somatic *NF2* mutations in familial multiple meningiomas. *J. Med. Genet.* 48(2):93–97
63. Boyd C, Smith MJ, Kluwe L, Balogh A, Maccollin M, Plotkin SR. 2008. Alterations in the *SMARCB1* (*INI1*) tumor suppressor gene in familial schwannomatosis. *Clin. Genet.* 74(4):358–66
64. Schmitz U, Mueller W, Weber M, Sévenet N, Delattre O, von Deimling A. 2001. INI1 mutations in meningiomas at a potential hotspot in exon 9. *Br. J. Cancer* 84(2):199–201
65. Clark VE, Erson-Omay EZ, Serin A, Yin J, Cotney J, et al. 2013. Genomic analysis of non-*NF2* meningiomas reveals mutations in *TRAF7*, *KLF4*, *AKT1*, and *SMO*. *Science* 339(6123):1077–80
66. Hornick JL, Dal Cin P, Fletcher CDM. 2009. Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma. *Am. J. Surg. Pathol.* 33(4):542–50
67. Hollmann TJ, Hornick JL. 2011. INI1-deficient tumors: diagnostic features and molecular genetics. *Am. J. Surg. Pathol.* 35(10):e47–63
68. Chbani L, Guillou L, Terrier P, Decouvelaere AV, Grégoire F, et al. 2009. Epithelioid sarcoma: a clinicopathologic and immunohistochemical analysis of 106 cases from the French sarcoma group. *Am. J. Clin. Pathol.* 131(2):222–27
69. Modena P, Lualdi E, Facchinetti F, Galli L, Teixeira MR, et al. 2005. *SMARCB1/INI1* tumor suppressor gene is frequently inactivated in epithelioid sarcomas. *Cancer Res.* 65(10):4012–19
70. Sullivan LM, Folpe AL, Pawel BR, Judkins AR, Biegel JA. 2013. Epithelioid sarcoma is associated with a high percentage of *SMARCB1* deletions. *Mod. Pathol.* 26(3):385–92
71. Flucke U, Slootweg PJ, Mentzel T, Pauwels P, Hulsebos TJM. 2009. Re: infrequent *SMARCB1/INI1* gene alteration in epithelioid sarcoma: a useful tool in distinguishing epithelioid sarcoma from malignant rhabdoid tumor: direct evidence of mutational inactivation of *SMARCB1/INI1* in epithelioid sarcoma. *Hum. Pathol.* 40(9):1361–64
72. Kohashi K, Izumi T, Oda Y, Yamamoto H, Tamiya S, et al. 2009. Infrequent *SMARCB1/INI1* gene alteration in epithelioid sarcoma: a useful tool in distinguishing epithelioid sarcoma from malignant rhabdoid tumor. *Hum. Pathol.* 40(3):349–55
73. Kohashi K, Oda Y, Yamamoto H, Tamiya S, Oshiro Y, et al. 2008. SMARCB1/INI1 protein expression in round cell soft tissue sarcomas associated with chromosomal translocations involving EWS: a special reference to SMARCB1/INI1 negative variant extraskeletal myxoid chondrosarcoma. *Am. J. Surg. Pathol.* 32(8):1168–74
74. Liu Q, Galli S, Srinivasan R, Linehan WM, Tsokos M, Merino MJ. 2013. Renal medullary carcinoma: molecular, immunohistochemistry, and morphologic correlation. *Am. J. Surg. Pathol.* 37(3):368–74
75. Calderaro J, Moroch J, Pierron G, Pedeutour F, Grison C, et al. 2012. *SMARCB1/INI1* inactivation in renal medullary carcinoma. *Histopathology* 61(3):428–35
76. Kreiger PA, Judkins AR, Russo PA, Biegel JA, Lestini BJ, et al. 2009. Loss of INI1 expression defines a unique subset of pediatric undifferentiated soft tissue sarcomas. *Mod. Pathol.* 22(1):142–50
77. Hasselblatt M, Oyen F, Gesk S, Kordes U, Wrede B, et al. 2009. Cribriform neuroepithelial tumor (CRINET): a nonrhabdoid ventricular tumor with INI1 loss and relatively favorable prognosis. *J. Neuropathol. Exp. Neurol.* 68(12):1249–55
78. Mobley BC, McKenney JK, Bangs CD, Callahan K, Yeom KW, et al. 2010. Loss of SMARCB1/INI1 expression in poorly differentiated chordomas. *Acta Neuropathol.* 120(6):745–53
