

SWI/SNF complex in disorder

SWItching from malignancies to intellectual disability

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Heterozygous germline mutations in components of switch/sucrose nonfermenting (SWI/SNF) chromatin remodeling complexes were recently identified in patients with non-syndromic intellectual disability, Coffin-Siris syndrome and Nicolaides-Baraitser syndrome. The common denominator of the phenotype of these patients is severe intellectual disability and speech delay. Somatic and germline mutations in SWI/SNF components were previously implicated in tumor development. This raises the question whether patients with intellectual disability caused by SWI/SNF mutations in the germline are exposed to an increased risk of developing cancer. Here we compare the mutational spectrum of SWI/SNF components in intellectual disability syndromes and cancer, and discuss the implications of the results of this comparison for the patients.

Introduction

The SWI/SNF (switch/sucrose nonfermenting) chromatin remodeling complex plays an important role in several distinct processes, such as transcription, cell differentiation and DNA repair. Moreover, it has also been implicated in tumor suppression and intellectual disability.^{1,2} Here, we will summarize what is known about the function of the SWI/SNF complex, its role in tumor formation and its involvement in intellectual disability, prior to discussing the comparison of the mutational spectrum between intellectual disability and tumor development.

The SWI/SNF Complex and its Function in the Cell

The storage of human chromosomes in the cell nucleus involves the formation of nucleosomes, which are formed by the wrapping of ~147 bp of DNA around histone proteins. Nucleosomes in turn are assembled into condensed chromatin, which forms a barrier that inhibits access to DNA for cellular proteins that drive chromatin-based processes, including transcription and DNA repair. A pivotal step in the regulation of these nuclear processes is the modulation of chromatin structure, which can be achieved by two mechanisms that either involve the modification of residues in the histone tails or the activity of ATP-dependent chromatin remodeling complexes.^{3,4} SWI/SNF is one of the many chromatin remodeling complexes present in human cells.^{2,4} It consists of at least 15–20 subunits and is thought to remodel chromatin through ATP-dependent sliding of nucleosomes along the DNA (reviewed by Hargreaves and Crabtree⁵). The function of the SWI/SNF complex in yeast is well characterized. It binds in close proximity to promoters to facilitate the binding of transcription factors and regulate the expression of hundreds of yeast genes, including those involved in sugar and iron uptake.⁶ In humans, however, its mode of action is much less clear. A large portion of SWI/SNF complexes do not bind near promoter sites, yet a substantial number of genes involved in many cellular processes are transcriptionally controlled by this

Keywords: SWI/SNF, chromatin remodeling, cancer, intellectual disability, Coffin-Siris syndrome

Abbreviations: SWI/SNF, switch/sucrose nonfermenting; CSS, Coffin-Siris syndrome; NBS, Nicolaides-Baraitser syndrome

Submitted: 08/29/12

Revised: 09/14/12

Accepted: 09/19/12

<http://dx.doi.org/10.4161/epi.22299>

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Table 1. The main subunits of the SWI/SNF complex and their function (based on refs. 2 and 5)

Official gene name	Alternative name	Putative function
SMARCA2 or SMARCA4	BRG1 hBRM	Performs ATP hydrolysis, binds acetylated histones, regulates transcription and acts as a tumor suppressor ^{2,5}
ARID1, ARID1B or ARID2	BAF250a BAF250b BAF200	Performs DNA target recognition, involved in protein-protein interactions, regulates transcription and acts as a tumor suppressor ^{2,5}
SMARCB1	BAF47/hSNF5	Regulates transcription, acts as a tumor suppressor ^{2,5}
SMARCE1	BAF57	Regulates transcription, ⁴⁰ acts as a tumor suppressor ³²
SMARCC1 and/or SMARCC2	BAF155 BAF170	Stabilizes the SWI/SNF complex, ⁴¹ acts as a tumor suppressor ⁴²
SMARCD1, SMARCD2 or SMARCD3	BAF60a BAF60b BAF60c	Acts as a tumor suppressor ²¹

There are many different combinations of subunits possible to form the SWI/SNF complex. The first column indicates if the subunits are mutually exclusive (such as SMARCA2/SMARCA4) or can occur together in the complex (such as SMARCC1/SMARCC2).

