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The role of ARID1B, a BAF chromatin remodeling complex subunit, in neural development and behavior

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Abstract

Haploinsufficiency of the chromatin remodeling factor *ARID1B* leads to autism spectrum disorder and intellectual disability. Several independent research groups, including our own, recently examined the effects of heterozygous deletion of *Arid1b* in mice and reported severe behavioral abnormalities reminiscent of autism spectrum disorders and intellectual disability as well as marked changes in gene expression and decreased body size. *Arid1b* heterozygous mice also display significant cortical excitatory/inhibitory imbalance due to altered GABAergic neuron numbers and impaired inhibitory synaptic transmission. Abnormal epigenetic modifications, including histone acetylation and methylation, are additionally associated with *Arid1b* haploinsufficiency in the brain. Treating adult *Arid1b* mutant mice with a positive GABA allosteric modulator, however, rescues multiple behavioral abnormalities, such as cognitive and social impairments, as well as elevated anxiety. While treating *Arid1b* haploinsufficient mice with recombinant mouse growth hormone successfully increases body size, it has no effect on aberrant behavior. Here we summarize the recent findings regarding the role of ARID1B in brain development and behavior and discuss the utility of the *Arid1b* heterozygous mouse model in neurodevelopmental and psychiatric research. We also discuss some of the opportunities and potential challenges in developing translational applications for humans and possible avenues for further research into the mechanisms of ARID1B pathology in the brain.

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Competing interests
None

Keywords

ARID1B; autism; intellectual disability; neural progenitor; brain development; interneuron; GABA intervention

Introduction

ARID1B encodes AT-rich-interactive-domain-containing protein 1B (ARID1B), a subunit of the BAF chromatin remodeling complex. Haploinsufficiency of this gene has been linked to autism spectrum disorder (ASD) and intellectual disability (ID) (Hoyer et al., 2012; Santen et al., 2012; Tsurusaki et al., 2012; Santen et al., 2014). Recent studies from our group and others have now examined the effects of heterozygous deletion of *Arid1b* in mice, which provides multiple novel insights into the mechanisms and roles of *Arid1b* in the developing brain and in behavior and suggest potential pharmacologic treatments for *ARID1B*-related neurodevelopmental disorders (Celen et al., 2017; Jung et al., 2017; Shibutani et al., 2017). In this review we summarize and analyze these findings and provide potential plans for future research. Further understanding of ARID1B and its functions in the developing brain are now much more feasible with the availability and description of animal models and may play an important role in the future of neurodevelopmental and psychiatric disorder research.

ARID1B mutations in human patients

ARID1B mutations are prevalent in ID, a developmental disorder characterized by significant limitations in both intellectual function and adaptive behavior. An overall incidence is estimated to be between 1 and 8% (Roeleveld et al., 1997; Simonoff et al., 2006; Westerinen et al., 2007). As ID is a severely incapacitating condition that imposes a significant burden on affected individuals and their families, much work has been done to identify its underlying causes. ID has a genetic origin in the majority of cases, and studies of X-linked, autosomal-recessive, syndromic and sporadic cases have resulted in the identification of more than two thousand ID-associated genes. Mutational analysis in 887 patients with unexplained ID reveals nine different *de novo* nonsense or frameshift mutations predicted to cause *ARID1B* haploinsufficiency, indicating haploinsufficiency of ARID1B as a common cause of ID (Hoyer et al., 2012), which was also confirmed in more recent exome sequencing studies of large cohorts of ID patients, which identify ARID1B as the most frequent cause of ID (Wright et al., 2015).

Although ID is a very heterogeneous disease, it has long been recognized that there are syndromic subtypes of ID which are delineated by combinations of external features and/or congenital anomalies as syndromes. Coffin-Siris Syndrome (CSS) is such a syndrome, and aside from mild to severe ID, patients often have hypoplastic nails on the fifth finger and/or toe, coarse facial features, growth deficiencies, sparse scalp hair and hypertrichosis elsewhere (Schrier Vergano et al., 1993). Corpus callosum abnormalities are also often observed in individuals with CSS (Halgren et al., 2012; Santen et al., 2014; Mignot et al., 2016). To identify the genetic basis of CSS, Santen et al. utilize whole-exome sequencing on three diagnosed individuals, revealing *de novo* truncating mutations in one copy of *ARID1B* in all cases. Array-based copy-number variation analysis in 2,000 individuals diagnosed with

ID reveals 3 subjects with deletions in the *ARID1B* gene who also have phenotypes partially overlapping with that of CSS (Santen et al., 2012). Using exome sequencing in 23 individuals with CSS, another group shows 6 patients with *de novo* heterozygous mutations in the *ARID1B* gene, providing further evidence of *ARID1B* haploinsufficiency as a cause of CSS (Tsurusaki et al., 2012). In addition, several targeted sequencing studies confirm mutations in BAF complex genes in patients with CSS (Santen et al., 2013; Wieczorek et al., 2013; Tsurusaki et al., 2014).

