Published in final edited form as:

Curr Opin Neurobiol. 2013 December ; 23(6): . doi:10.1016/j.conb.2013.09.003.

Creating a neural specific chromatin landscape by npBAF and nBAF complexes

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Abstract

Several features make the chromatin environment of neurons likely to be different than any other cell type. These include the fact that several hundred types of neurons exist, each requiring specialized patterns of gene expression and in turn specialized chromatin landscapes. In addition, neurons have the most stable morphology of any cell type, a unique feature essential for memory. Yet these stable morphologies must allow the emergence of new stable morphologies in response to environmental influences permitting learning to occur by altered morphology and new synapse formation. Several years ago we found that neurons have specific chromatin remodeling mechanisms not present in any other cell type that are produced by combinatorial assembly of ATP-dependent chromatin remodeling complexes. The neural specific subunits are essential for normal neural development, learning and memory. Remarkably, recreating these neural specific complexes in fibroblasts leads to their conversion to neurons. Recently, the subunits of these complexes have been found to have genetically dominant roles in several human neurologic diseases. The genetic dominance of these mutations suggests that less severe mutations will contribute to phenotypic variation in human neuronally derived traits.

Introduction

Several hundred types of neurons are present in mammals that are united by common characteristics including axons, dendrites, synapse formation and almost always a need for a remarkably stable morphology. Indeed, in certain species such as the long-lived Bowhead whale, dendritic morphologies might persist for over 200 years. Yet these stable morphologies must be modified to allow learning. One mechanism of maintaining a stable morphology would be to stabilize gene expression, particularly of genes involved in maintaining cytoskeletal features that underlie axon and dendrite formation. Such stabilization of gene expression might be produced by specialized chromatin regulatory mechanisms that also have the ability to be activated to allow new morphologies and synaptic plasticity in response to learning. Several years ago we began looking for such chromatin regulatory mechanisms and found that neurons do indeed have specialized chromatin remodeling complexes not found in any other tissue and that these complexes are necessary to convey signals produced by action potentials to regulate genes in the nucleus

[1*,2,3**,4]. We will focus this brief review on the biochemistry and genetics in mice and humans of these neuron specific chromatin regulators known as npBAF and nBAF in neural progenitors and neurons respectively.

Chromatin regulation

The mechanisms involved in packaging around 2 m of DNA into a 5 μ m nucleus, while retaining the ability to replicate and selectively express genes has been the focus of much of chromatin biology. At least three mechanisms are thought to be involved in this process including DNA methylation, histone modification and ATP-dependent chromatin remodeling. In vertebrates 29 known genes encode the ATPases of chromatin remodeling complexes; most of which have not been extensively characterized [5]. These ATPase complexes are generally thought to promote accessibility of regulatory DNA sequences by using the energy provided by the core ATPase to increase nucleosome mobility. This review will focus on ATP-dependent chromatin remodeling by complexes based on the Brg and Brm ATPases, which are alternative subunits of BAF (Brg/Brm Associated Factors) aka mSWI/SNF complexes. In higher vertebrates these complexes are produced by combinatorial assembly of subunits encoded by gene families resulting in many possible complexes, some of which are found only in the nervous system. In mammals the neural specific npBAF and nBAF complexes have 15 subunits encoded by 28 genes (Figure 1). Six of the 15 subunits are encoded by genes that have homologs in the yeast SWI/SNF complex, while the other subunits are of more recent evolutionary origin [6*]. When we initially purified the mammalian complexes [1*,3**,4,7*,8,9,10*, 11*, 12] we first called them mammalian or mSWI/SNF; however, upon more extensive study we learned that most of the subunits do not have yeast homologs and therefore prefer the nomenclature: BAF-molecular weight. The official HUGO nomenclature, Swi/Snf-like, Matrix associated, Actin-dependent Regulator of Chromatin (SMARC) was derived from our initial observation that the complexes contained β -actin and bound to the nuclear matrix fraction. Unfortunately, the SMARC nomenclature was extended to other proteins that are not associated with β -actin and are not matrix-associated.

The development of the nervous system is accompanied by sequential changes in chromatin remodeling mechanisms