complex, including those involved in cell adhesion and cell differentiation.⁷ Importantly, not only the catalytic subunits of SWI/SNF, the SMARCA2 and SMARCA4 ATPases, are important for transcription regulation, but also structural components, such as ARID1A and ARID1B, are required for this process. Moreover, these subunits can have antagonistic effects on transcription regulation of cell cycle regulators, such as c-Myc, illustrating their importance in determining SWI/SNF activity.⁸ Table 1 summarizes the core proteins of the SWI/SNF complex and their putative role. As illustrated by this table, there are many different possible combinations of subunits forming the SWI/SNF complex. Indeed, it has been shown that the composition of the complex changes upon differentiation of cells, suggesting that distinct forms of the SWI/SNF complex may be important for cell differentiation.⁶⁻⁸ Finally, recent work from Park and coworkers showed that SWI/SNF also plays an important role in DNA repair. SWI/SNF associates with sites of DNA damage and its inactivation leads to impaired DNA repair and reduced cell survival after exposure of cells to genotoxic agents.¹ DNA repair deficiencies often lead to genomic instability, which is one of the hallmarks of cancer. This may explain why inactivating mutations in SWI/SNF components lead to genomic instability and could fuel cancer development.

The SWI/SNF Complex and Tumor Suppression

Increasing evidence suggests that SWI/SNF complexes have a widespread function in tumor suppression. Inactivating mutations in several SWI/SNF components have recently been identified with high frequency in a wide variety of tumors, including rhabdoid and lung cancer tumors (Table 2).² The somatic mutations identified in SWI/SNF components in cancer cells range from homozygous deletions to heterozygous frame shift and truncating mutations.² Additionally, truncating and missense germline mutations in *SMARCB1* and truncating germline mutations in *SMARCA4* have been shown to lead to a cancer predisposition syndrome.^{9,10}

Work in mouse models supports a role for SWI/SNF components as bona fide tumor suppressors: mice carrying genetically engineered mutations in distinct SWI/SNF components (e.g., *SNF5* and *BRG1*, analogous to human *SMARCE1* and *SMARCA2* respectively) developed tumors more rapidly and efficiently.¹¹⁻¹³ It is becoming increasingly clear how SWI/SNF may act as a tumor suppressor. SWI/SNF complexes regulate many different cellular pathways, several of which are involved in cell differentiation, as well as in cell proliferation and migration. Inactivating mutations in SWI/SNF components may lead to dysregulation of these pathways, thereby affecting cancer

development (reviewed in Wilson and Roberts³).

The SWI/SNF Complex and Intellectual Disability

In 2011, mutations in several genes coding for key components of the SWI/SNF complex were implicated in intellectual disability syndromes. First, haploinsufficiency of *ARID1B* was implicated in non-syndromic intellectual disability, with the common features being severe intellectual disability, speech delay and in many cases agenesis of the corpus callosum. The first reports were of patients with translocations through *ARID1B* or deletions of *ARID1B* and several other genes.^{14,15}

In March 2012, Hoyer et al.¹⁶ published a study in which they identified 8 truncating mutations in *ARID1B* in an unselected group of 887 patients with intellectual disability (0.9%). Again, the phenotype of these patients appeared to be non-syndromic, with moderate to severe intellectual disability, speech delay and hypotonia as the main overlapping features. In this paper, MRI scanning did not identify agenesis of the corpus callosum in these patients.

The 2012 April issue of *Nature Genetics* included three papers on germline mutations in SWI/SNF complex proteins leading to intellectual disability syndromes: our group identified de novo truncating mutations in *ARID1B* in three patients with Coffin Siris syndrome (CSS, MIM

Table 2. Comparison of the different mutations identified in malignancies and in intellectual disability