ASD is characterized by significant communication and social interaction deficits as well as restricted interests and stereotyped behaviors (Walsh et al., 2011). ID is also a highly prevalent phenotype in individuals with ASD, seen in as many as 30-75% of those affected (Fombonne, 1999; O'Brien and Pearson, 2004; Perou et al., 2013; Baio et al., 2018). The SFARI Gene initiative, a comprehensive online database of genes and copy number variants associated with ASD, has identified ARID1B as one of the 25 high confidence genes related to autism. Indeed, many of the described ARID1B patients also have autism. Next generation sequencing and microarray analysis of samples from eight patients, all presenting with ID, shows *de novo* translocations or deletions resulting in a truncated copy of *ARID1B* in all cases (Halgren et al., 2012). Of these patients, 5 are diagnosed with ASD or have autistic traits. In addition, 4 of these 5 patients show corpus callosum abnormalities demonstrated by brain imaging. This finding suggests that structural defects may be associated with the cognitive and behavioral phenotypes stemming from *ARID1B* haploinsufficiency. A separate study shows that the transcript level of the ARID1B gene is reduced in individuals with ASD (Nord et al., 2011).

Taken together, these studies all emphasize the role ARID1B plays in proper brain development and behavior. Various *de novo* mutations resulting in haploinsufficiency cause ID, CSS, ASD, and corpus callosum abnormalities to varying degrees. These findings add to the growing evidence that mutations in chromatin-remodeling genes are important contributors to neurodevelopmental disorders (Ronan et al., 2013; Sokpor et al., 2017; Gabriele et al., 2018), and that several of these disorders with overlapping phenotypes have converging genetic causes.

Arid1b knockdown and neuronal development

Proper neurite outgrowth and maintenance, which involve coordinated changes between the actin cytoskeleton and the microtubule network, are critical for normal neural development and brain function (Tsaneva-Atanasova et al., 2009). This process is regulated by the BAF (SWI/SNF) complex (Weinberg et al., 2013; Choi et al., 2015; Bachmann et al., 2016). ARID1B is a component of the mammalian BRG1/BRM associated factor (BAF) chromatin remodeling complex (Ho and Crabtree, 2010; Ronan et al., 2013) and plays an essential role in neurite outgrowth and maintenance. Using in utero shRNA delivery, Ka et al. show that ARID1B is required for dendrite outgrowth and arborization in cortical and hippocampal pyramidal neurons during brain development (Ka et al., 2016). In addition to decreased dendritic branching, ARID1B-deficient neurons exhibit markedly decreased dendritic innervation into cortical layer I and fewer attachments of dendritic terminals at the pial surface (Ka et al., 2016). It is noteworthy that layer I of the cerebral cortex receives inputs

primarily from neurons in higher-order thalamic and cortical areas, and neurons in this layer preferentially increase their activity during attention-demanding processes (Baluch and Itti, 2011; van Gaal and Lamme, 2012; Larkum, 2013). Thus, the decreased dendritic innervation into cortical layer I caused by ARID1B deficiency may disrupt balanced excitatory and inhibitory inputs and thereby give rise to pathologic conditions of ID and ASD.

Dendritic spines are the major sites of excitatory synaptic input in the brain and, therefore, form the basis of synaptic circuitry (Harris and Kater, 1994; Bourne and Harris, 2008). Ka et al. show that ARID1B contributes to spine formation, maturation and maintenance (Ka et al., 2016). ARID1B-deficient neurons exhibit a decreased number of dendritic spines and a prevalence of filopodia-like immature spines (Ka et al., 2016). The aberrant dendrites and spines in ARID1B-deficient pyramidal neurons greatly resemble the unbranched dendritic and filopodia-like spine morphology observed in mouse models of ID and ASD, as well as in Rett, Down, and fragile-X syndrome (FXS) models (Irwin et al., 2002; McKinney et al., 2005; Jentarra et al., 2010). Thus, ARID1B abnormalities may contribute to clinical outcomes by creating inappropriate synaptic connectivity. Incorrect growth and differentiation of dendrites is linked to the pathology of many neurodevelopmental and psychiatric diseases including ID, ASD and schizophrenia (Machado-Salas, 1984; Kaufmann and Moser, 2000; Fiala et al., 2002; Chapleau et al., 2009; Penzes et al., 2011). Abnormalities in the dendritic differentiation of cortical pyramidal neurons are seen in postmortem brain samples from individuals with ID (Huttenlocher, 1974). A reduction in spine size along dendrites is also reported in Down syndrome (Marin-Padilla, 1976; Roberts et al., 1996) and altered dendrite arborization in cortical pyramidal neurons is found in the brains of Rett syndrome patients (Belichenko et al., 1994; Armstrong, 2005).

Neural phenotypes of *Arid1b* knockout mice

Three recent independent studies, including our own, describe abnormal brain anatomy and cellular composition in *Arid1b* heterozygous mice (Celen et al., 2017; Jung et al., 2017; Shibutani et al., 2017). We observe normal density and distribution of pyramidal neurons, oligodendrocytes and astrocytes in *Arid1b* heterozygous mice in our study but find that GABAergic interneuron numbers are significantly reduced in *Arid1b* mutant mice, due to increased apoptosis and decreased proliferation of progenitors in the ganglionic eminence (Jung et al., 2017). The ventral ganglionic eminence is essential for the generation of GABAergic interneurons (Pleasure et al., 2000; Brandao and Romcy-Pereira, 2015). GABAergic interneurons containing parvalbumin (PV), calretinin, somatostatin or calbindin-D_{28k} are the primary source of GABA in the nervous system and play an important role in neural circuitry and activity (Kelsom and Lu, 2013; Butt et al., 2017). Specifically, the number of PV-positive interneurons is reduced in several brain regions including the cortex, amygdala, thalamus, and hippocampus in *Arid1b* heterozygous mice, but *Arid1b* haploinsufficiency does not lead to significant changes in the somatostatin-, calbindin- or calretinin-positive interneuron number in *Arid1b* heterozygous cortices (Jung et al., 2017). Decreases in GABAergic interneuron numbers in the cortex and hippocampus have previously been linked to autism and schizophrenia (Benes and Berretta, 2001; Pizzarelli and Cherubini, 2011) and, more specifically, the number of PV-positive interneurons has been shown to be significantly reduced in autism and schizophrenia in both mouse models