As pluripotent embryonic stem (ES) cells develop to multi-potent neural progenitors and later to neurons, BAF complexes undergo sequential changes from esBAF to npBAF to nBAF (Figure 1). Pluripotent ES cells require the expression of esBAF chromatin remodeling complexes to fine-tune the expression of pluripotency genes such as Oct4 and Sox2 [13]. esBAF complexes are characterized by the presence of Brg, BAF250a, BAF155, BAF60a and 60b and the absence of Brm, BAF250b, BAF170, and BAF60c [11*]. Mutation of the genes selectively expressed in esBAF complexes leads to loss of pluripotency and preimplantation lethality, while the alternative subunits are dispensable for pluripotency and instead produce specific phenotypes later in development [1,2,14*,15**,16*,42**]. As ES cells are induced to differentiate into neurons these complexes begin to switch subunits with the initial appearance of BAF45c, BAF60c and BAF250b in neural progenitors eventually leading to a specific subunit composition in neurons, which to date has not been detected in any other cell type. Presently, it appears that no other chromatin remodeling mechanism is specific only to neurons, raising the question of the role of nBAF complexes in the nervous system. Interestingly, the neural specific subunits, BAF53b, BAF45b, BAF45c and CREST arose most recently in higher vertebrates, perhaps corresponding to the need for a more complex vertebrate nervous system. However, the role of BAF complexes in dendritic morphogenesis is evolutionarily conserved as genetic screens in *Drosophila* for genes that perturb dendritic patterns have identified orthologues of six BAF subunits [17**,18*].

Switching from the neural progenitor to the neural BAF complexes is controlled by a triple negative genetic switch

The switch of three subunits from npBAF to nBAF is remarkably precise with little overlap in expression patterns (Figure 2). The switch corresponds to mitotic exit and it appears that the switch must happen within one cell generation and perhaps within only a fraction of the last cell cycle. Removal of BAF53a, BAF45a or SS18 leads to cell cycle exit, while forcing the expression of the BAF45a subunit leads to additional cell cycles [3⁴,4]. Thus it appears one of the roles of the npBAF complex is to promote cell cycle progression. Deletion of the post mitotic subunits leads to developmental failure of neuronal specific traits such as dendritic morphogenesis and synaptogenesis with death at birth due to a failure to nurse [2,16⁵]. These genetic findings told us that the switching mechanism is critical to neural development, but what brought about the switch?

To uncover the mechanism underlying subunit switching we assumed that it would be controlled by a transcriptional switch. We analyzed BAF53a cis-regulation using carefully designed Bacterial Artificial Chromosomes-transgenic reporter mouse embryos. Surprisingly, all developmental regulation mapped to the evolutionarily conserved 3' untranslated region (UTR) of BAF53a [19⁶]. Further analysis of the BAF53a 3'UTR led to the realization that the critical sequences for BAF53a repression were predicted binding sites of the micro-RNA's miR-9* and miR-124 and that binding sites for both were required for full repression of BAF53a (Figure 3). The requirement of two microRNA's functions like a molecular 'AND' switch where both miR-9* and miR-124 function synergistically and are simultaneously required for full repression of BAF53a (reviewed in [20]). miR-9* and miR-124 are activated at the last mitotic division of neural progenitors in the cells lining the ventricles and in post mitotic neurons (Figure 2) [21]. This expression pattern nicely fits the disappearance of BAF53a, during the final neural progenitor division that is often asymmetric, generating a neural progenitor and a neuron. Thus as miR-9* and miR-124 appear, BAF53a is repressed. This turn of events focused attention on the regulators of miR-9* and miR-124. These microRNA's are each encoded by 3 genes and are under negative regulation by the transcriptional repressor REST [22]. REST restricts the expression of neuronal genes by repressing neuronal genes in non-neuronal cells. REST probably does not account for all of the repression of miR-9* and miR-124 because the level of repression produced by REST is about 3-fold to 5-fold, while miR-9* and miR-124 are activated several hundred fold at the time of the last mitotic division (Figure 2) [4,22]. This told us something about how BAF53a was repressed by miR-9*/miR-124, but what gave rise to the activation of the nBAF subunit BAF53b, which replaces BAF53a?

In part the activation of BAF53b at mitotic exit appears to be due to protein stability. When BAF53b is deleted we find that BAF53a attempts to take its place and persist into adult post mitotic neurons (unpublished results). However, replacing BAF53b with BAF53a is not sufficient to rescue lethality, because a unique protein domain of BAF53b (subdomain 2 shown in box in Figure 3c) is essential for dendritic morphogenesis, a function that cannot be replaced by BAF53a [2]. These observations lead us to propose a triple negative genetic switch, which drives the conversion of npBAF to nBAF (Figure 3a). It should be noted that this switch is coordinated with the replacement of a general splicing factor PTBP1 by a neural specific homolog that affects splicing patterns in neurons [21].