79. Agaimy A, Koch M, Lell M, Semrau S, Dudek W, et al. 2014. SMARCB1 (INI1)-deficient sinonasal basaloid carcinoma: a novel member of the expanding family of SMARCB1-deficient neoplasms. *Am. J. Surg. Pathol.* 38(9):1274–81
80. Bishop JA, Antonescu CR, Westra WH. 2014. SMARCB1 (INI-1)-deficient carcinomas of the sinonasal tract. *Am. J. Surg. Pathol.* 38(9):1282–89

81. Schneppenheim R, Frühwald MC, Gesk S, Hasselblatt M, Jeibmann A, et al. 2010. Germline nonsense mutation and somatic inactivation of *SMARCA4/BGRG1* in a family with rhabdoid tumor predisposition syndrome. *Am. J. Hum. Genet.* 86(2):279–84
82. Witkowski L, Lalonde E, Zhang J, Albrecht S, Hamel N, et al. 2013. Familial rhabdoid tumour "avant la lettre"—from pathology review to exome sequencing and back again. *J. Pathol.* 231(1):35–43
83. Smith MJ, O'Sullivan J, Bhaskar SS, Hadfield KD, Poke G, et al. 2013. Loss-of-function mutations in *SMARCE1* cause an inherited disorder of multiple spinal meningiomas. *Nat. Genet.* 45(3):295–98
84. Tsurusaki Y, Okamoto N, Ohashi H, Kosho T, Imai Y, et al. 2012. Mutations affecting components of the SWI/SNF complex cause Coffin–Siris syndrome. *Nat. Genet.* 44(4):376–78
85. Van Houdt JKJ, Nowakowska BA, Sousa SB, van Schaik BDC, Seuntjens E, et al. 2012. Heterozygous missense mutations in *SMARCA2* cause Nicolaides–Baraitser syndrome. *Nat. Genet.* 44(4):445–49
86. Ho AS, Kannan K, Roy DM, Morris LGT, Ganly I, et al. 2013. The mutational landscape of adenoid cystic carcinoma. *Nat. Genet.* 45(7):791–98
87. Love C, Sun Z, Jima D, Li G, Zhang J, et al. 2012. The genetic landscape of mutations in Burkitt lymphoma. *Nat. Genet.* 44(12):1321–25
88. Imielinski M, Berger AH, Hammerman PS, Hernandez B, Pugh TJ, et al. 2012. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. *Cell* 150(6):1107–20
89. Dulak AM, Stojanov P, Peng S, Lawrence MS, Fox C, et al. 2013. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. *Nat. Genet.* 45(5):478–86
90. Parsons DW, Li M, Zhang X, Jones S, Leary RJ, et al. 2011. The genetic landscape of the childhood cancer medulloblastoma. *Science* 331(6016):435–39
91. Jones DTW, Jäger N, Kool M, Zichner T, Hutter B, et al. 2012. Dissecting the genomic complexity underlying medulloblastoma. *Nature* 488(7409):100–5
92. Pugh TJ, Weeraratne SD, Archer TC, Pomeranz Krummel DA, Auclair D, et al. 2012. Medulloblastoma exome sequencing uncovers subtype-specific somatic mutations. *Nature* 488(7409):106–10
93. Dykhuizen EC, Hargreaves DC, Miller EL, Cui K, Korshunov A, et al. 2013. BAF complexes facilitate decatenation of DNA by topoisomerase IIα. *Nature* 497(7451):624–27
94. Jelinic P, Mueller JJ, Olvera N, Dao F, Scott SN, et al. 2014. Recurrent *SMARCA4* mutations in small cell carcinoma of the ovary. *Nat. Genet.* 46(5):424–26
95. Witkowski L, Carrot-Zhang J, Albrecht S, Fahiminiya S, Hamel N, et al. 2014. Germline and somatic *SMARCA4* mutations characterize small cell carcinoma of the ovary, hypercalcemic type. *Nat. Genet.* 46(5):438–43
96. Ramos P, Karnezis AN, Craig DW, Sekulic A, Russell ML, et al. 2014. Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in *SMARCA4*. *Nat. Genet.* 46(5):427–29
97. Jones S, Wang T-L, Shih I-M, Mao T-L, Nakayama K, et al. 2010. Frequent mutations of chromatin remodeling gene *ARID1A* in ovarian clear cell carcinoma. *Science* 330(6001):228–31
98. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, et al. 2010. *ARID1A* mutations in endometriosis-associated ovarian carcinomas. *N. Engl. J. Med.* 363(16):1532–43