Subunit	Mutations related to malignancies	Germline/somatic	Mutations related to intellectual disability	Germline/somatic	Domains with missense mutations in patients with intellectual disability ^{28,43}	Expression pattern ⁴⁴
ARID1A	Truncating/missense ^{23,45-47}	Somatic	Truncating ¹⁸	Germline		Ubiquitous
ARID1B	Truncating ²¹	Somatic	Truncating ¹⁶⁻¹⁸	Germline		Many tissues*
SMARCA2	-	-	Missense ¹⁶⁻¹⁸	Germline	Helicase ATP-binding (SNF2), helicase C-terminal,	Ubiquitous
SMARCA4	Truncating ^{10,31} missense ²⁷	Germline Somatic	Missense ¹⁸	Germline	Helicase ATP-binding (SNF2), helicase C-terminal, helicase/SANT-associated (HAS)	Ubiquitous
SMARCE1	Truncating ³²	Somatic (bi-allelic), one case	Missense ¹⁸	Germline	Binding of alternative DNA conformations (HMG)	Ubiquitous
SMARCB1	Truncating/missense ^{10,26,30}	Germline and somatic	Missense ¹⁸	Germline	Promoter targeting and chromatin remodeling activity (SNF5)	Ubiquitous

*Thymus, bone marrow, spleen, brain, spinal cord, heart, skeletal muscle, kidney, lung, liver, pancreas and prostate.

135900),¹⁷ Tsurusaki and colleagues¹⁸ reported mutations in *ARID1B*, *ARID1A*, *SMARCA4*, *SMARCE1* and *SMARCB1* in 19/22 (86%, excluding one patient as explained below) of patients with CSS. Van Houdt and colleagues¹⁹ reported mutations in *SMARCA2* in patients with Nicolaides-Baraitser syndrome (NBS, MIM 601358), which was later confirmed by Wolff et al.²⁰ Tsurusaki and colleagues also reported a patient with a *SMARCA2* mutation and CSS; however, the phenotype of this patient resembles NBS more than CSS (N. Matsumoto, personal communication).

CSS is characterized by severe intellectual disability, often accompanied by speech delay, as well as hypertrichosis and hypoplastic or absent fifth fingernails or toenails. Although mutations in *ARID1B* can cause CSS, both our data and the literature seem to indicate that not all patients with *ARID1B* mutations have the specific characteristics of CSS. Indeed, if the percentages of mutations in the different subunits (about 30% in *ARID1B*)¹⁸ is the same in CSS as in non-syndromic intellectual disability, one could hypothesize that up to 3% of unexplained intellectual disability is caused by mutations in genes encoding SWI/SNF components (as 0.9% of unexplained intellectual disability seems to be caused by *ARID1B* mutations).¹⁶ Interestingly, mutations in *SMARCA2* seem to cause a slightly

different phenotypic spectrum. NBS has some overlap with CSS, but differences are the observed frequency of early-onset seizures in NBS, digital anomalies and the typical sparse hair, although this has also been reported in CSS patients.

Types of Mutations in Tumors vs. Intellectual Disability Syndromes

Although it is too early to tell if a phenotypic distinction may be made among the CSS patients with mutations in different components of SWI/SNF, it is apparent that the type of mutation identified depends on the specific component. In cases involving *ARID1B*, haploinsufficiency seems to be the pathophysiological mechanism. Only nonsense and frame shift mutations have been identified thus far, as well as whole-gene deletions. *ARID1B* was recently linked to cancer, as truncating mutations (and one small in-frame deletion) in *ARID1B* were identified in breast cancer tissue and designated as driver mutations.²¹

Likewise, only truncating mutations have been described in *ARID1A*, pointing to haploinsufficiency as the pathophysiological mechanism. Zhang et al.²² recently showed that inactivating mutations in *ARID1A* are a common feature of gastric cancer. Similarly, others previously identified (mostly truncating) somatic mutations in endometriosis-associated ovarian

clear cell and endometrioid carcinomas.²³ As the *ARID1A* and *ARID1B* proteins are mutually exclusive in SWI/SNF complexes,²⁴ it seems that a distortion of the balance of these proteins may be the driver of further pathophysiological processes. Flores-Alcantar et al.²⁵ show that this ratio is dynamic and tissue specific, suggesting that the balance between *ARID1A* and *ARID1B* might be important for tissue differentiation.

