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Neuron-specific chromatin remodeling: A missing link in epigenetic mechanisms underlying synaptic plasticity, memory, and intellectual disability disorders

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Abstract

Long-term memory formation requires the coordinated regulation of gene expression. Until recently nucleosome remodeling, one of the major epigenetic mechanisms for controlling gene expression, had been largely unexplored in the field of neuroscience. Nucleosome remodeling is carried out by chromatin remodeling complexes (CRCs) that interact with DNA and histones to physically alter chromatin structure and ultimately regulate gene expression. Human exome sequencing and gene wide association studies have linked mutations in CRC subunits to intellectual disability disorders, autism spectrum disorder and schizophrenia. However, how mutations in CRC subunits were related to human cognitive disorders was unknown. There appears to be both developmental and adult specific roles for the neuron specific CRC nBAF (neuronal Brg1/hBrm Associated Factor). nBAF regulates gene expression required for dendritic arborization during development, and in the adult, contributes to long-term potentiation, a form of synaptic plasticity, and long-term memory. We propose that the nBAF complex is a novel epigenetic mechanism for regulating transcription required for long-lasting forms of synaptic plasticity and memory processes and that impaired nBAF function may result in human cognitive disorders.

Keywords

chromatin remodeling; nucleosome remodeling; epigenetics; long-term memory; long-term potentiation; intellectual disability disorder; autism spectrum disorder

1. Introduction

Researchers have known for several decades that long-term memory formation requires gene expression. Regulation of gene expression following learning requires access to DNA, which is highly compacted in chromatin (Alberini, 2009; Barrett and Wood, 2008). The basic repeating unit of chromatin is the nucleosome that consists of DNA wrapped around a histone octamer. Access to the DNA is controlled by many factors including changes in

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histone tail modifications, DNA methylation and the actual movement of nucleosomes along the DNA in a process called chromatin remodeling (Barrett and Wood, 2008; Hargreaves and Crabtree, 2011). To date the majority of the work on epigenetic regulation of gene expression during memory formation has focused on histone modifications (chromatin modification) and DNA methylation (see special issues in *Neurobiology of Learning and Memory* (2012) and *Neuropsychopharmacology Reviews* (2013)). Chromatin remodeling (not to be confused with chromatin modification), although widely studied in fields outside of neuroscience, had until recently only been examined in neuroscience in the context of neuronal development *in vitro*. The importance of further exploring this major epigenetic mechanism became increasingly apparent with recent human exome sequencing and genome wide association studies implicating mutations in components of the chromatin remodeling complex BAF (Brg1/hBrm Associated Factor) in intellectual disability disorders (Santen et al., 2012; Tsurusaki et al., 2012; Van Houdt et al., 2012), autism (Neale et al., 2012; O'Roak et al., 2012), and schizophrenia (Loe-Mie et al., 2010). It was unclear how the BAF subunit mutations were related to human cognitive deficits – were the deficits simply a by-product of developmental abnormalities or was there an additional role for chromatin remodeling complexes (CRCs) in the adult brain? The answer appears to be complex with an identified role for CRCs in both neuronal development and adult plasticity. This review will focus on the role of the neuron specific BAF complex (nBAF) in both neuronal development and long-term memory formation in the adult. Specifically, we propose that the nBAF complex is a novel epigenetic mechanism for regulating transcription required for long-lasting forms of synaptic plasticity and memory processes and that impaired nBAF function may result in human cognitive disorders.

2. Epigenetics in Long-Term Memory Formation

Many studies have recently focused on epigenetic mechanisms of transcriptional regulation in controlling gene expression underlying long-term memory formation (see special issues referenced above; and issues focused on this topic in this special issue of *Neuropharmacology*). In a broad sense, epigenetics refers to the regulation of gene expression via chromatin structure that is independent of changes in DNA sequence (Day and Sweatt, 2011; Vogel-Ciernia and Wood, 2012). There are at least five major epigenetic mechanisms by which chromatin structure is regulated to control gene expression: histone modification, histone variant insertion, DNA methylation, noncoding RNAs, and chromatin remodeling.

The consolidation of new learning requires coordinated expression of specific profiles of gene targets (for review see Alberini, 2009). Transcription initiation requires access to DNA for transcription factor and RNA polymerase binding. Within eukaryotic cells DNA is highly compacted (~10,000 fold) into chromatin. The repeating unit of chromatin is the nucleosome that consists of 147 base pairs of DNA wrapped around a histone octamer (canonically includes two of each of the following core histone proteins: H2A, H2B, H3, and H4) (Kouzarides, 2007). Histone variants can be incorporated into the nucleosome and may alter nucleosome stability (ie. H3.3/H2A.Z incorporation at active promoters and enhancers (Jin et al., 2009). Nucleosomes are spaced approximately every 10 to 50 base pairs, depending on the organism and cell type. At the entry and exit sites of the nucleosome core the DNA is bound by the linker histone H1 and under physiological conditions strings of nucleosomes form higher order secondary (ie. 30nm fiber) and tertiary structures (Clapier and Cairns, 2009).

Gaining access to regulatory regions of DNA (ie. promoters, enhancers and repressors regions) for transcriptional regulation can require modification of the surrounding chromatin environment including post translation modification of histone tails, DNA methylation,

histone variant insertion, nucleosome positioning, and alterations to higher order chromatin structure (e.g. *chromosomal looping* (Jiang et al., 2010). Post translation modification (phosphorylated, acetylated, methylated, etc) of histone tails can alter the interaction between DNA and the histone octamer, recruit histone or DNA-interacting proteins, and either promote or repress transcription (Bannister and Kouzarides, 2011). The regulation of histone modifications is one of the best studied epigenetic mechanisms in learning and memory and has been extensively reviewed elsewhere (Barrett and Wood, 2008; Gräff and Tsai, 2013; Peixoto and Abel, 2013; Vogel-Ciernia and Wood, 2012). Another increasingly studied epigenetic mechanism in learning and memory is DNA methylation (Baker-Andresen et al., 2013; Su and Tsai, 2012; Zovkic et al., 2013). DNA methylation appears to play a critical role in long-term memory (Lubin and Roth, 2008; Miller et al., 2010; Miller and Sweatt, 2007) and long-term potentiation (Levenson et al., 2006). Experience dependent DNA methylation has been proposed to alter the transcriptional response to subsequent learning events serving as a form of cellular metaplasticity (for review see (Baker-Andresen et al., 2013)). New evidence also points to a critical role for non-coding RNAs in regulating long-term memory (Bredy et al., 2011; Landry et al., 2013) and drug addiction (Bali and Kenny, 2013). Histone variant insertion has been largely unstudied in the context of learning and memory other than work demonstrating a requirement for polyADP-ribosylation of H1 for long-term memory formation in *Aplysia* (Cohen-Armon et al., 2004) and mammals (Goldberg et al., 2009). Until recently the role of CRCs in regulating long-term memory formation was completely unexplored. Given that this mechanism has received little attention within the field of learning and memory, this review will first provide a background on CRCs with a focus on BAF (Brg1/hBrm associated factor) complexes, one of the most highly studied CRCs. We then focus on the role of the neuron-specific CRC nBAF in neuronal development, the link between BAF subunit mutations and human cogitative disorders and finally on new work demonstrating a specific role for nBAF in long-term memory formation and synaptic plasticity.