and postmortem brain tissue (Gogolla et al., 2009; Lawrence et al., 2010). Consistently, ASD-like behavioral profiles, such as social interaction and communication deficits with repetitive and stereotyped behavior, can be observed in PV knockout mice (Wohr et al., 2015). Neuronal excitatory/inhibitory balance is regulated at the synaptic level, and a reduction in inhibitory synapse number or strength results in a shift of that balance (Gao and Penzes, 2015; Nelson and Valakh, 2015). As a result, excitatory/inhibitory imbalance leads to broken synaptic homeostasis and facilitates the risk of the neurological disorders such as autism and schizophrenia. *Arid1b* heterozygous mice exhibit fewer inhibitory synaptic puncta, namely vesicular inhibitory amino acid transporter- (VGAT) and glutamic acid decarboxylase 2- (GAD2) positive puncta, in the cerebral cortex (Jung et al., 2017). In addition, glutamic acid decarboxylase 1 (*Gad1*) and *Gad2* expression levels are markedly decreased in *Arid1b* haploinsufficient mouse brains. Heterozygous deletion of *Arid1b* also leads to abnormal miniature inhibitory postsynaptic currents (mIPSC) frequencies, characterized by increased inter-event intervals and increased inhibitory synaptic cleft width (Jung et al., 2017). Furthermore, GABAergic interneuron neurite number and length are decreased in *Arid1b* heterozygous mice (Jung et al., 2017). Thus, *Arid1b* haploinsufficiency results in excitatory/inhibitory imbalance via decreased GABAergic interneuron numbers and impaired synaptic transmission of inhibitory signals.

Two other reports indicate that a small subset of *Arid1b* heterozygous mice are born with hydrocephalus (Celen et al., 2017; Shibutani et al., 2017), which corresponds well with some individuals with ASD (Turner et al., 2016) and a portion of patients with CSS who present with Dandy-Walker malformations (Schrier Vergano et al., 1993; Imai et al., 2001). Celen et al. also report reductions in the size of the cerebral cortex, corpus callosum and dentate gyrus, as well as decreased adult hippocampal neurogenesis, in *Arid1b* mutant mice (Celen et al., 2017). Shibutani et al. report no neuroanatomical abnormalities in non-hydrocephalic *Arid1b* haploinsufficient mice, but they also did not make any detailed histological examinations in that study (Shibutani et al., 2017). We also do not report any corpus callosum abnormalities, as we did not explicitly investigate the corpus callosum in the cited study (Jung et al., 2017).

Gene expression changes in *Arid1b* knockout mice

The ATP-dependent BAF chromatin remodeling complex regulates gene expression via nucleosome remodeling (Singhal et al., 2010; Alver et al., 2017). Considering ARID1B's role as a member of the BAF chromatin remodeling complex, it is unsurprising that heterozygous deletion of *Arid1b* leads to broad changes in gene expression in the brain. Shibutani et al. report that many of the genes shown to be up- and down-regulated in *Arid1b* heterozygous brains are similarly altered in human patients with ASD and in another animal model of autism (*Cdh8* heterozygous mice) (Shibutani et al., 2017). Celen et al. also report multiple changes in gene expression in *Arid1b* heterozygous mice, when compared to wild-type controls. In the adult hippocampus they find that genes associated with nervous system development and psychological, behavioral and developmental disorders appear to be distinctly affected. More specifically, they describe marked expression changes in Ephrin, nNOS, axonal guidance and glutamate receptor signaling pathway-related genes (Celen et al., 2017). Of the 140 differentially-expressed genes they identify, 91 are thought to be

directly targeted by the BAF chromatin remodeling complex (Attanasio et al., 2014; Celen et al., 2017) and 14 are included amongst the highest ranking autism risk genes in the SFARI database (Basu et al., 2009; Celen et al., 2017). A list of these genes can be found in Table 1.

Histone modifications such as acetylation and deacetylation are important for the regulation of gene expression (Eberharter and Becker, 2002; Kurdistani and Grunstein, 2003; Shahbazian and Grunstein, 2007; Bannister and Kouzarides, 2011; Lawrence et al., 2016). We report that *Arid1b* haploinsufficiency leads to an overall decrease in the acetylation of histone H3 at lysine 9 (H3K9ac) and tri-methylation of histone H3 at lysine 4 (H3K4me3), both markers of transcriptional activation, and an increase in tri-methylation of histone H3 at lysine 27, a marker for transcriptional repression (Figure 1) (Jung et al., 2017). We do not, however, report any global changes in histone acetyl-transferase (HAT) or histone deacetylase (HDAC) activity in *Arid1b* heterozygous brains, but do observe decreases in the level of acetyl-CREB-binding protein (CBP), which has been shown to enhance HAT function (Vecsey et al., 2007; Jung et al., 2017). In a similar vein, a previous study shows that HAT and HDAC activities are regulated by the interaction of ARID1B with HATs or HDACs in mouse osteoblast cells (Nagl et al., 2007). We also report decreased protein levels for PCAF, a HAT, in *Arid1b* homozygous embryonic brains, but not in *Arid1b* heterozygous brains, and decreased binding of several HATs to H3K9 acetylated sites in *Arid1b* heterozygous brains (Jung et al., 2017).