Recapitulating the micro-RNA/chromatin switch converts human fibroblasts to neurons

During the course of these studies aimed at defining the genetic circuitry underlying epigenetic switching we noted that co-expression of miR-9* and miR-124 in non-neuronal cell types caused the cells to take on neuronal morphologies, express MAP-2 and activate each of the neuronal specific nBAF subunits: BAF45b, BAF45c, BAF53b and CREST. However, co-expression of miR9* and miR-124 alone converted cells with low efficiency (<5%) so neurogenic transcription factors were expressed with the miRNA's. MiR-9*/miR-124 plus Neu-roD2 increased the frequency of conversion to MAP2+ neurons to 50% and closer inspection of the converted human fibroblasts revealed that they produce functional synapses that take up synaptic components and in turn release them upon depolarization [23**]. The converted cells also made action potentials, but few developed repetitive action potentials. Thus the cells converted with miR-9*/miR-124 and NeuroD2 appeared to be immature neurons. Pioneering studies done in the laboratory of Marius Wernig provided a key helper factor. Wernig and colleagues had systematically examined the transcription factors that might convert fibroblasts into neurons in much the same way that Yamanaka and colleagues defined factors that could convert fibroblasts to IPS cells [24]. Their studies defined a group of transcription factors that when overexpressed in mouse fibroblasts lead to neuronal conversion, most remarkably they found that a combination of four transcription factors would produce fully functional, mature murine neurons [25**]. These observations lead us to try a combination of miR-9*/miR-124, NeuroD2, Ascl1 and Myt1L which turned out to be particularly effective at converting human fibroblasts to fully functional and mature neurons that made repetitive action potentials [23**]. Interestingly, miR-9*/miR-124 mediated conversion worked much better with human cells and could reprogram dermal fibro-blasts from individuals as old as 45, the oldest sample we tested. In contrast, the transcription factor mediated conversion worked better with murine cells and was not effective to convert the fibroblasts of older individuals [25**,26]. The mechanisms involved in the conversion of fibroblasts to neurons by this microRNA/chromatin switch have been recently reviewed [27].

Mutations in BAF subunits have genetically dominant roles in human intellectual disability

If the npBAF to nBAF genetic switch was a major determinant of the neuronal state then one might expect that mutations in its components would produce human neurologic disease. Within several months of our discovery of the instructive role of this circuitry in neuronal determination, human exome sequencing studies of neurologic diseases began to reveal that mutations in components of this circuitry were targets of several human neurologic diseases (Table 1). The first disease to be associated with mutations in BAF subunits was Nicolaides–Baraitser syndrome (NCBRS), which is characterized by marked language impairment, intellectual disability, occasional microcephaly, growth deficiency, coarse facial features, hair abnormalities (hypertrichosis and sparse scalp hair) and digit abnormalities [28**,29]. Thirty-six of 44 individuals with NCBRS had a missense or in-frame deletion of *BRM*. Very shortly after these reports, individuals with Coffin–Siris syndrome (CSS) were found to have mutations in one of 5 BAF subunits BAF250A, BAF250B, Brg, BAF57 and BAF47 [30**,31**,44,45]. Although CSS and NCBRS are different clinical entities, they are both characterized by intellectual disability, hair abnormalities and digit abnormalities (with CSS individuals exhibiting hypoplas-tic/absent fifth fingernails). Further, additional sequencing efforts revealed that mutation of one allele of BAF250b accounted for a very significant percentage, 0.9%, of sporadic intellectual disability [32*,33,34]. In each case the mutations involved appeared to occur on only one

allele indicating they are genetically dominant. Closer inspection of the actual BAF250a or *BAF250b* mutations indicates that all are non-sense or frameshift mutations or whole-gene deletions predicted to produce no protein indicating that they can be haploinsufficient. In contrast many of the NCBRS *BRM* and CSS *Brg* mutations are missense changes that cluster to the ATP binding and helicase domains suggesting that they might produce a structurally unchanged but catalytically compromised dominant negative or a minor reduction in function of BRM or Brg and hence the BAF complexes. On the basis of the prevalence of BAF subunit mutations in CSS and sporadic intellectual disability it has been suggested that up to 3% of unexplained intellectual disability might be caused by mutations in genes encoding BAF subunits [30[•],33,35]. The genetic dominance is consistent with studies in mice, where heterozygous mice with null mutations of *Brg* or *Baf155* show neural developmental phenotypes such as a failure of neural tube closure [14[•],36].

Infrequent mutation of BAF subunits in autism and schizophrenia

Exome sequencing studies of autism have found mutations in BAF250b, BAF180, BAF170, BAF155 and REST, the later of which controls BAF subunit switching (Table 1) [37[•],38]. *De novo* mutations in *BAF250b* have been discovered in rare cases of human schizophrenia. Single nucleotide polymorphisms (SNPs) in *BRM* have been associated with schizophrenia [39]. The rarity of these mutations make it difficult to comment on their potential role in these diseases and additional studies will be necessary to determine if the infrequency with which they have been identified is due to genetic background or environmental interactions that determine the penetrance of these mutations. However, the finding that the defects in *Brm*-mutant and BAF53b-mutant mice appear to derive from abnormal postsynaptic components, such as dendritic spine structure and function, that ultimately leads to deficits in synaptic plasticity is consistent with defects found in humans with schizophrenia [16[•],40].