3. Chromatin Remodeling Complexes—subunit combinatorial complexity

Chromatin remodeling complexes (CRCs) are large, multi protein complexes that possess nucleosome and DNA-dependent ATPase function. Chromatin remodeling complexes fall into four large families depending on their ATPase: BAF (Brg1, hBrm), INO80/SWR1 (hINO80, hDomino, SRCAP), ISWI or NURF (hSNF2H, hSNF2L), and CHD or NuRD (CHD1-9) (Hargreaves and Crabtree, 2011). Standard biochemical methods for examining CRC function have examined nucleosome positioning using *in vitro* DNA templates with artificially assembled nucleosome arrays. In general, in these assays CRCs interact with DNA and nucleosomes and hydrolyze ATP to disrupt nucleosome DNA contacts, slide nucleosomes along DNA, and evict or exchange nucleosomes (Clapier and Cairns, 2009; Hargreaves and Crabtree, 2011) (Figure 1). This review will focus on the BAF complex (formerly called the mammalian SWI/SNF complex) since it is the only known chromatin remodeling complex to contain a neuronspecific subunit and is the most extensively studied CRC in regards to neuronal function in both development and the adult. The BAF complex was originally characterized as the mammalian homolog of the yeast SWI/SNF complex (Kwon et al., 1994; Wang et al., 1996a). The complex is defined by a DNA-dependent ATPase subunit that is conserved across yeast (*SWI2*), *Drosophila* (*brahma* or *brm*), and mammals (*Brg1* and *hBrm*) (Khavari et al., 1993; Muchardt and Yaniv, 1993). Across species the homologous complexes share several characteristics including subunits with domains that recognize histone modifications, an ATPase, and regulatory domains (Clapier and Cairns, 2009; Hargreaves and Crabtree, 2011).

Mammalian BAF complexes are composed of an assembly of at least 15 subunits encoded by 28 genes (Ronan et al., 2013; Staahl et al., 2013) and contain either the Brg1 or hBrm

ATPase. Mammalian BAF complexes exhibit evolutionary divergence from the yeast SWI/SNF complex in that 9 of the 15 BAF subunits do not have yeast homologs and several BAF subunits have homologs in non-SWI/SNF yeast complexes. In addition to both the loss and gain of subunits over time, BAF complexes, unlike the yeast SWI/SNF complex, are combinatorially assembled. All identified BAF complexes have an ATPase (Brg1 or hBrm) and the following subunits: BAF47 (SMARCB1), BAF57 (SMARCE1), BAF60 (A, B, or C; SMARCD1, 2, or 3), BAF155 (SMARCC1), BAF45 (A, B, C or D; PHF10, DPF1, 3 or 2), BAF53 (A or B; ACTL6A or B), BAF250 (A or B) and monomeric beta-actin (Middeljans et al., 2012; Ronan et al., 2013) (see Figure 2). Recent affinity purification and mass spectrometry based analysis of BAF complexes in several cell types expanded the BAF subunits to include BLC7A, BLC7B, BLC7C, BCL11A, BCL11B, BRD9, and SS18 (or SS18L1) (Kadoch et al., 2013; Kaeser et al., 2008; Middeljans et al., 2012). In addition the unique Polybromo BAF (PBAF) (Lemon et al., 2001; Xue et al., 2000; Yan et al., 2005) complex is defined by the presence of the BAF180 (polybromo) (Lemon et al., 2001; Wang et al., 1996a; Xue et al., 2000), Brd7 (Kaeser et al., 2008) and BAF200 (ARID2) (Wang et al., 1998; Xue et al., 2000; Yan et al., 2005) subunits and a lack of BAF250A/B (ARID1A/B) (Lemon et al., 2001; Wang et al., 1998) and Brd9 (Middeljans et al., 2012). Altering the subunit composition allows for an extensive diversity with both tissue and cell-type specific roles depending on the specific BAF subunit composition (Ho and Crabtree, 2010; Ronan et al., 2013).

Combinatorial assembly of BAF subunits can dramatically alter the function of the complex with developmental specificity. For example, the two BAF ATPase subunits that compose nBAF (Brg1 and hBrm) share 75% sequence homology (Kadam and Emerson, 2003) and both types of BAF complexes possess nucleosome remodeling capabilities (Wang et al., 1996b) similar to those first characterized in the yeast SWI/SNF complex (Côté et al., 1994). However, null mutations in the two proteins produce very different phenotypes. Homozygous deletions of *Brg1* are embryonically lethal while mice with deletions of *hBrm* appear to develop normally (Bultman et al., 2000; Reyes et al., 1998). The phenotypic differences may be driven by the inclusion of Brg1, but not hBrm, in BAF complexes found exclusively in embryonic stem cells (Ho et al., 2009b). Why one ATPase is included preferentially over the other is potentially due to the divergence in the N-terminal regions of Brg1 and hBrm that allow interactions with different classes of transcription factors. Brg1 interacts with zinc finger proteins where as hBrm interacts with components of the Notch signaling pathway (Kadam and Emerson, 2003). Consequently, the selection of the ATPase subunit can potentially drive interactions with different promoters during cellular proliferation and differentiation and may result in unique remodeling functions (Kadam and Emerson, 2003).