Corresponding with the overall reduction in PV-positive interneurons in *Arid1b* heterozygous cortices, we observe a decrease in *Pvalb* and *Ntrk2* transcripts in mutant brains. We further report that ARID1B binds to the *Pvalb* promoter in wild-type brains and that this localized binding is decreased in *Arid1b* heterozygous brains along with decreased H3K9ac in this region. One presumed effect of these changes is the decrease in transcriptional initiation for the *Pvalb* gene, shown by lower levels of the phosphorylated (ser5)-carboxy-terminal-domain of RNA polymerase II at the *Pvalb* promoter (Figure 1) (Jung et al., 2017). Therefore, ARID1B is likely an essential factor in regulating GABA neuron-associated genes through recruiting histone modification molecules to specific promoters and promoting chromatin remodeling for RNA polymerases to initiate gene transcription. These findings, in particular, provide insight into novel mechanisms for ARID1B-mediated gene regulation, as it appears that ARID1B-histone modifier interactions may act to facilitate gene transcription. It remains to be seen whether this is the case at the promoters of other genes altered in the *Arid1b* heterozygous mouse brain. These findings also suggest that the gross neural effects of *Arid1b*-deletion may be due to impaired stem cell differentiation via gene regulation during early development, as only a subset of inhibitory neurons are significantly decreased in *Arid1b* heterozygote mice.

Particularly, ARID1B may regulate histone modification at the Wnt signaling genes because *Arid1b* haploinsufficiency reduces the expression of Wnt-α-catenin signaling-related genes including *Cyclin D1, c-Myc, n-Myc, Creb, Lef1, Ctnnb1*, and others in inhibitory neural progenitors (Jung et al., 2017). A number of studies show that histone modifications can regulate cell proliferation and differentiation as well as cell death (Mehnert and Kelly, 2007; Roidl and Hacker, 2014; Li et al., 2018). Wnt signaling plays important roles in ventral progenitor proliferation during brain development (Liebner et al., 2008; Brandao and

Romcy-Pereira, 2015). Furthermore, expression of c-Myc, a key target of Wnt signaling and a cell cycle regulator, is decreased in ARID1B-deficient cells (Nagl et al., 2007). ARID1B deficiency also prevents the self-renewal capacity of embryonic stem cells (Yan et al., 2008). Thus, future studies should consider whether ARID1B can control Wnt-β-catenin signaling in ventral progenitor proliferation and development.

It should be noted that a number of studies have reported that the BAF complex and/or ARID1B repress Wnt-β-catenin signaling in vivo and in vitro in a subset of cell types (Vasileiou et al., 2015; Wu et al., 2016). A previous study, however, finds that BRG1, the central component of the BAF complex, physically interacts with β-catenin and facilitates target gene expression (Barker et al., 2001). Numerous studies demonstrate an extensive assortment of BAF complex configurations dependent on cell type and developmental stage (de la Serna et al., 2001; Olave et al., 2002; Lickert et al., 2004; Ohkawa et al., 2006; Cvekl and Duncan, 2007; Lessard et al., 2007; Li et al., 2013; Xiong et al., 2013; Son and Crabtree, 2014; Yu et al., 2015). This may explain the existence of apparently contradictory results regarding BAF complex regulation of Wnt-β-catenin. It is also possible that ARID1B's regulation of Wnt-β-catenin signaling in the developing brain occurs in a BAF-independent manner.

Arid1b haploinsufficiency and mouse behavior

ASD is associated with a variety of mutated genes or copy-number variants. Because experimental mouse models are important for discovering the causes and pathogeneses of human disorders, there have been many attempts to develop genetic animal models of ASD based on human ASD-linked genetic mutations (Kazdoba et al., 2014). Typical hallmarks of ASD include impaired social behavior and communication, and repetitive and/or stereotyped behaviors. Additionally, ASD often presents with other co-occurring conditions, including depression, epilepsy, anxiety (Wing and Gould, 1979), attention deficit hyperactivity disorder (ADHD), ID, and motor coordination problems (Purpura et al., 2016). Similar behaviors are seen in animal models of ASD using specific tests developed to measure these behavioral abnormalities. One of the most commonly inherited genetic causes of ASD is FXS, which is caused by an expanded CGG repeat in the 5' untranslated portion of the fragile X mental retardation 1 gene (*FMR1*), leading to deficiency or absence of the FMR1 protein (Harris et al., 2008; Kogan et al., 2009). Mouse models of FXS (*Fmr1* knockout mice) exhibit several ASD- and ID-like behaviors such as anxiety, social behavior deficits, and cognitive deficiencies, although different groups report varying degrees of behavioral abnormalities and sometimes contradict one another (Harris and Kater, 1994; Peier et al., 2000; Yabe et al., 2004; McNaughton et al., 2008; Pietropaolo et al., 2011; Kazdoba et al., 2014). Due to the multiple variables present in mouse colony maintenance and in the inconsistent environmental conditions between laboratories, reproducing animal behavior, even in the same mouse model, is a difficult task. Without complete and detailed reporting of all protocols and experimental conditions, determining the grounds for discordant behavioral results is next to impossible. Contradictory results in the same mouse strains in different environments can be beneficial, however, as assays performed in standardized conditions actually have an increased likelihood of reporting false-positives (Richter et al., 2009). In

order to draw more accurate conclusions, it is therefore beneficial to compare behavioral experiment results between groups using the same or similar animal models.