99. Katagiri A, Nakayama K, Rahman MT, Rahman M, Katagiri H, et al. 2012. Loss of ARID1A expression is related to shorter progression-free survival and chemoresistance in ovarian clear cell carcinoma. *Mod. Pathol.* 25(2):282–88
100. Liang H, Cheung LWT, Li J, Ju Z, Yu S, et al. 2012. Whole-exome sequencing combined with functional genomics reveals novel candidate driver cancer genes in endometrial cancer. *Genome Res.* 22(11):2120–29
101. Cancer Genome Atlas Res. Netw. 2013. Integrated genomic characterization of endometrial carcinoma. *Nature* 497(7447):67–73
102. Le Gallo M, O'Hara AJ, Rudd ML, Urick ME, Hansen NF, et al. 2012. Exome sequencing of serous endometrial tumors identifies recurrent somatic mutations in chromatin-remodeling and ubiquitin ligase complex genes. *Nat. Genet.* 44(12):1310–15
103. Guichard C, Amaddeo G, Imbeaud S, Ladeiro Y, Pelletier L, et al. 2012. Integrated analysis of somatic mutations and focal copy-number changes identifies key genes and pathways in hepatocellular carcinoma. *Nat. Genet.* 44(6):694–98

104. Huang J, Deng Q, Wang Q, Li K-Y, Dai J-H, et al. 2012. Exome sequencing of hepatitis B virus-associated hepatocellular carcinoma. *Nat. Genet.* 44(10):1117–21
105. Cancer Genome Atlas Res. Netw. 2012. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* 489(7417):519–25
106. Wang K, Kan J, Yuen ST, Shi ST, Chu KM, et al. 2011. Exome sequencing identifies frequent mutation of *ARID1A* in molecular subtypes of gastric cancer. *Nat. Genet.* 43(12):1219–23
107. Zang ZJ, Cutcutache I, Poon SL, Zhang SL, McPherson JR, et al. 2012. Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes. *Nat. Genet.* 44(5):570–74
108. Cancer Genome Atlas Netw. 2012. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 487(7407):330–37
109. Biankin AV, Waddell N, Kassahn KS, Gingras M-C, Muthuswamy LB, et al. 2012. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 491(7424):399–405
110. Jiao Y, Yonescu R, Offerhaus GJA, Klimstra DS, Maitra A, et al. 2014. Whole-exome sequencing of pancreatic neoplasms with acinar differentiation. *J. Pathol.* 232(4):428–35
111. Jiao Y, Pawlik TM, Anders RA, Selaru FM, Streppel MM, et al. 2013. Exome sequencing identifies frequent inactivating mutations in *BAP1*, *ARID1A* and *PBRM1* in intrahepatic cholangiocarcinomas. *Nat. Genet.* 45(12):1470–73
112. Treon SP, Xu L, Yang G, Zhou Y, Liu X, et al. 2012. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *N. Engl. J. Med.* 367(9):826–33
113. Sausen M, Leary RJ, Jones S, Wu J, Reynolds CP, et al. 2013. Integrated genomic analyses identify *ARID1A* and *ARID1B* alterations in the childhood cancer neuroblastoma. *Nat. Genet.* 45(1):12–17
114. Li M, Zhao H, Zhang X, Wood LD, Anders RA, et al. 2011. Inactivating mutations of the chromatin remodeling gene *ARID2* in hepatocellular carcinoma. *Nat. Genet.* 43(9):828–29
115. Fujimoto A, Totoki Y, Abe T, Boroevich KA, Hosoda F, et al. 2012. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. *Nat. Genet.* 44(7):760–64
116. Manceau G, Letouzé E, Guichard C, Didelot A, Cazes A, et al. 2013. Recurrent inactivating mutations of *ARID2* in non-small cell lung carcinoma. *Int. J. Cancer* 132(9):2217–21
117. Hodis E, Watson IR, Kryukov GV, Arold ST, Imielinski M, et al. 2012. A landscape of driver mutations in melanoma. *Cell* 150(2):251–63