Different subunit compositions may lead to differential regulation of specific target gene sets. The type of ARID (AT-rich Interactive Domain) subunit present in the complex can alter the transcriptional targets. For example, in HeLa cells BAF (contains BAF250A (ARID1A) or BAF250B (ARID1B)) and P-BAF (contains BAF200 and not BAF250A/B) complexes differentially regulate interferon-responsive genes, a selectivity conferred by the BAF200 subunit (Yan et al., 2005). Even though the alternate BAF subunits BAF250A and BAF250B are expressed within the same cell types (not tissue or cell-type specific) (Wang et al., 2004), the two subunits result in different BAF complexes with differential regulation of gene expression. The BAF250 subunits do not possess sequence specific DNA binding domains (Dallas et al., 2000; Wang et al., 2004), indicating that they alter BAF complex function through differences in protein-protein interactions. BAF250A containing BAF complexes form repressive complexes with Sin3A and HDAC1/2 that represses cell cycle gene expression while BAF250B-containing BAF complexes interact with the histone acetyltransferase Tip60 and HDAC3 that serves to activate some of the same genes. By

forming these two unique complexes the type of BAF250 subunit can dictate the direction of cell cycle gene expression (Nagl et al., 2007). Work on the BAF200 and BAF250 subunits highlight the impact of combinatorial assembly on regulating gene expression, where the substitution of a single subunit can serve as a switch from a gene regulatory program of activation to repression. Future work will be needed to more completely delineate how the unique subunit composition of BAF complexes contributes to coordinated regulation of gene expression. An intriguing idea is that this combinatorial complexity may correspond with the spectrum of intellectual disability disorders observed in humans.

4. Chromatin Remodeling Complexes—cell type specificity

Different cell types also have specialized BAF complexes that regulate unique sets of genes required for cell-specific functions. Currently there are several complex variants, each with unique combinations of subunits that confer either cell-type specific expression or function: embryonic stem cell BAF (esBAF) (Ho et al., 2009a), neuronal progenitor BAF (npBAF) (Lessard et al., 2007), and neuronal BAF (nBAF) (Olave et al., 2002) (Figure 2). Embryonic stem cells (ESCs) express esBAF that is defined by the inclusion of Brg1, BAF155 (homodimer), and BAF60A or B subunits and the absence of Brm, BAF170, and BAF60C (Ho et al., 2009b) (Figure 2). This unique complex is required for ESC pluripotency and self-renewal through interactions with ESC unique transcription factors (Ho et al., 2009b; 2009a; 2011). Genome-wide mapping found that Brg1 was enriched specifically at genes that were uniquely down-regulated in ESCs including developmental and lineage-determinant genes, indicating that esBAF plays a role in preventing premature differentiation. In contrast, Brg1 also repressed several genes uniquely expressed in ESCs indicating a more subtle role for esBAF in refining the ESC transcriptional network (Ho et al., 2009a; Kidder et al., 2009). Similarly, a PBAF complex isolated from an ESC line differentially regulated transcription targets compared to the esBAF containing BAF250A (Kaeser et al., 2008). The findings in ESCs demonstrate how a unique composition of BAF subunits (i.e. esBAF) directs gene expression profiles required for maintaining cellular identity (i.e. ESC pluripotency).

During brain development the BAF complex undergoes a highly coordinated exchange of subunits as ESCs differentiate into neuronal precursors and then into mature, post-mitotic neurons. For the transition from esBAF to a neural stem/progenitor specific version of the complex (npBAF) several specific subunits are exchanged. The npBAF complex is defined by the inclusion of BAF170, decreased incorporation of BAF60b and the presence of either Brg1 (same as esBAF) or Brm (not present in esBAF) (Lessard et al., 2007; Staahl et al., 2013) (Figure 2). Microarray analysis of E12.5 mouse brains with deletion of Brg1 specifically in neural stem/progenitors cells suggests that the npBAF complex regulates stem cell self-renewal and/or maintenance by enhancing expression of components in the Notch signaling pathway while also repressing expression of components and downstream targets of the Sonic Hedgehog pathway (Lessard et al., 2007). Manipulations that decrease npBAF function (i.e. knockdown of BAF45a, BAF53a (Lessard et al., 2007), or SS18 (Staahl et al., 2013)) impair neural stem/progenitor proliferation. Together these findings point to a unique role for npBAF in regulating gene expression required for neuronal progenitor proliferation

The transition (E13.5 in mice) from npBAF to the post mitotic neuron-specific nBAF requires the developmentally regulated switch in subunits from BAF45a to BAF45b/c, BAF53a to BAF53b (Lessard et al., 2007; Wu et al., 2007), and SS18 to CREST (Staahl et al., 2013). The nBAF complex contains at least 15 assembled subunits, two of which are neuron specific (BAF53b and BAF45b). The exchange of BAF53a for BAF53b is regulated by the microRNAs miR-9* and miR-124 (Yoo et al., 2009). Prior to neuronal differentiation, miR-9* and miR-124 expression are repressed, allowing BAF53a expression and neuronal

progenitor proliferation (ie. npBAF). When neural progenitors differentiate, miR-9* and miR-124 are expressed which in turn represses BAF53a and allows expression of BAF53b (Yoo et al., 2009). The highly orchestrated regulation of subunit exchange highlights the importance of neuronspecific subunits in nBAF's role in neuronal differentiation.

As one of the neuron-specific subunits of nBAF, BAF53b seems to play a critical role in nBAF function. BAF53b was first identified by its homology to the non-neuronal isoform of BAF53a (Actl6a) (Harata et al., 1999). BAF53a was first identified as an actin related protein (ARP) within the BAF complex in T lymphocytes (Zhao et al., 1998). BAF53a and b are encoded by two separate genes that share 93% similarity (Harata et al., 1999; Olave et al., 2002). Both proteins localize to the nucleus, specifically in regions enriched in euchromatin, but not in heterochromatin regions (Harata et al., 1999). While BAF53b is expressed only in neurons and is only within nBAF, BAF53a is found within all human tissues except the nervous system and in several distinct CRCs other then BAF (Olave et al., 2002; Park et al., 2002).

The neuron-specific subunits of nBAF appear to confer a critical role for nBAF's regulation of neuronal gene expression required for dendritic arborization, branching and synapse formation (Staahl et al., 2013; Wu et al., 2007). Mice lacking BAF53b (also known as hArpNalpha or Actl6b) die at two days postnatal. Neuronal cultures made from BAF53b knockout mice have severe deficits in synapse formation, activity-dependent dendritic outgrowth, and axonal myelination. The absence of BAF53b does not disrupt formation of the nBAF complex, as the remaining subunits show normal assembly (Wu et al., 2007). The dendritic phenotype depended on miR-9* and miR-124 binding sites in the BAF53a 3'UTR, indicating that the miR-mediated switch from BAF53a to BAF53b is critical for nBAF's function in neuronal development (Yoo et al., 2009). As predicted from these findings, disrupting the transition from npBAF to nBAF by over-expression of BAF45a and BAF53a in the developing chicken neural tube blocked neuronal differentiation of specific classes of neurons (Lessard et al., 2007).

