NEUROBIOLOGY OF ARID1B HAPLOINSUFFICIENCY RELATED TO NEURODEVELOPMENTAL AND PSYCHIATRIC DISORDERS

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Abstract

ARID1B haploinsufficiency is a frequent cause of intellectual disability (ID) and autism spectrum disorder (ASD), and also leads to emotional disturbances. In this review, we examine past and present clinical and preclinical research into the neurobiological function of ARID1B. The presentation of ARID1B-related disorders (ARID1B-RD) is highly heterogeneous, including varying degrees of ID, ASD and physical features. Recent research includes the development of suitable clinical readiness assessments for the treatment of ARID1B-RD, as well as similar neurodevelopmental disorders. Recently developed mouse models of Arid1b haploinsufficiency successfully mirror many of the behavioral phenotypes of ASD and ID. These animal models have helped to solidify the molecular mechanisms by which ARID1B regulates brain development and function, including epigenetic regulation of the Pvalb gene and promotion of Wnt/β-catenin signaling in neural progenitors in the ventral telencephalon. Finally, preclinical studies have identified the use of a positive allosteric modulator of the GABAA receptor as an effective treatment for some Arid1b haploinsufficiency-related behavioral phenotypes, and there is potential for the refinement of this therapy in order to translate it into clinical use.

Keywords

ARID1B; intellectual disability; autism; BAF; neurodevelopment

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Introduction

Advances in genetic sequencing and enhancements in the development of animal models provide avenues for discovering mutations underlying neurodevelopmental disorders and deciphering the roles of these mutated genes in brain development and behavior. In 2010 a patient that presented with agenesis of the corpus callosum, intellectual disability (ID) and features of autism spectrum disorder (ASD) was found to harbor a mutation resulting in haploinsufficiency of the ARID1B gene. Not long thereafter, a separate research group identified 8 additional patients with similar symptoms caused by ARID1B haploinsufficiency. Then, in 2012, three groups independently identified haploinsufficiency of ARID1B as a relatively frequent cause of syndromic and non-syndromic intellectual disability. Since that time, numerous studies have further validated and defined the important role of ARID1B mutations in neurodevelopmental disorders.

ARID1B encodes the AT-rich interactive domain-containing protein 1B (ARID1B), also known as BAF250B, a large subunit of the BRG1/BRM-associated factor (BAF) chromatin remodeling complex (mammalian SWI/SNF complex). Following the discovery of ARID1B mutations as a monogenic cause for ID and ASD, preclinical research examining the neurodevelopmental and neurobiological functions of ARID1B has accelerated. This work has begun to shed light on the potential for pharmacological interventions targeting the root causes of ID and ASD due to ARID1B haploinsufficiency, which ameliorate a host of symptoms in animal models. Translating similar treatments for neurodevelopmental disorders into clinical use has proved challenging and controversial up to this point.

In this review we discuss recent advances in preclinical and clinical research regarding ARID1B haploinsufficiency, with a lens toward developing targeted and effective treatments for affected individuals.

Disorders and neurobehavioral phenotypes associated with ARID1B mutations

ID is a developmental disorder affecting approximately 1–8% of the overall population. It is characterized by significant limitations in cognitive function and adaptive behaviors, imposing a considerable burden on affected individuals and their caregivers. Several studies report that the underlying cause of ID is of primarily genetic origin, with over two thousand associated genes identified. Mutational analysis in 887 patients with nonspecific ID revealed nine patients (0.9%) with de novo nonsense or frameshift mutations resulting in a truncated copy of ARID1B. Exome sequencing studies on large cohorts of children with undiagnosed developmental disorders from the Deciphering Developmental Disorders (DDD) study in the United Kingdom also identified ARID1B mutations as the most frequent cause of ID; out of the 271 DDD diagnoses examined, 11 patients exhibited ARID1B mutations, which represent 4.7% of total ID diagnoses. Two of these individuals also exhibited comorbid ASD (9.1% of total ASD diagnoses), and one of those also presented with seizures (2.6% of patients with seizures).