Recently, three independent groups, including our own, developed mouse models of ARID1B haploinsufficiency. Two of the groups delete exon 5 of the *Arid1b* gene (Celen et al., 2017; Jung et al., 2017) while the other removes exon 3 (Shibutani et al., 2017), but both strategies appear to result in haploinsufficiency due to frameshift mutations. Celen et al. and Shibutani et al. generate the mutant mice using CRISPR/Cas9 gene editing while Jung et al. use a more traditional knockout strategy. The genetic background of the three mouse models is C57BL/6. Each group performed a different array of behavioral assays, many overlapping, and the results are generally concurrent, with a few exceptions. A summary of each group's results is described in Table 2. All three groups performed the elevated plus maze test for anxiety-like behavior. *Arid1b* heterozygous mice spend less time in the open arms of the maze and exhibit a lower percentage of entries into open arms, which indicates heightened anxiety (Celen et al., 2017; Jung et al., 2017; Shibutani et al., 2017). In the open field test, *Arid1b* heterozygous mice spend less time in the center area and enter the center area less frequently than controls, although their total travel distance is not different, which may also indicate anxiety-like behavior (Celen et al., 2017; Jung et al., 2017). In addition, *Arid1b* heterozygous mice avoid exploring the brightly-lit section in the light-dark box test, another common anxiety assay (Celen et al., 2017). *Arid1b* heterozygous mice also spend more time immobile in the forced swim and tail suspension tests, used to assess depression-like behavioral phenotypes (Jung et al., 2017), although Shibutani et al. report opposite results in the forced swim test (Shibutani et al., 2017).

As discussed above, one of the key characteristics of ASD is deficits in social behavior (Cohen et al., 1988). We use the three-chamber social assay to assess social interaction and social novelty preference. *Arid1b* heterozygous mice spend less time in the chamber containing an unfamiliar mouse than in the empty chamber, indicative of impaired social interaction, and also spend less time with a novel stranger mouse than they do with a more-familiar stranger (Jung et al., 2017). Celen et al. report that *Arid1b* heterozygous mice spend less time interacting with unfamiliar juvenile mice compared to WT littermates, when placed together in a fresh cage (Celen et al., 2017).We additionally report that *Arid1b* heterozygous mice spend less time interacting with one another when two unfamiliar mice of the same genotype are placed in the open field, compared with WT controls (Jung et al., 2017). Shibutani et al. evaluate social behavior between mice of the same genotype in a home-cage environment and observe decreased interaction between *Arid1b* heterozygous mice, compared with WT controls. In open field social interaction and three-chamber sociability and social novelty tests, however, Shibutani et al. do not report any differences between *Arid1b* heterozygous and control mice (Shibutani et al., 2017). This discrepancy could be due to a multitude of factors including animal stress, differences in protocols or environmental stimuli. Taken together, however, all three groups report significant impairments in social behavior in *Arid1b* heterozygous mice (Celen et al., 2017; Jung et al., 2017; Shibutani et al., 2017). These results agree with those seen in other mouse models of ASD, including haploinsufficiency of *Chd8* (Katayama et al., 2016).

Intellectual disability is a common comorbid disorder with ASD and is present in patients with haploinsufficient mutations of ARID1B (Santen et al., 2014), as well as in FXS (Harris et al., 2008). *Arid1b* heterozygous mice present with learning and memory deficits (Jung et al., 2017), which have also been observed in previous animal models of ASD (Kim et al., 2014). We use the Morris water maze test to assess cognitive function in *Arid1b* heterozygous mice. These mutant mice exhibit increased escape latencies during training trials and spend less time in the target quadrant during probe trials, with no changes in the distance or speed of swimming, compared with controls (Jung et al., 2017). However, another group reports that *Arid1b* heterozygous mice do not exhibit cognitive deficits as measured by the Morris water maze test (Celen et al., 2017). Celen and colleagues' results are unexpected and somewhat surprising given the strong neurogenetic evidence of *Arid1b* haploinsufficiency causing intellectual disability (Halgren et al., 2012; Hoyer et al., 2012; Santen et al., 2012). In the Barnes maze task, another assay of spatial learning and memory, Shibutani et al. report that *Arid1b* heterozygous mice demonstrate a similar latency to escape compared with wild type littermates, but, when the escape box is moved to the opposite side of the maze in a reversal task, mutant mice display a significantly longer latency to escape (Shibutani et al., 2017). This is indicative of increased perseveration or behavioral inflexibility. We also perform the novel-object recognition test to assess recognition memory. We find that *Arid1b* heterozygous mice demonstrate no preference for a novel object over a familiar one, whereas control mice spend considerably more time interacting with the novel object (Jung et al., 2017). *Arid1b* heterozygous mice are also less successful in the T-maze test, compared to controls (Jung et al., 2017). However, Shibutani et al. report that their *Arid1b* heterozygous mice do not demonstrate any deficiencies in the T-maze test, although they did not publish any of this data or report the method or protocol used (Shibutani et al., 2017). In addition, Celen et al. report that *Arid1b* heterozygous mice respond normally to foot shocks and perform similarly to controls in fear conditioning tests, while Shibutani et al. report that *Arid1b* heterozygous mice display a heightened response to foot shocks and enhanced performance in fear conditioning tests (Shibutani et al., 2017). Reports on FXS mouse models are also inconsistent in contextual and cued fear conditioning tests (Paradee et al., 1999; Dobkin et al., 2000; Van Dam et al., 2000; Auerbach et al., 2011; Ding et al., 2014; Kazdoba et al., 2014), which implies that these fear conditioning paradigms may be unreliable methods for testing cognitive deficits in genetic mouse models of ID.