5. BAF53b: A key neuron-specific subunit of nBAF

As a dedicated member of nBAF, BAF53b plays a critical and unique role in neuronal branching and synapse formation. There was no rescue of lethality or dendritic phenotype by over expression of BAF53a in $Baf53b^{-/-}$ knockout mice (Wu et al., 2007). BAF53a and BAF53b show the largest sequence divergence within subdomain2 (aa 39–82). Switching the subdomain2 region of BAF53a for b restored dendritic outgrowth and rescued deficits in gene expression (see below) in $Baf53b^{-/-}$ knockout neuronal cultures. The reverse swap (BAF53b with subdomain 2 from BAF53a) failed to rescue the phenotype, suggesting a critical role for subdomain 2 of BAF53b (Wu et al., 2007). RNAi mediated knockdown of Brahma associated protein 55 (Bap55), a homolog of both BAF53a and b, reduces dendritic arborization and routing in *Drosophila* (Parrish et al., 2006). Similarly, BAP55 knockouts produce mistargeting of olfactory projection neurons *in vivo* (Tea and Luo, 2011). The phenotype can be rescued by expression of BAP55, BAF53a, or BAF53b. The rescue of the dendritic phenotype by BAF53a may at first appear contradictory to BAF53b's selective role in dendritic arborization in mammals. However, in *Drosophila* BAP55 has approximately equal homology to both BAF53a and b and is found in additional CRCs outside of the BAF complex. These findings indicate that BAF53b confers a unique function to the mammalian nBAF complex that cannot be replaced by the non-neuronal BAF53a, further highlighting the specialization of combinatorally assembled and cell-type specific BAF complex function.

Even though targeting BAF53b may be one of the most direct ways of manipulating nBAF, siRNA knockdown of other nBAF components (*Brg1, Baf57* or *Baf45b*) in primary mouse neuronal cultures results in deficits in dendritic growth comparable to BAF53b knockout neuronal cultures (Wu et al., 2007). Similarly, in *Drosophila* deletion of other BAP (BAF complex homolog in *Drosophila*) components including *Brm* and *Snr1* (*Baf47*) produce global mistargeting and abnormalities in cell morphology (Tea and Luo, 2011) and RNAi mediated knockdown of *Brm, Bap60* (*Baf60*), or *Snr1* alter dendritic routing and branching (Parrish et al., 2006). In *Caenorhabditis elegans* deletion of *ham-3* (*Baf60*) disrupts the expression of genes associated with serotonin synthesis and transport within a specific subset of serotonergic neurons and produces deficits in axon pathfinding (Weinberg et al., 2013). These findings indicate that nBAF is a critical regulator of dendritic arborization and branching and that disruption of nBAF function results in abnormal dendritic maturation across multiple species.

In primary cortical neuron cultures, BAF53b coordinates expression of specific transcriptional profiles required for dendritic arborization and branching. For example, loss of BAF53b in neuronal cultures results in misregulation of several Rho family GTPase regulators that are critically important for activity-dependent dendritic development. At least one of these Rho GTPases, *Ephexin1*, appears critical for BA53b mediated dendritic development. *Baf53b*$^{-/-}$ knockout cultures have reduced *Exphexin1* expression, BAF53b has been shown to bind to the *Ephexin1* promoter, and overexpression of *Ephexin1* rescued the dendritic phenotype in *Baf53b*$^{-/-}$ knockout cultures (Wu et al., 2007). Together these findings suggest a critical role for BAF53b and the nBAF complex in regulating a transcriptional profile required for normal dendritic development.

How nBAF specifically targets and regulates neuronal genes required for dendritic maturation is unclear; however BAF53b appears to play a critical role in targeting nBAF and the transcription factor Calcium-responsive transactivator (CREST or SS18L1) to specific promoter regions (Wu et al., 2007). CREST is activated by calcium influx in response to neuronal depolarization (Aizawa et al., 2004), CREST and nBAF directly interact (Qiu and Ghosh, 2008; Staahl et al., 2013; Wu et al., 2007) and CREST is now considered a subunit of the nBAF complex (Staahl et al., 2013). This is a significant finding as the interaction between CREST and nBAF subunits provides a potential link between nBAF-mediated nucleosome remodeling and calcium-dependent neuronal activity. While BAF53b is not required for the CREST-nBAF interaction, loss of BAF53b disrupts localization of nBAF and CREST to target promoters and disrupts gene expression involved in dendritic outgrowth (Wu et al., 2007). Similar to the dendritic branching and arborization deficits observed in BAF53b knockout neuronal cultures, cultures from CREST knockout mice have severe deficits in activity-dependent dendritic development (Aizawa et al., 2004; Qiu and Ghosh, 2008). Blocking the transition from SS18 (found in npBAF) to CREST (nBAF specific) during neuronal differentiation by over-expressing SS18 also impairs activity-dependent dendritic growth and branching (Staahl et al., 2013). These findings suggest BAF53b and CREST are key components of activity-dependent nucleosome remodeling required for dendritic spine dynamics.

There also appears to be a link between CREST function and human neurodegenerative disease. Recent exome sequencing in patients with sporadic amyotrophic lateral sclerosis (ALS), a neurodegenerative disease characterized by motor neuron loss, identified a *de novo* truncation mutation in CREST. This truncation mutation specifically deleted the portion of CREST that interacts with CREB binding protein (CBP) (Aizawa et al., 2004; Qiu and Ghosh, 2008), a histone acetyl transferase required for long-term memory formation (for review see (Barrett and Wood, 2008; Peixoto and Abel, 2013). Over-expressing this truncated version of CREST in primary cortical or motor neuron cultures impaired activity-

dependent dendritic outgrowth and branching. Similar deficits in dendritic development were found with over-expression of CREST with missense mutation identified in an ALS patient with a known family history of ALS (Chesi et al., 2013). Together these findings indicate a critical role for the nBAF component CREST in dendritic development and human disease. Further work will be needed to clarify the function of CREST in the adult nervous system and how CREST mutations may be causally linked to sporadic ALS and other neurodegenerative diseases.