While ID is a highly heterogenous disorder, there are multiple syndromic subtypes. Coffin-Siris syndrome (CSS) is characterized by mild to severe ID, speech impairment, coarse
Facial features, growth deficiencies, and hypoplastic or absent fifth fingernail or toenail. Additionally, agenesis of the corpus callosum is frequently seen in CSS patients. Utilizing whole-exome sequencing to identify the genetic origins of CSS in three diagnosed individuals, Santen et al. revealed heterozygous, de novo truncating mutations in the ARID1B gene in all cases. Additionally, copy-number variation analysis in 2,000 individuals with ID showed that three subjects with ARID1B gene deletions exhibited phenotypes overlapping with CSS. Exome sequencing done by Tsurusaki et al. also revealed that out of 23 individuals diagnosed with CSS, six patients had de novo heterozygous mutations in ARID1B, further suggesting haploinsufficiency of ARID1B as a cause of CSS. Further targeted sequencing studies also identified mutations in other BAF complex genes in individuals affected with CSS (SMARCA4, SMARCB1, SMARCA2, SMARCE1, ARID1A, DPF2, and ARID2) and the specific gene that is mutated appears to influence the presentation and severity of associated symptoms. Disorders caused by ARID1B are better described as being on a spectrum including non-syndromic ID and CSS cases, either with or without additional physical and/or neurological symptoms, and referred to under the umbrella term, ARID1B-related disorders (ARID1B-RD).

ASD is a neurodevelopmental disorder characterized by significant social and communication deficits as well as stereotyped behaviors, affecting approximately 1 in 54 individuals. ID is also a prevalent phenotype in ASD patients, seen in 30–75% of affected individuals. Next generation sequencing and microarray analysis from eight ID patients showed de novo translocations or deletions that resulted in a truncated copy of the ARID1B gene in each case. Of these, five patients exhibited phenotypes consistent with ASD. Further, brain imaging indicates that four patients also had corpus callosum defects. An additional study revealed that ASD patients have a decreased transcript level of the ARID1B gene. The SFARI Gene initiative, a comprehensive database of genes and copy number variants associated with ASD, also classified ARID1B as one of 25 high confidence genes related to autism.

ASD often presents with other co-occurring conditions, including epilepsy and attention-deficit/hyperactivity disorder (ADHD). Approximately one third of individuals with ARID1B mutations experience epileptic seizures, particularly of the tonic-clonic type, characterized by full-body muscle stiffening followed by rhythmic jerking of the body. Epilepsy is a common comorbidity in pediatric patients with ID/global developmental delay (ID/GDD-EP), with an estimated prevalence of about 22.2%. In a study of 143 ID patients with ARID1B mutations, 27.5% individuals suffered from epileptic seizures. Additionally, a copy number variation analysis on seven pediatric patients with nonspecific ID/GDD-EP revealed one individual with an ARID1B gene deletion presenting with CSS phenotypes and epilepsy. While the overall prevalence is unknown, individuals with ARID1B-related disorders also appear to be at an increased risk of attention-deficit/hyperactivity disorder (ADHD) diagnoses.

A list of all the human studies discussed in this review can be found in Table 1. The results of these studies underscore the crucial role that ARID1B plays in normal brain development and behavior. Several mutations leading to ARID1B haploinsufficiency cause developmental disorders including ID, CSS, and ASD, as well as abnormalities of the corpus callosum.
These findings further support the hypothesis that deficits in chromatin remodelers play a significant role in neurodevelopmental disorders.

**Behavioral phenotypes of Arid1b haploinsufficient mice**

Three groups recently developed mouse models of ARID1B haploinsufficiency. Two groups generated heterozygous mice by removing exon 5 of the Arid1b gene,\textsuperscript{9,19} while the other group removed exon 3.\textsuperscript{52} Celen et al. and Shibutani et al. used the CRISPR/Cas9 gene editing system to generate mutant mice, while Jung et al. used a more traditional knockout strategy. All methods resulted in frameshift mutations and loss of function of one copy of the gene. Each group performed a variety of assays to characterize the behavioral phenotypes of Arid1b haploinsufficient mice. A summary of each group’s results is described in Table 2.