In summary, *Arid1b* heterozygous mice demonstrate anxiety-like behavior, social behavior deficits and learning/memory impairments. Although there exists some contradiction regarding the results of a subset of individual behavioral assays, *Arid1b* heterozygous mice conveniently recapitulate many ASD-like and ID-like behavioral profiles, similar to those seen in other mouse models (Bilousova et al., 2009; Kazdoba et al., 2014; Katayama et al., 2016). Therefore, *Arid1b* heterozygous mouse models present a useful opportunity for advancing our understanding of the pathogenesis and underlying mechanisms of neurodevelopmental disorders and related behavioral defects.

GABA modulation as therapeutic interventions for *Arid1b* haploinsufficiency-induced neurodevelopmental conditions

As stark decreases in PV-positive interneurons are seen in *Arid1b* heterozygous cortices, in our study we attempt to rescue some of the behavioral deficits in these mice using a positive allosteric modulator for the $GABA_A$ receptor, clonazepam (Jung et al., 2017). Clonazepam is shown to be effective in treating seizures and anxiety in humans (Dahlin et al., 2003) and also effectively ameliorates some of the behavioral deficits in the BTBR mouse ASD model (Han et al., 2014). Accordingly, we observe that a single intraperitoneal injection of clonazepam at a concentration of 0.0625 mg/kg for 0.5 to 1h prior to behavioral assays is sufficient to rescue impaired recognition memory, social memory and heightened anxiety-like behavior in adult *Arid1b* heterozygous mice but has no measurable effect on depression-like behaviors. Clonazepam treatment also rescues the decreased mIPSC frequency in *Arid1b* heterozygous mice (Jung et al., 2017). While it is encouraging to see that treatment with a GABA allosteric modulator is sufficient to rescue several of the hallmark behavioral abnormalities in this mouse model of ASD and ID, attempted restoration of the excitatory/inhibitory imbalance in *Arid1b* heterozygous mice does not lead to improvements in all behavioral tests. Thus, there appears to be more at play in this mouse model than a gross reduction in the interneuron population. Clonazepam, or related drugs, may still prove to alleviate some of the symptoms caused by excitatory/inhibitory imbalance, be it due to *ARID1B* haploinsufficiency or other causes. It is especially promising that this treatment leads to improved behavior in adult mice, which may indicate that treatment during a critical developmental window may not be entirely necessary to treat all consequences of *ARID1B* haploinsufficiency. A deeper understanding of the cell-types and circuits regulating the behaviors related to ASD and ID will be required to develop more targeted therapies.

Arid1b haploinsufficiency and body growth

All three groups find reduced body weight at multiple ages in *Arid1b* heterozygous mice, compared with controls (Celen et al., 2017; Jung et al., 2017; Shibutani et al., 2017). Jung et al. report that females show less obvious weight differences than males (Jung et al., 2017). Mice lacking one copy of *Arid1b* also develop disproportionately small kidneys and hearts (Celen et al., 2017). Celen et al. hypothesize that the growth hormone-releasing hormone–growth hormone–Insulin-like growth factor (GHRH-GH-IGF) axis deficiencies could be responsible for the smaller body size observed in *Arid1b* heterozygous mice and the short stature reported in *ARID1B* human patients (Santen et al., 2014; Celen et al., 2017). They report reduced IGF1 protein levels in the plasma and lower *Igf1* mRNA levels in the liver but no changes in GH in the pituitary gland or fasting plasma of *Arid1b* heterozygous mice. The pituitary gland also appears to respond normally to GHRH stimulation and they detect no change in *Ghrh* mRNA levels in the hypothalamus.

To ascertain whether this reduction in IGF1 in *Arid1b* heterozygous mice is indeed due to a problem with central nervous system (CNS) control of the GHRH-GH-IGF axis, Celen et al. conditionally delete one copy of *Arid1b* in the CNS and peripheral nervous system or in the liver by crossing $Arid1b^{Fl/+}$ mice with *Nestin-Cre* mice or *Albumin-Cre* mice, respectively.

The *Nestin-Cre; Arid1b*$^{Fl/+}$ mice present with a similar growth impairment and a reduction in plasma IGF1 levels with no accompanying increase in GH. *Albumin-Cre; Arid1b*$^{Fl/+}$ mice do not demonstrate any significant differences in body size or in plasma IGF levels, when compared to controls. Therefore, nervous system-based haploinsufficiency of *Arid1b* is likely the cause of the growth retardation and GHRH-GH-IGF deficiencies observed in *Arid1b* heterozygous mice (Celen et al., 2017). It should be noted, however, that the *Nestin-Cre* mouse driver line has been reported to have hypopituitarism, decreased anxiety-like behavior and lower body weight (Galichet et al., 2010; Harno et al., 2013; Giusti et al., 2014; Declercq et al., 2015). As Celen et al. do not include the Cre-driver lines as controls in their conditional knockout experiments (Celen et al., 2017), these results should be cautiously interpreted until they can be independently confirmed. Celen et al. also attempt to treat the smaller body size and weight by correcting the apparent GHRH-GH-IGF deficiencies. They first treat *Arid1b* heterozygous mice with recombinant human IGF1, but this does not have any measurable effects on body weight or anxiety-like behavior. Treatment with recombinant mouse GH for 40 consecutive days, however, is sufficient to rescue the growth deficits and grip weakness in *Arid1b* haploinsufficient mice but has no measurable effect on anxiety-like behavior (Celen et al., 2017).