6. Chromatin Remodeling Complexes and Disorders of Human Cognition

Recently, whole exome sequencing in human patients with several distinct types of intellectual disability disorders identified mutations in several BAF subunits. Tsurusaki and colleagues (2012) performed whole exome sequencing on five patients with Coffin-Siris syndrome (CSS), a developmental disorder characterized by cognitive delay, microcephaly, abnormal facial features, and either hypoplasia or absence of the nail on the fifth digit of hands or feet (Coffin and Siris, 1970). Two of the five patients had *de novo* heterozygous mutations in *Baf47* (*SMARCB1*). The authors then examined 23 additional CSS patients by melting analysis for potential mutations in 15 of the various BAF subunits. In total, 20 of the 23 CSS individuals had a mutation in one of six BAF subunits (*Brm, Brg1, Baf47, BAF250b, BAF250a*, and *Baf57*) giving an overall mutation detection rate of 87% (Tsurusaki et al., 2012). Similarly, an independent group found *de novo* truncation mutations in *BAF250b* (*ARID1B*) using exome sequencing of three CSS patients (Santen et al., 2012). Deletions and mutations that produce haploinsufficiency of *BAF250b* have been found in patients with intellectual disability disorder, corpus callosum abnormalities, speech impairments, and autism (Backx et al., 2011; Halgren et al., 2011; Hoyer et al., 2012; Nord et al., 2011).

Recent human exome sequencing has also revealed a role for the BAF complex in Nicolaides-Baraitser syndrome (NBS), an intellectual disability disorder characterized by impaired language and attention span, seizures, sparse hair, short stature, abnormal facial features, microcephaly, and severe intellectual disability (Nicolaides and Baraitser, 1993; Sousa et al., 2009). In eight out of ten patients with NBS whole exome sequencing identified *de novo* mutations in *Brm*. Additional targeted sequencing of *Brm* in 34 additional NBS patients identified 28 *Brm* mutations, none of which were present in 1,300 screened control samples. The majority of mutations occurred within conserved protein motifs including domains for DNA binding, acetylated lysine recognition (bromo), and ATP hydrolysis (Van Houdt et al., 2012). In parallel, SNP arrays followed by targeted sequencing of three NBS patients identified *de novo* heterozygous mutations in the C-terminal helicase domain predicted to disrupt ATPase function (Wolff et al., 2011).

In addition to intellectual disability disorders, mutations in components of the BAF complex have also been linked to autism. Whole exome sequencing of ASD patients and their parents identified *de novo* single nucleotide variants in *Baf155, Baf170, Baf180*, and *Baf250b* in ASD individuals (Neale et al., 2012; O'Roak et al., 2012). Furthermore, when these data were combined with those from two other recent exome sequencing studies (Iossifov et al., 2012; Sanders et al., 2012) (965 ASD individuals and a total of 121 gene disrupting mutations), a higher proportion of disruptive mutations belonging to the 'chromatin regulator' gene ontology category was observed in ASD cases compared to controls, supporting the contribution of this category to ASD risk (Ben-David and Shifman, 2012).

The BAF complex has also been recently implicated in schizophrenia (SZ). Functional interactome models using genome-wide association studies (GWAS) found an interacting network between *Brm* and eight other GWAS identified genes involved in schizophrenia (Loe-Mie et al., 2010). In a Japanese population four different single nucleotide

polymorphisms (SNPs) in *Brm* were found to associate with schizophrenia (Koga et al., 2009). Two of the intronic SNPS (intron 12 and 19) that were found more frequently in schizophrenics were correlated with lower overall expression levels of *Brm* in the postmortem human prefrontal cortex. A SNP identified in exon 33 of *Brm* of schizophrenic patients alters the amino acid sequence at position 1546 from aspartic acid (D) to glutamic acid (E). When over-expressed in cell culture the E risk allele altered cell morphology and produced a partial mislocalization of Brm out of the nucleus, indicating a decrement in Brm and BAF function. This was further supported by an examination of gene expression following transfections with either E or D variants compared to siRNA targeted to *Brm*. Expression changes with siRNA to *Brm* were similar to those with the E variant further supporting a loss of Brm function for the E variant (Koga et al., 2009). Furthermore, gene expression changes following siRNA knockdown of *Brm* correlated with expression observed in prefrontal cortex from Brm knockout mice and postmortem prefrontal cortex of schizophrenics. Brm knockout mice are viable and develop normally (see above) but have impaired social interactions in that they spend less time exploring a novel intruder mouse even though they have normal novelty seeking behavior. The impairment in social interaction is particularly interesting given that social interaction problems are also one of the key hallmarks in ASD. It appears that Brm may also be a viable therapeutic target for SZ given that antisychotic drug treatment (4 wks haloperidol or olanzapine) increased *Brm* expression (Koga et al., 2009).

One of the key hallmarks found in postmortem brains from patients with SZ or ASD is alterations in dendritic spine density. Layer 3 pyramidal neurons in prefrontal and temporal cortex from SZ patients have a marked decrease in spine density compared to non-SZ controls (Garey et al., 1998; Glantz and Lewis, 2000). Conversely, spines on apical dendrites of pyramidal cells in layer 2 of frontal, temporal and parietal cortex and layer 5 of temporal cortex show a higher density in ASD patients compared to matched controls. The density of spines was also inversely related to IQ (Hutsler and Zhang, 2010). GWAS and whole exome sequencing in humans have identified mutations in various BAF subunits in human disorders including CCS, NBS, ASD, and SZ, indicating a critical role for the loss of transcriptional regulation in the etiology of these disorders. It is tempting to speculate that BAF may control a transcriptional network required for dendritic development in humans and that mutations altering BAF function consequently produces dendritic abnormalities characteristic of these disorders. In support of this hypothesis, BAF53b plays a key role in dendritic arborization and spine formation *in vitro* (Tea and Luo, 2011; Wu et al., 2007). SiRNA knockdown of *Brm* in primary mouse cortical cultures increases spine number, specifically due to an increase in mushroom spines (Loe-Mie et al., 2010). A shift towards increased mushroom type spines is also observed *in vivo* with a dominant negative BAF53b transgene over-expression (Vogel-Ciernia et al., 2013). Mice with heterozygous knockout of BAF53b have altered gene expression profiles including genes found involved in actin cytoskeletal remodeling and the post synaptic density (discussed below) (Vogel-Ciernia et al., 2013). The findings on nBAF's regulation of gene expression involved in synaptic function both during development (Chesi et al., 2013; Staahl et al., 2013; Tea and Luo, 2011; Wu et al., 2007) and in the adult (Vogel-Ciernia et al., 2013) are consistent with the dendritic spine abnormalities observed in humans with SZ and ASD. However, future work will be needed to elucidate how the specific mutations found in various human cognitive disorders impact nBAF structure (physical subunit composition) and activity, as well as the precise role of different subunits of various CRCs in their specific cellular functions.