The mutations found in subunits other than *ARID1A* and *ARID1B* are highly conserved missense mutations. In the case of *SMARCA2*, all missense mutations identified thus far are in the SNF2_N ATPase and HELICASE_C domain of the protein. For *SMARCA4* the same holds, and in addition a three-base pair deletion located 13 aminoacids outside of the small helicase/SANT-associated (HAS) domain (p.Lys546del) has been reported.¹⁸ Interestingly, as van Houdt et al.¹⁹ pointed out, haploinsufficiency of *SMARCA2* does not result in an NBS phenotype. Larger deletions including *SMARCA2* as well as many of its neighboring genes have been documented (<http://decipher.sanger.ac.uk>), but to our knowledge no patient with isolated *SMARCA2* haploinsufficiency has been described. Likewise, *SMARCA4* haploinsufficiency does not result in CSS, but in rhabdoid tumor predisposition syndrome (MIM 613325).^{9,26} At this point, we can only

speculate about the reasons why missense mutations cause severe intellectual disability and haploinsufficiency gives rise to an increased tumor risk. Truncating mutations may result in insufficient amounts of functional SWI/SNF complexes, thereby reducing the ability to control differentiation and cell cycle processes (and thus lead to tumorigenesis). A possible explanation for the more severe phenotype of the missense mutations is that these mutations result in a gain of function, switching the SMARCA2/4 proteins to a constantly “on” state. However, it seems unlikely that so many different missense mutations as well as in-frame deletions could cause the same gain-of-function effect. A more likely scenario is that the missense phenotype results from defective SMARCA2/4 protein being incorporated into the SWI/SNF complex, thereby blocking binding sites for functional SWI/SNF complexes (competitive inhibition). Thus, it is conceivable that missense mutations will also result in an increased risk of malignancies, as the ability of the SWI/SNF complex to control cell cycle processes may be diminished. Recently, missense mutations in the helicase domain of SMARCA4 were identified in medulloblastoma, lending support to this hypothesis.²⁷

The missense mutations in *SMARCB1* causing CSS have until now only been described in its last two exons (8 and 9). Only a SNF5 domain (unique to SMARCB1), which was shown to be important for promoter targeting and chromatin remodeling, is reported by Uniprot.^{28,29} Interestingly, the p.Arg377His mutation that occurred de novo in one of the patients with CSS¹⁸ was also identified as somatic mutations in four meningiomas.³⁰ Truncating as well as missense mutations in *SMARCB1* in the germline have also been described in patients diagnosed with Schwannomatosis, a tumor suppressor syndrome.¹⁰

The last subunit in which a mutation was identified in CSS patients is *SMARCE1*. In one patient a de novo missense mutation was identified in the high mobility group (HMG) domain of this protein.¹⁸ The HMG domain has a high affinity for alternative DNA-conformations and is often found in subunits of chromatin remodeling

complexes.³¹ *SMARCE1* mutations have not been unequivocally linked to tumor formation, although two truncating mutations which are thought to lead to haploinsufficiency were reported in the breast cancer tissue of 1/95 patients.³² However, to our knowledge, this latter finding has not yet been replicated.

What is the Link Between Tumor Suppression and Intellectual Disability?

At first glance, there is no obvious link between tumor suppression and intellectual disability. However, the involvement of the SWI/SNF complex in tissue differentiation may provide a clue. Problems in tissue differentiation and neuronal differentiation are a possible cause of intellectual disability. Likewise, it does not require much imagination to assume that erroneous tissue differentiation may lead to aberrant growth and, therefore, tumor formation. Lessard et al.³³ elegantly showed that the change in subunit composition of the SWI/SNF complex is a required event in the differentiation of neural stem and progenitor cells. This indicates that subunit alteration of the SWI/SNF complex could play an important role in tissue differentiation in general.

The involvement of epigenetic factors in the origin of both tumorigenesis and intellectual disability was recently also described by Gilissen et al. and does not seem to be unique to SWI/SNF. They noted that mutations in epigenetic modifiers seem to have a dual role in human disease.³⁴ For example, somatic mutations in *NSDI* (a histone methyltransferase that has been shown to be involved in transcriptional regulation) and *ASXL1* (involved in transcriptional regulation mediated by ligand-bound nuclear hormone receptors) have been identified in hematological malignancies, whereas germline mutations cause Sotos syndrome and Bohring-Opitz syndrome, respectively.^{35,36} Recently, germline mutations in *EZH2*, the catalytic component of the histone methyltransferase polycomb repressive complex 2 (PRC2) were identified in Weaver syndrome,^{37,38} a syndrome which has clinical overlap with Sotos syndrome. There is evidence that *EZH2* may

function both as oncogene and tumor suppressor gene.³⁹ Similar to what we noted for *SMARCB1*, some of the germline mutations identified in Weaver syndrome are the same as the somatic mutations described in tumor cells. Interestingly, although tumors have been described in Weaver syndrome, they are not as common a feature as might be expected based on the similarity in mutations.