Concluding remarks/future directions

ARID1B research has made rapid advances in recent years, thanks in part to the development of *Arid1b* mutant mouse models. Because they closely recollect the behavioral effects of *ARID1B* mutations in the human population and resemble other ASD and ID mouse models, *Arid1b* mutant mice have the potential to provide profound insights into ARIDIB's broad role in brain development and activity. *Arid1b* heterozygous mice may also continue to prove useful as preclinical models of excitatory/inhibitory imbalance in the brain.

Further research should continue to decipher the molecular mechanisms by which ARID1B regulates gene expression and, thus, brain function. Additionally, *Arid1b* heterozygous mice could be used to dissect neural circuits that regulate behaviors related to ASD and ID. Mouse models in which *Arid1b* can be conditionally deleted in specific neuronal subtypes will also provide more mechanistic insight, seeing as *Arid1b* homozygous mice do not survive postnatally (Celen et al., 2017; Jung et al., 2017; Shibutani et al., 2017). For example, we have already shown that hemizygous deletion of *Arid1b* in GABAergic interneurons recapitulates many of the behavioral abnormalities present in *Arid1b* heterozygous mice (Jung et al., 2017), but it may prove fruitful to further exam the effects of cell-type specific *Arid1b* deletion in other neuronal subsets. Drugs that influence histone modifiers may be another avenue worth exploring. Future studies are required to provide a better understanding of ARID1B's gene regulatory mechanisms. Overall, ARID1B is critical in regulating proper nervous system development and behavior. Recent advances in technology and the utilization and sharing of large data sets will help provide the tools necessary for major breakthroughs in neurodevelopmental disorder research around *ARID1B* haploinsufficiency.

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Highlights

- *Arid1b* haploinsufficiency leads to autistic behavior and intellectual dysfunction.
- *Arid1b* haploinsufficiency causes E/I imbalance due to abnormal GABA interneurons.
- Altered epigenetic modifications are associated with *Arid1b* haploinsufficiency.
- GABA PAM rescues abnormal behaviors induced by *Arid1b* haploinsufficiency.
- Recombinant growth hormone increases body size in *Arid1b* haploinsufficient mice.