Mutation of the BAF subunit CREST in amyotrophic lateral sclerosis (ALS)

ALS, also known as Lou Gehrig's disease, is a fatal adult-onset neurodegenerative disease characterized by loss of motor neurons [41]. Although ~10% of cases have a family history of ALS, the majority of cases are sporadic. Exome sequencing of ALS trios (ALS patient and both unaffected parents) found *de novo* mutations in the nBAF subunit CREST [42[•]]. CREST is a paralog of SS18, appears to have co-evolved with vertebrate tetrapod evolution and is required for activity dependent dendritic morphogenesis [4,15[•]]. The pathophysiological connection between the neurodevelopmental and neurodegenerative roles of BAF complexes will be an area of future study that will benefit from sequencing BAF genes in patients with ALS and testing the resulting alleles in assays designed to test molecular mechanisms of development and disease.

BAF subunits as determinants of human phenotypic variation

One of the most exciting results of exome sequencing studies in human disease is that they will almost certainly give insight into human phenotypic variation resulting from mutations that produce only minor compromised function of a gene product. The genes that are dominant for a trait would be expected to contribute more to phenotypic variation, because only one allele needs to be mutated to produce a phenotype. Exome sequencing studies have found that mutations in BAF subunits are contributors to intellectual disability syndromes and sporadic intellectual disability. Analysis of the mutations that produce these syndromes strongly support a genetically dominant role, since alleles of BAF subunits predicted to produce no protein give rise to intellectual disability. These observations permit one to speculate that a series of weak alleles will be associated with variations in human intellectual ability. Needless to say this speculation will need much additional testing.

On the basis of the genetic dominance of BAF subunits in neural development and function we predict that some aspect of chromatin structure regulated by BAF complexes is rate limiting for one or more steps within the genetic circuitry of neural development. This is consistent with the instructive regulatory ability of BAF subunit switching in neural fate determination, because modulation of rate limiting steps within a circuitry or pathway will in general result in greater phenotypic change than modulation of the steps that are not rate limiting. Discovery of these rate limiting steps carried out by the cell type specific, combinatorially assembled BAF complexes will likely contribute to our understanding of human neural development and intellectual abilities.

Acknowledgments

We thank all members of the Crabtree Lab for engaging discussions on this topic and especially thank Dr. Andrew Yoo for critically reading the manuscript. GRC is funded by grants from the National Institutes of Health and the Howard Hughes Medical Institute.

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Figure 1.

BAF complexes switch subunits when REST protein levels decrease relieving repression on miR-9* and miR-124 which both repress BAF53a. Exome sequencing has implicated different subunits (indicated by color) in the human diseases indicated on the left. Note the large number of domains that recognize histone modifications and bind DNA directly and hence could target the complexes to different genomic loci without the need for DNA binding proteins.

Figure 2.

(a) Mutually exclusive expression of BAF45a and BAF45b in the murine neural tube at E11.5. Proliferating cells lining the neural tube ventricle contain BAF complexes with BAF45a, while post mitotic neurons contain BAF complexes with BAF45b. **(b)** Expression of miR-9* (green) [19**]. Note that miR-9* is first expressed along the ventricle of the developing neural tube, in what is probably the last progenitor cell division and then continues to be expressed as new-born neurons migrate laterally through the progenitor zone into the **(c)** β -Tubulin III positive post mitotic zone. MiR-124 has been shown to be expressed in a similar pattern [21]. Thus both miR-9* and miR-124 are first activated just before the repression of BAF53a, BAF45a, and SS18 which is consistent with the genetic circuitry shown in Figure 3.

Figure 3.

A MicroRNA/chromatin switch is required for mammalian neural development. **(a)** Summary of regulatory relationships by which miR-9* and miR-124 control neuronal specific splicing, Notch signaling and neuronal specific chromatin. The positive autoregulatory mechanisms shown with a '?' indicate that they are not validated. **(b)** MiR-9* and miR-124 bind to three sites in the BAF53a 3'UTR and silence it near mitotic exit. **(c)** Predicted structures of BAF53a and BAF53b showing that subdomain 2 (shown in the box) is the most divergent region [43].