As mentioned previously, ID is characterized by severe limitations in cognitive function.\textsuperscript{25,53} Arid1b heterozygous mice present with significant deficits in learning and memory. Using the Morris water maze to assess spatial reference memory, Jung et al. showed that heterozygous mice have increased escape latencies during training and spend less time in the target quadrant during probe trials.\textsuperscript{9} Surprisingly, Celen et al. detected no cognitive deficits using Morris water maze test.\textsuperscript{19} The T-maze is another test used to assess spatial reference memory. Jung et al. reported that Arid1b heterozygous mice are less successful in the T-maze test,\textsuperscript{9} however Shibutani et al. did not find any deficits in mutant mice.\textsuperscript{52} To assess recognition memory, Jung et al. also performed the novel object test. They found that heterozygous mice show no preference for a novel object over a familiar one, while control mice prefer the novel object.\textsuperscript{9} Additionally, Jung et al. assessed motor learning ability using the rotarod test and report that mutant mice exhibit a decreased latency to fall off the rotating rod and limited ability to learn throughout training days.\textsuperscript{9} Both other groups also assessed fear learning. While Shibutani et al. showed that Arid1b heterozygous mice have enhanced performance in fear conditioning tests,\textsuperscript{52} Celen et al. reported that mutant mice perform similarly to controls.\textsuperscript{19}

The core characteristics of ASD include deficits in social interaction and communication as well as repetitive, stereotyped behaviors.\textsuperscript{38,39} All three groups assessed sociability with an array of tests. In the open field social interaction test, both Jung et al. and Celen et al. reported reduced interaction time when an Arid1b heterozygous mouse is introduced to an unfamiliar mouse in an open arena.\textsuperscript{9,19} Using the 3-chamber test for sociability, Jung et al. also showed that mutant mice spend more time in the empty chamber while controls prefer the chamber with an unfamiliar mouse.\textsuperscript{9} The 3-chamber test for social novelty also indicated that mutant mice spend less time with a novel stranger than they do with a more familiar stranger.\textsuperscript{9} Interestingly, Shibutani et al. reported no change in sociability/social novelty in either the open field or 3-chamber tests; however, they did observe reduced interaction between Arid1b heterozygous mice in a home-cage environment.\textsuperscript{52} To assess changes in communication between mice, Celen et al. examined ultrasonic vocalizations (USVs) and reported that mutant mice emit USVs that are longer in duration and of abnormal pitch compared to controls.\textsuperscript{19} All three groups examined the incidence of repetitive behaviors by assessing grooming. Both Jung et al. and Celen et al. reported an
increase in time spent self-grooming in Arid1b heterozygous mice\textsuperscript{9, 19}, while Shibutani et al. detected no change in grooming times compared to controls\textsuperscript{52}.

Anxiety and depression-like behaviors are common comorbidities seen with ASD\textsuperscript{54, 55}. All three groups utilized the elevated plus maze to assess anxiety-like behavior in Arid1b heterozygous mice. Mutant mice spend less time in, and exhibit fewer entries into, the open arms of the maze in all cases\textsuperscript{9, 19, 52}. In the open field test, Arid1b heterozygous mice also spend less time in, and have fewer entries into, the center of the arena\textsuperscript{9, 19}. Additionally, Celen et al. reported that mutant mice avoid exploring the brightly-lit section of the light-dark box test\textsuperscript{19}, while Shibutani et al. identified no changes in exploratory behavior compared to controls\textsuperscript{52}. In assessing depression-like behavior, Jung et al. reported that Arid1b heterozygous mice exhibit greater immobility time in the forced swim and tail suspension tests\textsuperscript{9}. Interestingly, Shibutani et al. reported contradictory results in the forced swim test\textsuperscript{52}.

Together, results from these three studies consistently show that Arid1b heterozygous mice recapitulate the majority of behavioral phenotypes seen in ASD and ID, thus providing a useful tool moving forward to better understand the pathology underlying these disorders. The few discrepancies among the results of individual behavioral assays can likely be explained by differences in specific protocols, mouse handling and stressors, and environmental stimuli.