7. Neuron-Specific Chromatin Remodeling in Long-Term Memory Formation

While BAF53b's unique contribution to nBAF's role in dendritic development *in vitro* was becoming apparent, how the impaired function of nBAF leads to adult cognitive impairments was unknown. In order to address this question Vogel-Ciernia and colleagues (2013) targeted the neuron-specific nBAF subunit BAF53b to examine the role of nBAF in long-term memory, long-term potentiation (a form of synaptic plasticity), and gene expression. The unusual dedication of BAF53b to a single neuronal complex makes it an ideal target for genetic manipulations designed at elucidating the role of the nBAF complex in neuronal function. The authors used both traditional BAF53b heterozygous knockout mice and transgenic mice over-expressing a dominant negative form of BAF53b (deletion of a hydrophobic domain predicted to mediate protein-protein interactions (Park et al., 2002)) under the CamKIIα promoter (restricts expression to forebrain excitatory neurons and postnatal development (Kojima et al., 1997; Mayford et al., 1996)). Both the dominant negative and heterozygous knockouts showed severe long-term memory deficits, but normal short-term memory. Importantly, the normal short-term memory performance indicates that the genetically altered animals were able to perform the task (ie. normal exploration, attention, etc) and that the memory deficits at the long-term time point were due to a failure of memory consolidation.

To further assess the role of BAF53b in the adult brain compared to its role in development, Vogel-Ciernia and colleagues (2013) performed a rescue experiment in the BAF53b heterozygous knockout mice by injecting an adeno-associated virus expressing wildtype BAF53b in the dorsal hippocampus of adult animals. Hippocampal expression of wildtype BAF53b in the BAF53b heterozygous knockouts rescued the long-term object location memory (hippocampal dependent) deficits indicating that BAF53b is required for long-term memory formation in the adult animal independent of its role in development. In the same animals, the hippocampal BAF53b reintroduction failed to rescue (as predicted) the hippocampal independent object recognition task further implicating a specific role for BAF53b in memory processing and not an alteration in brain state or processing.

In parallel to the observed deficits in long-term memory, the BAF53b mutant mice also showed deficits in the maintenance of long-term potentiation (LTP), an electrophysiological correlate of long-term memory. In acute hippocampal slices theta burse stimulation (TBS) was used to induce robust potentiation in slices from BAF53b heterozygous knockout animals, the dominant negative BAF53b transgenics, and wildtype littermate controls. The heterozygous knockout animals and the lower expressing dominant negative mice both showed a normal LTP induction (short-term potentiation) and a failure to stably maintain the potentiation with a decay back to baseline. The highly expressing dominant negative line had an increase in the initial potentiation followed by a lack of LTP maintenance similar to the other lines. The increase in short-term potentiation in the high expressing dominant negative appears to be due depressed axon excitability and increased neurotransmitter mobilization. All other measures of baseline physiology including response to the TBS were normal in these animals as well as the other BAF53b mutant lines. Overall, it is evident that BAF53b is necessary for stabilizing long-lasting forms of potentiation, correlating with observed long-term memory impairments.

In support of the deficits in synaptic plasticity observed with perturbations to BAF53b, the BAF53b heterozygous knockouts have deficits in synaptic signaling following TBS. Specifically, BAF53b heterozygous knockout mice lack the induction of phosphorylated cofilin (p-cofilin), with no change in PSD95 expression, following TBS that is observed in slices from wildtype animals. This deficit indicates a breakdown in the signaling cascade

leading to actin cytoskeleton remodeling and may underlie the deficits in LTP in these animals (Lynch et al., 2013). In addition, the high expressing dominant negative animals show an alteration in dendritic spine morphology at three weeks of age. The BAF53b mutant mice show a decrease in thin and an increase in mushroom spines on both the main stem and oblique apical branches of hippocampal CA1 pyramidal neurons. It is currently unknown if these spine alterations maintain into adulthood and whether or not they contribute to the deficits in memory or synaptic plasticity observed in these mice.

The specific deficits in long-term memory and maintenance of LTP indicate a transcription dependent mechanism for BAF53b function. To assess a role for BAF53b in regulating transcription following a learning event, Vogel-Ciernia, et al. (2013) conducted an RNA Sequencing experiment to assess gene expression in dorsal hippocampus from wildtype and BAF53b heterozygous knockout mice sacrificed either from the homecage (baseline) or 30min following object location training. The resulting gene expression profiles indicated that the majority of genes were not differentially regulated at baseline. There were a group of genes that increased in expression in both genotypes following training and interestingly this group contained almost all of the identified immediate early genes (IEGs). The normal induction of IEGs in the BAF53b heterozygous knockout mice indicates that the long-term memory impairments observed in these animals are not due to misregulation of IEG expression but to a different mechanism. There were genes increased following training in the wildtype animals that failed to increase in the BAF53b mutant mice, as well as genes that did not turn on in the wildtype following training that aberrantly activated in the BAF53b heterozygous knockouts. These misregulated genes were enriched for gene ontology terms involving regulation of transcription, neurogenesis, and higher order chromatin structure. Within the misregulated gene profiles were several targets related to the actin cytoskeleton and post synaptic density (PSD) that could potentially link the deficits in transcription to the deficits in p-cofilin induction and synaptic plasticity. These genes included miroRNAs and members of the Rac-PAK and RhoA-LIMK pathways, all critical components of activity-dependent cytoskeletal remodeling machinery in the PSD (Boda and Dubos, 2010; Impey et al., 2010; Rex et al., 2009). Together the RNA-Seq and synaptic signaling (p-cofilin) results indicate a role for nBAF in regulating gene expression required for synaptic structure and function and that the failure of these mechanisms in the BAF53b mutant mice may underlie their deficits in synaptic plasticity and long-term memory.

8. Conclusion

The BAF complex appears to play a key role in normal human brain development such that even heterozygous mutations that produce haploinsufficiency can lead to severe intellectual disability and developmental abnormality. Any disruption to the BAF complex appears to disrupt function since mutations in different BAF subunits can lead to similar phenotypes (intellectual impairments). To date all identified BAF mutations associated with intellectual disability disorders, ASD, and SZ have been to subunits commonly shared among P-BAF, esBAF, npBAF, and nBAF. Given that each of these complexes regulates unique gene expression profiles, it is currently unclear how mutations in the various BAF complexes alter either cell-type or developmental stage specific gene expression that ultimately contributes to human disorders.

The finding that nBAF plays a critical role in adult long-lasting forms of synaptic plasticity and memory (Vogel-Ciernia et al., 2013) provided the first evidence that nBAF may be playing a role beyond early brain development in human intellectual disability disorders. The deficits in synaptic plasticity (LTP maintenance and p-cofilin levels) and expression of genes found in both the PSD and cytosketetal remodeling machinery indicate a potential role for BAF53b and the nBAF complex in regulating dendritic spine formation and plasticity.