Table 1

BAF subunit mutations found in individuals with intellectual disabilities and neurological disease

Disease	Human gene	BAF subunit	Position	CDS mutation	AA mutation	Type of mutation	Inheritance	Mutation count	PMID	Reference
ALS	<i>CREST</i>	CREST	123	c.369T>G	p.Ile123Met	Substitution_missense	family history	1	23708140	Chesi <i>et al.</i> [42••]
ALS	<i>CREST</i>	CREST	388	c.1162C>T	p.Gln388*	Substitution_nonsense, deletes last 9aa	<i>de novo</i>	1	23708140	
ASD	<i>SMARCC1</i>	BAF155	742	c.2225A>G	p.Gln742Arg	Substitution_missense	family history	1	22495311	Neale <i>et al.</i> [38]
ASD	<i>SMARCC2</i>	BAF170		c.1770+1;c.1863+1		Splice Site	<i>de novo</i>	1	22495311	
ASD	<i>PBRM1</i>	BAF180	763		p.Asp763Gly	Substitution_missense	<i>de novo</i>	1	22495309	O’Roak <i>et al.</i> [37]
ASD	<i>ARID1B</i>	BAF250B	514	chr6:157,192,247_157,473,298del	p.514fs*20_0.2 Mb deletion_exons 4–6	Deletion_frameshift	<i>de novo</i>	1	21448237	Nord <i>et al.</i> [46]
ASD	<i>ARID1B</i>	BAF250B	1797	chr6:157527664	p.Leu1797fs	Frameshift	<i>de novo</i>	1	22495309	
ASD	<i>REST</i>	REST	993	c.2978C>G	p.Pro993Arg	Substitution_missense	<i>de novo</i>	1	22495311	
CSS	<i>SMARCB1</i>	BAF47	363	c.1089G>T	p.Lys363Asn	Substitution_missense	<i>de novo</i>	1	23929686	Santen <i>et al.</i> [44]
CSS	<i>SMARCB1</i>	BAF47	364	c.1091_1093del AGA	p.Lys364del	Deletion_inframe	<i>de novo</i> , 6/9, nc, 3/9	9	22426308/23815551/23929686	Tsunasaki <i>et al.</i> [30••]/ Tsunasaki <i>et al.</i> [45]
CSS	<i>SMARCB1</i>	BAF47	377	c.1130G>A	p.Arg377His	Substitution_missense	<i>de novo</i>	1	22426308	
CSS	<i>SMARCE1</i>	BAF57	73	c.218A>G	p.Tyr73Cys	Substitution_missense	<i>de novo</i>	1	22426308	
CSS	<i>SMARCE1</i>	BAF57	105	c.314G>A	p.Arg105Gln	Substitution_missense	in affected mother	1	23929686	
CSS	<i>SMARCA4</i>	Brγ	450	c.1349C>A	p.Ala450Asp	Substitution_missense	<i>de novo</i>	1	23929686	
CSS	<i>SMARCA4</i>	Brγ	458	c.1372_1395del	p.Lys458_Glu465del	Deletion_inframe	<i>de novo</i>	1	23815551	
CSS	<i>SMARCA4</i>	Brγ	546	c.1636_1638del AAG	p.Lys546del	Deletion_inframe	<i>de novo</i>	1	22426308	
CSS	<i>SMARCA4</i>	Brγ	859	c.2576C>T	p.Thr859Met	Substitution_missense	<i>de novo</i>	1	22426308	
CSS	<i>SMARCA4</i>	Brγ	885	c.2653C>T	p.Arg885Cys	Substitution_missense	<i>de novo</i>	1	22426308	
CSS	<i>SMARCA4</i>	Brγ	885	c.2654G>A	p.Arg885His	Substitution_missense	<i>de novo</i>	1	23815551	
CSS	<i>SMARCA4</i>	Brγ	921	c.2761C>T	p.Leu921Phe	Substitution_missense	<i>de novo</i>	1	22426308	
CSS	<i>SMARCA4</i>	Brγ	1011	c.3032T>C	p.Met1011Thr	Substitution_missense	<i>de novo</i>	1	22426308	
CSS	<i>SMARCA4</i>	Brγ	1043	c.3127C>T	p.Arg1043Trp	Substitution_missense	<i>de novo</i>	1	23929686	
CSS	<i>SMARCA4</i>	Brγ	1127	c.3380A>G	p.Asp1127Gly	Substitution_missense	<i>not in mother</i>	1	23929686	