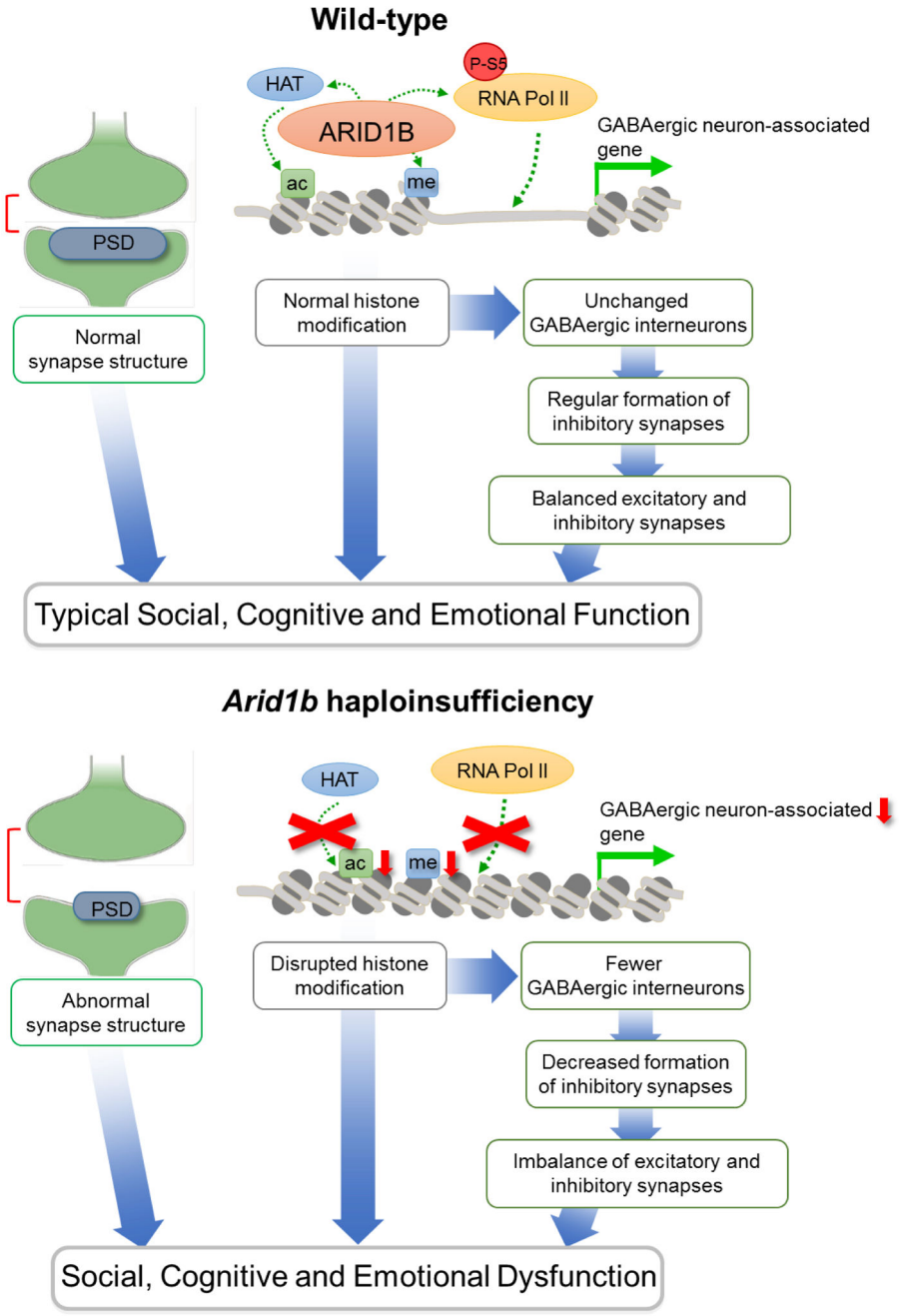

Figure 1. Graphical model of the neuronal effects of *Arid1b* haploinsufficiency.

Arid1b heterozygous mice exhibit wider inhibitory synaptic clefts and narrower postsynaptic density (PSD). The mutant mice also show lower levels of transcription-activating histone post-translational modifications at specific GABAergic neuron-associated promoters. The latter leads to decreased phosphorylation of Ser 5 within the CTD of RNA polymerase II at these DNA loci, which is necessary for gene transcription. These changes in gene expression contribute to the functional, anatomical and behavioral abnormalities observed in *Arid1b* mutant mice.

Table 1.

Selected genes with altered expression in *Arid1b* heterozygous mice

GENE	FUNCTION/DESCRIPTION	ASD ASSOCIATION*
ARID1B	Chromatin remodeling subunit	High confidence (syndromic)
GRIN2B	NMDA receptor subunit	High confidence
ZBTB20	Transcription factor	Suggestive evidence (syndromic)
PRICKLE1	Nuclear receptor	Suggestive evidence
PRICKLE2	Nuclear receptor	Suggestive evidence
RBFOX1	Alternative splicing regulator	Suggestive evidence
HOMER1	Postsynaptic density scaffolding	Minimal evidence
LAMA1	Lamanin alpha 1 subunit	Minimal evidence
MKL2	Transcriptional coactivator	Minimal evidence
NBEA	A-kinase anchor protein	Minimal evidence
NTNG1	Neurite outgrowth-promoting protein	Minimal evidence
SOX5	Transcription factor	Minimal evidence
SSPO	Neuronal aggregation modulator	Minimal evidence
EGR2	Transcription factor	Hypothesized
EPHA6	Receptor tyrosine kinase	Hypothesized
ITGA4	Integrin subunit	Hypothesized
ROBO1	Membrane protein involved in axon guidance and cell migration	Hypothesized

*Based on Simons Foundation Autism Research Initiative (SFARI) numerical gene scoring: 1 = High confidence; 2 = Strong candidate; 3 = Suggestive evidence; 4 = Minimal evidence; 5 = Hypothesized; 6 = Not supported.

Table 2.

Summary of behavioral findings from three studies utilizing *Arid1b* heterozygous mice

HUMAN BEHAVIORAL CORRELATE	BEHAVIORAL ASSAY	CELEN ET AL. 2017	JUNG ET AL. 2017	SHIBUTANI ET AL. 2017
ANXIETY	Elevated Plus Maze	Heightened Anxiety	Heightened Anxiety	Heightened Anxiety
ANXIETY	Open Field	Heightened Anxiety	Heightened Anxiety	Unclear
ANXIETY	Light-Dark Box	Heightened Anxiety	n/a	No Change
DEPRESSION	Forced Swim	n/a	Increased Depression	Increased Activity
DEPRESSION	Tail Suspension	n/a	Increased Depression	n/a
SOCIAL INTERACTION	Three-Chamber Test for Sociability	n/a	Decreased Social Interaction	No Change
SOCIAL INTERACTION	Three-Chamber Test for Social Novelty Preference	n/a	Decreased Social Interaction	No Change
SOCIAL INTERACTION	Home-Cage Social Interaction	n/a	n/a	Decreased Social Interaction
SOCIAL INTERACTION	Open Field Social Interaction	Decreased Social Interaction	Decreased Social Interaction	No Change
COMMUNICATION	Ultrasonic Vocalizations	Altered Communication	n/a	n/a
REPETITIVE BEHAVIOR	Grooming	Increased Repetitive Behavior	Increased Repetitive Behavior	No Change
BEHAVIORAL INFLEXIBILITY	Barnes Maze	n/a	n/a	Decreased Behavioral Flexibility
INTELLECTUAL DISABILITY	Morris Water Maze	No Change	Impaired Spatial Memory	n/a
INTELLECTUAL DISABILITY	Novel Object Recognition	n/a	Impaired Recognition Memory	n/a
INTELLECTUAL DISABILITY	T-Maze	n/a	Impaired Learning	No Change
INTELLECTUAL DISABILITY	Barnes Maze	n/a	n/a	No Change
INTELLECTUAL DISABILITY/FEAR LEARNING	Fear Conditioning	No Change	n/a	Increased Long-Term Fear Memory and Fear Generalization
PAIN RESPONSE	Response to Foot Shock	No Change	n/a	Heightened Response to Stimulus

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