118. India Proj. Team Int. Cancer Genome Consort. 2013. Mutational landscape of gingivo-buccal oral squamous cell carcinoma reveals new recurrently-mutated genes and molecular subgroups. *Nat. Commun.* 4:2873
119. Guo G, Gui Y, Gao S, Tang A, Hu X, et al. 2012. Frequent mutations of genes encoding ubiquitin-mediated proteolysis pathway components in clear cell renal cell carcinoma. *Nat. Genet.* 44(1):17–19
120. Sato Y, Yoshizato T, Shiraishi Y, Maekawa S, Okuno Y, et al. 2013. Integrated molecular analysis of clear-cell renal cell carcinoma. *Nat. Genet.* 45(8):860–67
121. Cancer Genome Atlas Res. Netw. 2013. Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature* 499(7456):43–49
122. Varela I, Tarpey P, Raine K, Huang D, Ong CK, et al. 2011. Exome sequencing identifies frequent mutation of the SWI/SNF complex gene *PBRM1* in renal carcinoma. *Nature* 469(7331):539–42
123. Kapur P, Peña-Llopis S, Christie A, Zhrebker L, Pavía-Jiménez A, et al. 2013. Effects on survival of *BAP1* and *PBRM1* mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation. *Lancet Oncol.* 14(2):159–67
124. De Keersmaecker K, Real PJ, Gatta GD, Palomero T, Sulis ML, et al. 2010. The *TLX1* oncogene drives aneuploidy in T cell transformation. *Nat. Med.* 16(11):1321–27
125. Satterwhite E, Sonoki T, Willis TG, Harder L, Nowak R, et al. 2001. The *BCL11* gene family: involvement of *BCL11A* in lymphoid malignancies. *Blood* 98(12):3413–20
126. Zani VJ, Asou N, Jadayel D, Heward JM, Shipley J, et al. 1996. Molecular cloning of complex chromosomal translocation t(8;14;12)(q24.1;q32.3;q24.1) in a Burkitt lymphoma cell line defines a new gene (*BCL7A*) with homology to caldesmon. *Blood* 87(8):3124–34

127. Van Doorn R, Zoutman WH, Dijkman R, de Menezes RX, Commandeur S, et al. 2005. Epigenetic profiling of cutaneous T-cell lymphoma: promoter hypermethylation of multiple tumor suppressor genes including *BCL7a*, *PTPRG*, and *p73*. *J. Clin. Oncol.* 23(17):3886–96
128. Naka N, Takenaka S, Araki N, Miwa T, Hashimoto N, et al. 2010. Synovial sarcoma is a stem cell malignancy. *Stem Cells* 28(7):1119–31
129. Kohashi K, Oda Y, Yamamoto H, Tamiya S, Matono H, et al. 2010. Reduced expression of SMARCB1/INI1 protein in synovial sarcoma. *Mod. Pathol.* 23(7):981–90
130. Kadoch C, Crabtree GR. 2013. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. *Cell* 153(1):71–85
131. Zorludemir S, Scheithauer BW, Hirose T, Van Houten C, Miller G, Meyer FB. 1995. Clear cell meningioma. A clinicopathologic study of a potentially aggressive variant of meningioma. *Am. J. Surg. Pathol.* 19(5):493–505
132. Mackay B, Ordónez NG, Khoursand J, Bennington JL. 1987. The ultrastructure and immunocytochemistry of renal cell carcinoma. *Ultrastruct. Pathol.* 11(5–6):483–502
133. Ohkawa K, Amasaki H, Terashima Y, Aizawa S, Ishikawa E. 1977. Clear cell carcinoma of the ovary: light and electron microscopic studies. *Cancer* 40(6):3019–29
134. Kwon TJ, Ro JY, Tornos C, Ordonez NG. 1996. Reduplicated basal lamina in clear-cell carcinoma of the ovary: an immunohistochemical and electron microscopic study. *Ultrastruct. Pathol.* 20(6):529–36
135. Kurman RJ, Scully RE. 1976. Clear cell carcinoma of the endometrium: an analysis of 21 cases. *Cancer* 37(2):872–82
136. Matias-Guiu X, Lerma E, Prat J. 1997. Clear cell tumors of the female genital tract. *Semin. Diagn. Pathol.* 14(4):233–39
137. Steinberg P, Störkel S, Oesch F, Thoenes W. 1992. Carbohydrate metabolism in human renal clear cell carcinomas. *Lab. Investig.* 67(4):506–11