Disease	Human gene	BAF subunit	Position	CDS mutation	AA mutation	Type of mutation	Inheritance	Mutation count	PMID	Reference
CSS	<i>SMARCA4</i>	Brg	1157	c.3469C>G	p.Arg1157Gly	Substitution_missense	<i>de novo</i>	1	22426308	
CSS	<i>SMARCA4</i>	Brg	1203	c.3608G>A	p.Arg1203His	Substitution_missense	<i>nc</i>	1	23929686	
CSS	<i>ARID1A</i>	BAF250A	11	c.31_56del	p.Ser11Alafs*91	Deletion_frameshift	<i>nc</i>	1	22426308	
CSS	<i>ARID1A</i>	BAF250A	920	c.2758C>T	p.Gln920*	Substitution_nonsense	<i>nc</i>	1	22426308	
CSS	<i>ARID1A</i>	BAF250A	1335	c.4003C>T	p.Arg1335*	Substitution_nonsense	<i>de novo</i>	1	22426308	
CSS	<i>ARID1A</i>	BAF250A	1113	c.1113del	p.Gln372Serfs*19	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1A</i>	BAF250A	3679	c.3679G>T	p.Glu1227*	Substitution_nonsense	<i>de novo</i>	1	23929686	
CSS	<i>ARID1A</i>	BAF250A	6493	c.6493G>T	p.Glu2165*	Substitution_nonsense	Not in father	1	23929686	
CSS	<i>ARID1A</i>	BAF250A	6532	c.6532del	p.Asp2178Thrfs*22	Deletion_frameshift	<i>nc</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	exons 1–20	Whole gene deletion	<i>p.0</i>	Deletion	<i>nc</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	408	c.1222dup	p.Gln408Profs*127	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	413	c.1235dup	p.Ser413Valfs*122	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	420	c.1259dup	p.Asn420Lysfs*115	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	449	c.1346del	p.Pro449Argfs*53	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	464	c.1389_1398del	p.Ala464Serfs*35	Deletion_frameshift	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	467	c.1392_1402del	p.Gln467Argfs*64	Deletion_frameshift	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	exon 1	c.1542+1G>A	r.sp1?	Substitution_splice site	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	560	c.1678_1688del	p.Ile560Glyfs*89	Deletion_frameshift	<i>de novo</i>	1	22426308	
CSS	<i>ARID1B</i>	BAF250B	572	c.1713del	p.Gly572Gluifs*21	Deletion_frameshift	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	635	c.1903C>T	p.Gln635*	Substitution_nonsense	<i>de novo</i>	1	22426308	
CSS	<i>ARID1B</i>	BAF250B	688	c.2062del	p.Leu688Serfs*9	Deletion_frameshift	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	715	c.2144C>T	p.Pro715Leu	Substitution_missense	<i>de novo</i>	1	22426308	
CSS	<i>ARID1B</i>	BAF250B	exons 6–9	exon 6–9del	<i>p.0</i>	Deletion	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	867	c.2598del	p.Tyr867Thrfs*47	Deletion_frameshift	<i>nc</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	935	c.2803dup	p.Met935Asnfs*7	Deletion_frameshift	<i>nc</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	959	c.2877del	p.Ser959Argfs*9	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	964	c.2891_2892insAC	p.Phe964Leufs*5	Deletion_frameshift	<i>de novo</i>	1	23815551	

Disease	Human gene	BAF subunit	Position	CDS mutation	AA mutation	Type of mutation	Inheritance	Mutation count	PMID	Reference
CSS	<i>ARID1B</i>	BAF250B	1000	c.2998del	p.Ala1000Argfs*5	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	exon 11	c.3135+1G>C	r.sp!?	Substitution_splice site	not in mother	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	1075	c.3223C>T	p.Arg1075*	Substitution_nonsense	<i>de novo</i>	1	22426309	Santen <i>et al.</i> [31••]
CSS	<i>ARID1B</i>	BAF250B	1102	c.3304C>T	p.Arg1102*	Substitution_nonsense	<i>de novo</i>	1	22426308	
CSS	<i>ARID1B</i>	BAF250B	1161	c.3481G>T	p.Glu1161*	Substitution_nonsense	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	1283	c.3846dup	p.Gly1283Trpfs*38	Duplication_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	1366	c.4098C>G	p.Tyr1366*	Substitution_nonsense	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	1337	c.4009C<T	p.Arg1337*	Substitution_nonsense	<i>nc</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	1489	c.4448_4449ins14	p.Pro1489Leufs*10	Insertion_frameshift	<i>nc</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	1540	c.4620C>A	p.Tyr1540*	Substitution_nonsense	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	1541	c.4619_4628del	p.Gln1541Argfs*35	Deletion_frameshift	<i>de novo</i>	1	22426309	
CSS	<i>ARID1B</i>	BAF250B	1607	c.4820_4825delinsAGGCT	p.Thr1607Lysfs*7	Deletion_frameshift	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	1609	c.4821del	p.Pro1609Leufs*5	Deletion_frameshift	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	1637	c.4911_4915del	p.Trp1637Cysfs*6	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	1637	c.4911G>A	p.Trp1637*	Substitution_nonsense	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	1639	c.4916_4917del	p.Val1639Aspfs*5	Deletion_frameshift	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	1777	c.5329A>T	p.Lys1777*	Substitution_nonsense	<i>de novo</i>	1	22426309	
CSS	<i>ARID1B</i>	BAF250B	1798	c.5394_5397del	p.Phe1798Leufs*52	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	1875	c.5623_5625delins-TGACGTCT	p.Ala1875*	Substitution_nonsense	<i>nc</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	1878	c.5632del G	p.Asp1878Metfs*96	Deletion_frameshift	<i>nc</i>	1	22426308	
CSS	<i>ARID1B</i>	BAF250B	1879	c.5635delG	p.Asp1879Thrfs*95	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	1990	c.5968C>T	p.Arg1990*	Substitution_nonsense	Not in mother/nc/ <i>de novo</i>	3	23929686	
CSS	<i>ARID1B</i>	BAF250B	2013	c.6038G>A	p.Trp2013*	Substitution_nonsense	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	2040	c.6120C>G	p.Tyr2040*	Substitution_nonsense	<i>nc</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	2078	c.6233del	p.Pro2078Leufs*21	Deletion_frameshift	<i>de novo</i>	1	23929686	
CSS	<i>ARID1B</i>	BAF250B	2128	c.6382C>T	p.Arg2128*	Substitution_nonsense	<i>de novo</i>	1	23815551	