Is there Tumor Predisposition in Patients Harboring SWI/SNF Mutations?

We reasoned that examining the mutational spectrum of patients with intellectual disability and the mutations related to carcinogenesis may shed light on whether the patients with intellectual disability might be predisposed to tumor development. As shown in Table 2 for *ARID1A*, *SMARCB1* and possibly *ARID1B*, the same type of mutations causing intellectual disability syndromes in the germline has also been observed as somatic mutations in tumors. Therefore, an increased risk of malignancies in CSS-patients with mutations in these genes should be considered a possibility. Unfortunately, since SWI/SNF components are expressed in almost every tissue (Table 2), it seems impossible to predict what type of malignancies might be expected.

For *SMARCA4* the mutational spectrum differs between the intellectual disability and tumor predisposition syndrome cases. For intellectual disability syndromes, missense mutations specific to the ATPase domain are seen, whereas haploinsufficiency causes a tumor predisposition syndrome. However, as we have speculated above, one could easily conceive that missense mutations in the ATP binding domain observed in CSS-patients might also increase the probability of malignancies as they probably impair the function of the SWI/SNF complex. Therefore, with the data available to us, we cannot rule out an increased susceptibility to cancer in CSS patients carrying *SMARCA4* mutations. The same applies to a lesser extent for *SMARCE1*, since two truncating somatic mutations were identified in breast tumor

tissue of a single patient whereas a germline missense mutation was identified as a cause in CSS.

Lastly, as no mutations in *SMARCA2* have been described in malignancies, we can tentatively infer that patients with *SMARCA2* mutations might not have an increased tumor risk.

Contrary to what might be expected, there have been no reports of increased susceptibility to malignancies in CSS or NBS so far. However, as these patients are often not followed up after their childhood, we cannot exclude that some of these patients might have developed cancer. An alternative explanation is that the tumor risk is not significantly increased, e.g., because a plethora of mutations elsewhere in the genome contribute to tumor development in the reported tumors with SWI/SNF mutations.

Future Studies

The literature on the SWI/SNF complex is expanding rapidly, as can be seen by the number of citations in PubMed [76 in 2012 (queried on August 29th) and 105 in 2011, compared with 39 in 2000]. Consequently, we expect that we will learn much more about the function of the SWI/SNF complex in the coming years. However, whereas in past years the focus has been on elucidating the mechanisms that lead to an increased risk of malignancies, we expect this shift to also include the investigation of possible pathophysiological mechanisms leading to intellectual disability syndromes.

Furthermore, for (the parents of) patients with germline mutations in SWI/SNF components it is important to know if they have an increased susceptibility to malignancies. Future studies may shed some light on this issue by investigating how often malignancies are observed in these patients. To this end, it will be important to keep following up on the patients with germline mutations and record any malignancy that is detected.

Since inactivating mutations in SWI/SNF have been shown to lead to DNA repair defects and impair cell survival in response to genotoxic insult,¹ we may expect tumor sensitivity after local radiation therapy (which kills cancer cells

by damaging their DNA) in SWI/SNF patients. However, whole-body exposure of these patients to, for example, DNA-damaging chemotherapies should probably be avoided until more research has been done on this subject. Hopefully, the following years will provide us with enough information to be able to inform the patients and their parents on prognosis and better treatment of SWI/SNF-related malignancies.

Acknowledgments

We would like to thank Thomas Costelloe and Emmelien Aten for their valuable comments on an earlier version of this manuscript. HvA receives funding from the Netherlands Organization for Scientific Research (VIDI and TOP-GO grants) and Human Frontiers Science Program (HFSP-CDA grant).

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