138. Wang L, Zhao Z, Meyer MB, Saha S, Yu M, et al. 2014. Carm1 methylates chromatin remodeling factor BAF155 to enhance tumor progression and metastasis. *Cancer Cell* 25(1):21–36
139. Wang S-CM, Dowhan DH, Eriksson NA, Muscat GEO. 2012. CARM1/PRMT4 is necessary for the glycogen gene expression programme in skeletal muscle cells. *Biochem. J.* 444(2):323–31
140. Gresh L, Bourachot B, Reimann A, Guigas B, Fiette L, et al. 2005. The SWI/SNF chromatin-remodeling complex subunit SNF5 is essential for hepatocyte differentiation. *EMBO J.* 24(18):3313–24
141. Helming KC, Wang X, Wilson BG, Vazquez F, Haswell JR, et al. 2014. ARID1B is a specific vulnerability in *ARID1A*-mutant cancers. *Nat. Med.* 20(3):251–54
142. Oike T, Ogiwara H, Tominaga Y, Ito K, Ando O, et al. 2013. A synthetic lethality-based strategy to treat cancers harboring a genetic deficiency in the chromatin remodeling factor BRG1. *Cancer Res.* 73(17):5508–18
143. Hoffman GR, Rahal R, Buxton F, Xiang K, McAllister G, et al. 2014. Functional epigenetics approach identifies BRM/SMARCA2 as a critical synthetic lethal target in BRG1-deficient cancers. *PNAS* 111(8):3128–33
144. Prensner JR, Iyer MK, Balbin OA, Dhanasekaran SM, Cao Q, et al. 2011. Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. *Nat. Biotechnol.* 29(8):742–49
145. Prensner JR, Iyer MK, Sahu A, Asangani IA, Cao Q, et al. 2013. The long noncoding RNA SChLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. *Nat. Genet.* 45(11):1392–98
146. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, et al. 2013. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. *Sci. Signal.* 6(269):pl1
147. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, et al. 2012. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov.* 2(5):401–4
148. Knutson SK, Warholic NM, Wigle TJ, Klaus CR, Allain CJ, et al. 2013. Durable tumor regression in genetically altered malignant rhabdoid tumors by inhibition of methyltransferase EZH2. *PNAS* 110(19):7922–27
149. Lee S, Cimica V, Ramachandra N, Zagzag D, Kalpana GV. 2011. Aurora A is a repressed effector target of the chromatin remodeling protein hSNF5/INI1 required for rhabdoid tumor cell survival. *Cancer Res.* 71(9):3225–35

150. Kerl K, Moreno N, Holsten T, Ahlfeld J, Mertins J, et al. 2014. Arsenic trioxide inhibits tumor cell growth in malignant rhabdoid tumors in vitro and in vivo by targeting overexpressed Gli1. *Int. J. Cancer* 135(4):989–95
151. Filippakopoulos P, Qi J, Picaud S, Shen Y, Smith WB, et al. 2010. Selective inhibition of BET bromodomains. *Nature* 468(7327):1067–73
152. Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, et al. 2011. BET bromodomain inhibition as a therapeutic strategy to target c-MYC. *Cell* 146(6):904–17
153. Tang Y, Gholamin S, Schubert S, Willardson MI, Lee A, et al. 2014. Epigenetic targeting of Hedgehog pathway transcriptional output through BET bromodomain inhibition. *Nat. Med.* 20(7):732–40
154. Wang X, Sansam CG, Thom CS, Metzger D, Evans JA, et al. 2009. Oncogenesis caused by loss of the SNF5 tumor suppressor is dependent on activity of BRG1, the ATPase of the SWI/SNF chromatin remodeling complex. *Cancer Res.* 69(20):8094–101

Annual Review of Pathology: Mechanisms of Disease

Volume 10, 2015

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Pathology: Mechanisms of Disease* articles may be found at http://www.annualreviews.org/errata/pathol