Disease	Human gene	BAF subunit	Position	CDS mutation	AA mutation	Type of mutation	Inheritance	Mutation count	PMID	Reference
CSS	<i>ARID1B</i>	BAF250B	2172	c.6516C>G	p.Tyr2172*	Substitution_nonsense	<i>de novo</i>	1	23815551	
CSS	<i>ARID1B</i>	BAF250B	2234	c.6700_6701del	p.Leu2234Glyfs*7	Deletion_frameshift	nc	1	23929686	
CSS	<i>ARID1B</i>	BAF250B				Microdeletion	nc	1	22426308	
ID	<i>ARID1B</i>	BAF250B	372		p.Arg372Profs*163	Frameshift	<i>de novo</i>	1	22405089	Hoyer <i>et al.</i> [33]
ID	<i>ARID1B</i>	BAF250B	1102		p.Arg1102*	Substitution_nonsense	<i>de novo</i>	1	22405089	
ID	<i>ARID1B</i>	BAF250B	1108		p.Lys1108Argfs*9	Frameshift	<i>de novo</i>	1	22405089	
ID	<i>ARID1B</i>	BAF250B	1307		p.Gln1307*	Substitution_nonsense	<i>de novo</i>	1	22405089	
ID	<i>ARID1B</i>	BAF250B	1338		p.Arg1338Argfs*76	Frameshift	<i>de novo</i>	1	22405089	
ID	<i>ARID1B</i>	BAF250B	1346		p.Tyr1346*	Substitution_nonsense	<i>de novo</i>	1	22405089	
ID	<i>ARID1B</i>	BAF250B	2155		p.Ser2155Leufs*33	Frameshift	<i>de novo</i>	1	22405089	
ID	<i>SMARCB1</i>	BAF47	37	c.110G>A	p.Arg37His	Substitution_missense	<i>de novo</i>	1	22726846	Kleefstra T, Am J Hum Genet. 2012
ID/ASD/ACC/SSI	<i>ARID1B</i>	BAF250B		Breakpoint intron 5; chr6: 157,292,076– 157,292,079	3 bp deletion/insertion of 22 bps that match uniquely to a LINE sequence at chromosome 7	Translocation t(1;6)(p31.1;q25.3), truncation	<i>de novo</i>	1	21801163	Halgren <i>et al.</i> [32]
ID/ASD/ACC/SSI	<i>ARID1B</i>	BAF250B		Breakpoint intron 5	<i>ARID1B-MRPP3</i> fusion and reciprocal fusion	Translocation t(6; 14)(q25.3; q13.2), gene fusion	<i>de novo</i>	1	21042007	Backx <i>et al.</i> [34]
ID/ASD/ACC-ne/SSI	<i>ARID1B</i>	BAF250B			0.2 Mb deletion_exons 4–8	Deletion	<i>de novo</i>	1	21801163	
ID/ASD/ACC-ne/SSI	<i>ARID1B</i>	BAF250B			0.6 Mb deletion_exons 2–20	Deletion	<i>de novo</i>	1	21801163	
ID/ASD/SSI	<i>ARID1B</i>	BAF250B			1.0 Mb deletion_exons 1–8	Deletion	<i>de novo</i>	1	21801163	
ID/ASD-ne/ACC-ne/SSI	<i>ARID1B</i>	BAF250B			2.7 Mb deletion_5 RefSeq genes incl. <i>ARID1B</i>	Deletion	<i>de novo</i>	1	21801163	
ID/ASD/ACC- partial/SSI	<i>ARID1B</i>	BAF250B			4.6 Mb deletion_15 RefSeq genes incl. <i>ARID1B</i> , exons 1–7	Deletion	<i>de novo</i>	1	21801163	