The misregulation of genes required for proper activation of activity-dependent cytoskeletal remodeling is reminiscent of recent findings of perturbations of the cytoskeletal machinery in individuals with ASD. For example, deletions in genes involved in GTPases/Ras signaling and specifically the Rho GTPases are more common in individuals with ASD than controls (Pinto et al., 2010), and network level analysis of rare de novo CNVs found in ASD individuals (but not controls) suggests a role for genes found in the PSD that are linked with spine formation and plasticity in ASD (Gilman et al., 2011). These findings are consistent with the hypothesis that a critical component of the pathology of both ASD and SZ is alterations of dendritic spines (Penzes et al., 2011). However, there is increasing evidence for the role of transcription regulation, via nucleosome remodeling, in ASD (Ben-David and Shifman, 2012) potentially as an upstream regulator of coordinate gene expression required for the expression of synaptic and cytoskeleton associated genes. If nBAF regulates some of these same genes in humans as in mice, restoring or augmenting nBAF function could serve as a powerful method for therapeutically targeting a specific set of misregulated target genes.

In order to more fully understand the role of nBAF in neuronal function further work is needed to characterize how CRCs act *in vivo* to alter chromatin structure and regulate gene expression. To date most of the information regarding mechanisms of CRC function comes from artificially assembled arrays that lack the secondary and tertiary structure of chromatin that is observed *in vivo* and often utilize only a single promoter or defined DNA regulatory domain. There is growing evidence that CRCs may mediate secondary or even higher order chromatin structure. Even on artificially assembled polynucleosome arrays, a single yeast SWI/SNF complex can interact with multiple DNA/nucleosome sites resulting in the formation of DNA loops (Bazett-Jones et al., 1999) (see Figure 1). Brg1 has been shown to be required for cell-type specific chromosomal loop formation between unique up-stream regulatory elements and the beta-globin (Kim et al., 2009b) and alpha-globin promoters (Kim et al., 2009a). Thus, one exciting possibility is that nucleosome remodeling via CRCs provides the chromosomal flexibility to allow chromosomal looping for coordinate gene regulation.

Recent high throughput genomic studies (RNA-Seq, ChIP-Seq, Mnase-Seq, Hi-C, etc.) will be needed to delineate the role of CRCs in regulating chromatin structure on a larger scale and across multiple gene targets. For example, Mnase-Seq (micrococcal nuclease digestion followed by high throughput sequencing to extract nucleosome positions across the genome) experiments were recently used to examine the impact of knocking out either Brg1 or BAF47 (Snf5) on nucleosome positioning in murine embryonic fibroblasts. Loss of either subunit resulted in disruption of nucleosome occupancy and altered nucleosome phasing around the transcription start site of a large number of promoters (Tolstorukov et al., 2013). Similarly, Brg1 knockdown with shRNA alters nucleosome positioning at specific enhancer elements indicating that BAF complexes may act to shift flanking nucleosomes away from these sites to allow access to the underlying DNA during cellular differentiation (Hu et al., 2011). In addition, Hi-C methods (chromatin conformation capture followed by next generation sequencing) have also been recently used to characterize the global three-dimensional genome organization of several cell lines and the mouse cortex and revealed large chromatin interaction domains that were conserved across cell types (Dixon et al., 2012). It will become increasingly important to understand how nBAF, and BAF53b, mediates nucleosome remodeling necessary for chromosomal looping mechanisms that direct coordinate gene expression for specific cell function.

Considering that the nBAF complex is required for dendritic development (Chesi et al., 2013; Staahl et al., 2013; Tea and Luo, 2011; Wu et al., 2007) as well as synaptic plasticity and memory in the adult (Vogel-Ciernia and Wood, 2012), it is not surprising that mutations

in components of the BAF complex in humans are found in multiple cognitive disorders (ASD, ID, and SZ) as well as the neurodegenerative disorder ALS. Future work will be needed to further characterize the role for BAF complexes in the etiology of these disorders and to clarify the transcriptional networks they regulate. However, given that both the developmental phenotype (Tea and Luo, 2011; Wu et al., 2007) and adult memory deficits (Vogel-Ciernia et al., 2013) were reversible upon reintroduction of BAF53b, targeting specific BAF subunits may prove a valuable therapeutic option for the future treatment of human cognitive disorders.

Acknowledgments

Abbreviations

CRC	Chromatin Remodeling Complex
BAF	Brg1/hBrm Associated Factor
P-BAF	Polybromo-BAF
esBAF	embryonic stem cell BAF
npBAF	neuronal progenitor BAF
nBAF	neuronal BAF
ID	intellectual disability
ASD	autism spectrum disorder
SZ	schizophrenia

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Highlights

- Neurons contain a specific chromatin remodeling complex (nBAF)

- nBAF is required for dendritic arborization and spine formation

- BAF53b is a critical neuron-specific subunit of nBAF

- BAF53b is required for long-term memory, long-term potentation and gene expression in the adult