**Interneuron subtype-specific behavior**

Many neurodevelopmental disorders are characterized by significant deficits in inhibitory interneuron development\textsuperscript{56–58}. In a recent study, Smith and colleagues highlighted distinct roles of two interneuron subtypes in mediating ASD- and ID-associated behaviors\textsuperscript{59}. To examine interneuron subtype-specific behavior in mice, they generated conditional knockout mice exhibiting Arid1b haploinsufficiency in either parvalbumin- (PV) or somatostatin-expressing (SST) interneurons. Smith et al. showed that haploinsufficiency in PV subtypes alters social and emotional behaviors, while haploinsufficiency in SST subtypes affects cognitive function and repetitive behavior\textsuperscript{59}, together recapitulating the phenotypes of global Arid1b haploinsufficiency\textsuperscript{9}. Table 3 summarizes the behavioral phenotypes observed with global Arid1b haploinsufficiency in comparison to haploinsufficiency specifically in PV and SST interneurons. These results provide further insight into how individual interneuron subtypes may contribute to neurodevelopmental disorders, paving the way for even more targeted therapeutic strategies.

**The role of ARID1B in neural development**

The BAF complex, including ARID1B, is essential for neurodevelopmental processes such as neural stem cell generation, proliferation, migration, and differentiation into neuronal subtypes. ARID1B haploinsufficiency causes abnormal regulation of cell cycle re-entry in developmentally arrested cells\textsuperscript{60}. Thus, ARID1B mutations impair developmental processes by abnormal initiation of progenitor cell proliferation\textsuperscript{6}. In addition, homozygous knockout of Arid1b in mice is embryonic-lethal, but Arid1b knockout embryonic stem cells demonstrate a reduced proliferation rate and perturbation of differentiation and the cell
cycle 61. It is unclear, however, how ARID1B deletion is linked to neural proliferation and eventual functional neurodevelopmental deficits, but recent studies exploring these questions are addressed in greater detail below.

The BAF complex is important for neuronal morphogenesis during brain development. Arid1b is highly expressed in differentiated neurons in the developing and postnatal mouse brain, and knockdown of Arid1b influences the expression of several genes known to promote neuronal migration and neurite outgrowth, such as Gap43, Gprn1, and Stmn2 8. It was previously reported that another BAF subunit, BAF53b, also has a critical role in activity-dependent dendritic outgrowth via regulation of Gap43 and Ephexin1 transcription 62. Knockdown of ARID1B in cortical pyramidal neurons leads to abnormal dendrite arborization and dendritic spine formation through suppression of c-Fos and Arc 8, which play critical roles in dendritic and synaptic development 63, 64. Moreover, knockdown of ARID1B markedly decreases dendritic innervation into cortical layer I, with fewer apparent attachments of dendritic terminals at the pial surface 8. Apical dendritic attachments in layer I are crucial for feedback interactions in the cerebral cortex involved in associative learning and attention 65–67. Furthermore, targeting the let-526 gene in C. elegans, an ARID1B ortholog, also leads to aberrant dendritic arborization, and the severity of these effects are gene dose-dependent 68.

Consistently, many BAF complex subunits are involved in regulating neurite architecture during brain development. For example, the BAF complex subunit, BAF100a, is required for terminal maturation and morphogenesis of dorsal spinal neurons during spinal cord development 69. Moreover, the BAF complex mechanistically plays a role in the calcium-mediated transcription activation function of calcium-responsive trans-activator (CREST), which is a key factor for proper dendrite outgrowth, arborization, and refinement 70. Thus, ARID1B and the BAF complex play a crucial role in neuronal morphogenesis and dendrite formation. Importantly, dendritic impairments are found in neurodevelopmental disorders associated with ARID1B mutations 71, 72.