Disease	Human gene	BAF subunit	Position	CDS mutation	AA mutation	Type of mutation	Inheritance	Mutation count	PMID	Reference
ID/ACC- partial/SSI	<i>ARID1B</i>	BAF250B			8.2 Mb deletion_33 RefSeq genes incl. <i>ARID1B</i>	Deletion	<i>de novo</i>	1	21801163	
ID/ACC- hypoplasia/SSI	<i>ARID1B</i>	BAF250B			14.5 Mb deletion_73 RefSeq genes incl. <i>ARID1B</i>	Deletion	<i>de novo</i>	1	21801163	
NBS	<i>SMARCA2</i>	Brm	752	c.2255G>C	p.Gly752Ala	Substitution_missense	<i>de novo</i>	2	22366787	Van Houdt <i>et al.</i> [28••]
NBS	<i>SMARCA2</i>	Brm	755	c.2264A>G	p.Lys755Arg	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	756	c.2267C>T	p.Thr756Ile	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	851	c.2551G>C	p.Asp851His	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	852	c.2556A>C	p.Glu852Asp	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	852	c.2554G>A	p.Glu852Lys	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	854	c.2560C>A c.2562C>A	p.His854Leu	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	854	c.2561A>G	p.His854Arg	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	855	c.2563C>G	p.Arg855Gly	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	881	c.2642G>T	p.Gly881Val	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	881	c.2641G>C	p.Gly881Arg	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	883	c.2648C>T	p.Pro883Leu	Substitution_missense	<i>de novo</i>	3	22366787	
NBS	<i>SMARCA2</i>	Brm	939	c.2815C>T	p.His939Tyr	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	946	c.2837T>C	p.Leu946Ser	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	946	c.2838A>T	p.Leu946Phe	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	1105	c.3313C>T	p.Arg1105Cys	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	1105	c.3314G>C	p.Arg1105Pro	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	1132		p.Gly1132Asp	Substitution_missense	<i>de novo</i>	1	22822383	Wolff <i>et al.</i> [29]
NBS	<i>SMARCA2</i>	Brm	1135	c.3404T>C	p.Leu1135Pro	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	1146	c.3436A>C	p.Ser1146Arg	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	1158	c.3473A>T	p.Asp1158Val	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	1159	c.3476G>A	p.Arg1159Gln	Substitution_missense	<i>de novo</i>	2	22366787	
NBS	<i>SMARCA2</i>	Brm	1159	c.3475C>G	p.Arg1159Gly	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	1159	c.3476G>T	p.Arg1159Leu	Substitution_missense	<i>de novo</i>	1	22366787	
NBS	<i>SMARCA2</i>	Brm	1162	c.3485G>A	p.Arg1162His	Substitution_missense	<i>de novo</i>	2	22366787	

Disease	Human gene	BAF subunit	Position	CDS mutation	AA mutation	Type of mutation	Inheritance	Mutation count	PMID	Reference
NBS	SMARCA2	Brr1	1188	c.3562G>C	p.Ala1188Pro	Substitution_missense	de novo	1	22366787	
NBS	SMARCA2	Brr1	1188		p.Ala1188Glu	Substitution_missense	de novo	1	22822383	
NBS	SMARCA2	Brr1	1201	c.3602C>T	p.Ala1201Val	Substitution_missense	de novo	3	22366787	
NBS	SMARCA2	Brr1	1202	c.3604G>T	p.Gly1202Cys	Substitution_missense	de novo	1	22366787	
NBS	SMARCA2	Brr1	1205	c.3614A>G	p.Asp1205Gly	Substitution_missense	de novo	1	22366787	
NBS	SMARCA2	Brr1	1213	c.3637C>T	p.Arg1213Trp	Substitution_missense	de novo	1	22366787	
NBS*	SMARCA2	Brr1	852	c.2554G>C	p.Glu852Gln	Substitution_missense	de novo	1	23929686	
NBS*	SMARCA2	Brr1	939	c.2815C>T	p.His939Tyr	Substitution_missense	de novo	1	23929686	
NBS*	SMARCA2	Brr1	1098	c.3293G>A	p.Gly1098Asp	Substitution_missense	nc	1	23929686	
NBS*	SMARCA2	Brr1	1105	c.3314G>A	p.Arg1105His	Substitution_missense	de novo	1	23929686	
SZ	SMARCA2	Brr1	Intron 12	rs3763627		SNP	de novo	1	19363039	Koga et al. [39]
SZ	SMARCA2	Brr1	Intron 19	rs3793490		SNP	de novo	1	19363039	
SZ	SMARCA2	Brr1	1546	rs2296212	p.Asp1546Glu	SNP	de novo	1	19363039	

Abbreviations: ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; CSS, Coffin–Siris syndrome; ID, intellectual disability; NBS, Nicolaides–Baraitser syndrome; SZ, schizophrenia; SNP, single nucleotide polymorphism; ACC, agenesis of corpus colosum; SSI, Severe speech impairment; ne, not examined; nc, In the inheritance column indicates that parental DNA was not available for testing.

* Reclassified as NBS [44].