- Mutations in nBAF subunits are linked to intellectual disability, autism, and schizophrenia
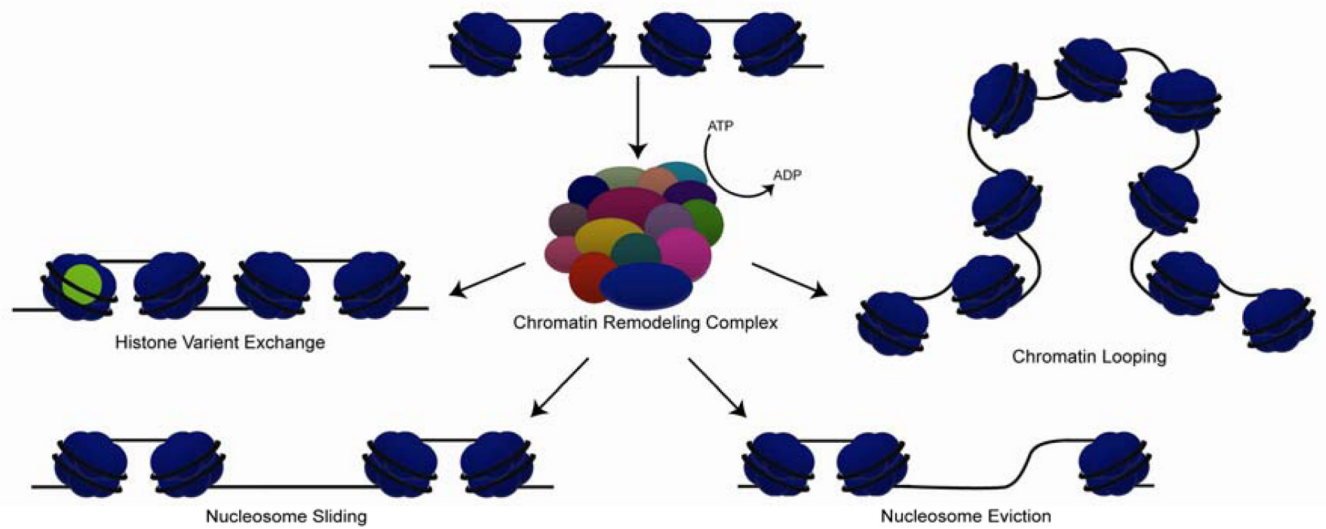
Figure 1.
Potential Roles for Chromatin Remodeling Complexes in Modifying Chromatin Structure. Based primarily on *in vitro* work done in the yeast homolog complex SWI/SNF, BAF complexes may play a key regulatory role in altering chromatin structure by any combination of the following: histone variant insertion, nucleosome sliding, nucleosome eviction, and chromatin looping or other higher order chromatin organization.
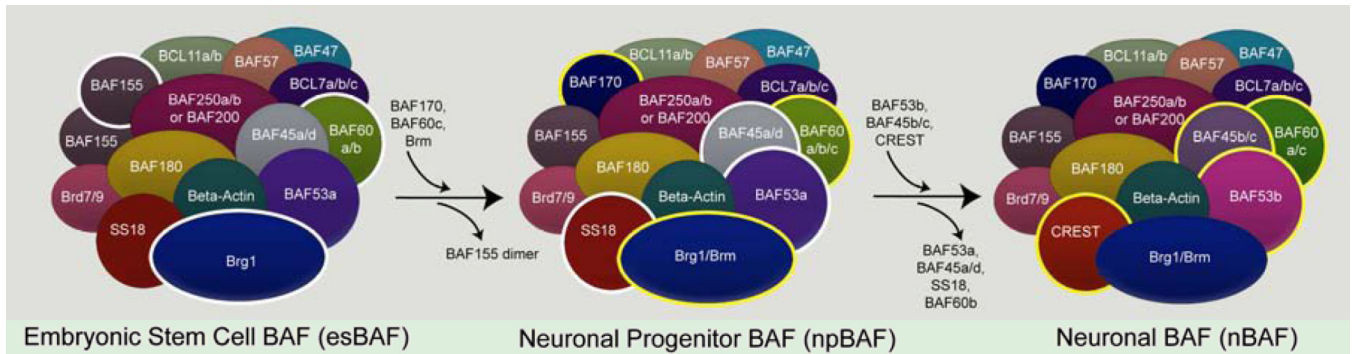
Figure 2.
Combinatorial Assembly of BAF Complexes. Unique BAF complexes are found in embryonic stem cells (esBAF), neuronal progenitors (npBAF), and neurons (nBAF). esBAF is characterized by a BAF155 dimer (no BAF170), Brg1, and BAF60a/b (without BAF60c) (white outline). During the transition from embryonic stem cells to neuronal progenitors esBAF is replaced by npBAF. In npBAF one of the BAF155 subunits is replaced with BAF170, BAF60 can be a, b, or c and Brm can serve as the ATPase (yellow outline). npBAF is also characterized by the presence of SS18, BAF45a/d and BAF53a (white outline). During neuronal differentiation BAF53a is replaced by BAF53b, BAF45a/d is replaced by BAF45b/c, and SS18 is replaced by CREST (outlined in yellow). In nBAF the presence of BAF60b is also greatly reduced. The Polybromo BAF complex (P-BAF) is not shown here as a unique complex but is defined by the inclusion of BAF180, BAF200, and Brd7 and the absence of BAF250A/B and Brd9.
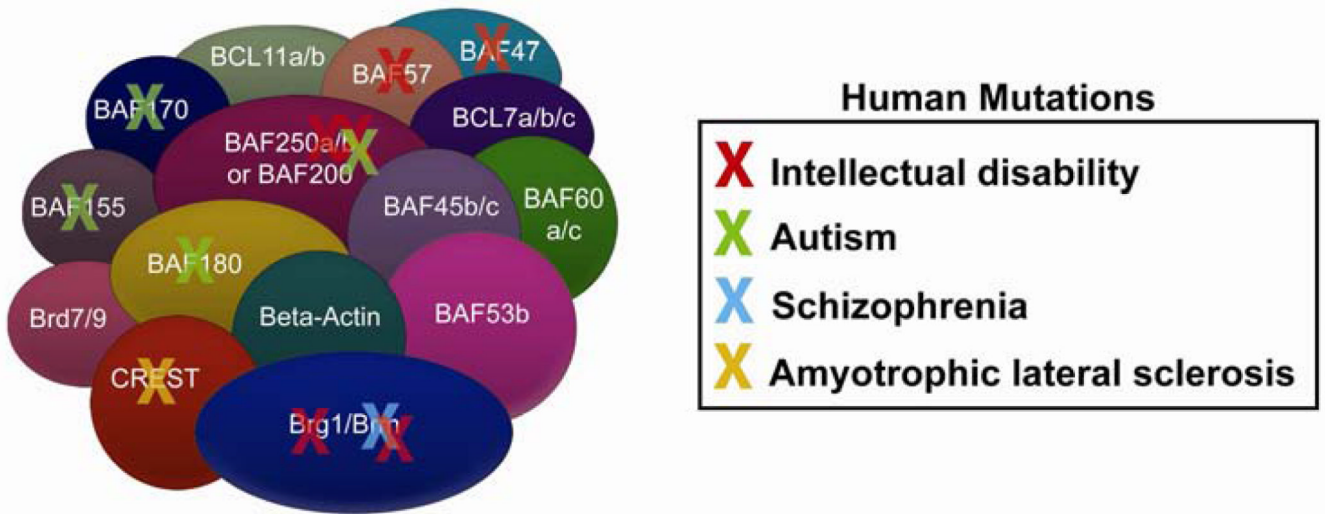
Figure 3.
Mutations in BAF complexes Identified in Human Patients. Each colored "X" represents an identified mutation for the given human disorder (either by whole exome sequencing or gene wide association studies). All mutations are shown in the context of the nBAF complex, but many of the mutant subunits are also shared with esBAF and npBAF.