Role of ARID1B in inhibitory neural communication

Gamma-aminobutyric acid-ergic (GABAergic) inhibitory interneurons represent around 10–20% of the total cortical cell population 73. GABAergic inhibitory interneurons inhibit a complex network of excitatory and inhibitory neurons in multiple cortical circuits 74. GABAergic inhibitory interneurons, such as parvalbumin- (PV), somatostatin- (SST), calretinin, calbindin 1- and neuropeptide Y-expressing subtypes are the source of GABA in the nervous system and play an important role in neural function and activity 75–77. Cortical inhibitory interneurons are generated by progenitor cells originating from the ganglionic eminence 78. Alterations in GABAergic inhibitory interneuron density and number are involved in human neurodevelopmental disorders and associated mouse models 79, 80. For instance, GABA levels are lower in frontal, motor, somatosensory and auditory cortices in ASD patients 81–84. Haploinsufficiency of the gene encoding the voltage-gated sodium channel SCN1A, another monogenic cause of ASD, in mice decreases GABAergic inhibitory interneuron density 85, while SH3 And Multiple Ankyrin Repeat Domains 1 (Shank1) mutations lead to elevated PV-positive cell numbers in the mouse brain 86. In
addition, knockout of the gene encoding Contactin-associated protein-like 2 (Cntnap2) leads to downregulation of PV expression levels in various brain regions. Malfunctions in GABAergic inhibitory interneurons induce social deficits and repetitive behavior. Jung and colleagues showed that PV-positive and total GABAergic interneuron numbers are significantly decreased in Arid1b haploinsufficient mice. In addition, the number of total and PV-positive GABAergic interneurons are also decreased following heterozygous conditional deletion of Arid1b in interneuron progenitors. However, GABAergic interneuron migration routes and speeds remain normal in Arid1b haploinsufficient mice. Furthermore, the numbers of vesicular GABA transporter (VGAT) and glutamic acid decarboxylase-positive (GAD) inhibitory synapses, which are responsible for GABA transport and synthesis in synaptic vesicles, are decreased in Arid1b haploinsufficient mice. However, the number of excitatory synapses expressing vesicular glutamate transporter 1 (VGLUT1), is unchanged in Arid1b haploinsufficient mice, compared to wild type littermates. Moreover, heterozygous knockout of Arid1b reduces the number of GABAergic inhibitory interneurons by inhibiting proliferation of ganglionic eminence progenitors and by accelerating apoptosis of developing interneurons. The altered number and density of GABAergic interneurons in Arid1b haploinsufficient brains likely leads to abnormal neuronal connectivity, thus breaking a systemic balance between excitation and inhibition (E/I imbalance) and influencing behavior.

Normal morphology and molecular composition of synapses are essential for proper synaptic function. Deletion of the gene encoding ELKS2alpha/CAST limits the size of the readily-releasable pool of synaptic vesicles at the active zone of inhibitory synapses and engenders abnormal behavior. In addition to the reduced number of inhibitory interneurons, Jung et al. showed that Arid1b haploinsufficiency results in an expanded inhibitory synaptic cleft and shortened postsynaptic density length, potentially contributing to E/I imbalance. Miniature excitatory postsynaptic currents (mEPSCs) and miniature inhibitory postsynaptic currents (mIPSC) coincide with the spontaneous release of small quantities of excitatory or inhibitory chemical neurotransmitters from presynaptic terminals. Therefore, the mEPSC or mIPSC frequency and amplitude in postsynaptic neurons is assumed to relate to factors operating presynaptically. Using whole-cell patch-clamp recording on cortical slices, Jung et al. reported that the mIPSC frequency and amplitude in pyramidal neurons diminish with heterozygous deletion of Arid1b. In contrast, there are no significant changes in the frequency or amplitude of mEPSCs between control and Arid1b haploinsufficient neurons. These results suggest that Arid1b haploinsufficiency disrupts inhibitory presynaptic inputs via abnormal formation and transmission of inhibitory synapses, resulting in an E/I imbalance and influencing behavior (Figure 1).

The E/I balance in neural circuits is important for normal development and function of the brain. In ASD, the E/I balance in key cortical neuronal circuits is disrupted. For this reason, ASD patients have irregular brain rhythms due to abnormal connectivity and neural integration. GABAergic interneurons are important for maintaining E/I balance and many ASD-associated genes are expressed in interneurons. Specifically, PV-positive GABAergic interneurons drive gamma rhythms and promote cortical circuit performance, and have been shown to be dysregulated in patients with ASD. Recent
clinical reports indicated that ASD-related behaviors can be caused by altered development of PV-positive GABAergic interneurons. In mice, Pralb knockout results in impaired social interaction and communication, along with repetitive and stereotyped behavior patterns. Also, Mecep2 deletion restricted to PV-positive interneurons leads to social deficits. Furthermore, ASD animal models such as Fmr1 knockout mice, the prenatal valproate mouse model, and Cutnap2 knockout mice all show abnormal PV-positive GABAergic interneuron function. These results collectively suggest a pattern of E/I imbalance caused by malfunctions in PV-expressing interneurons in ASD patients and mouse models. Importantly, Arid1b haploinsufficiency induces ASD-like neuroanatomical and electrophysiological phenotypes, similar to those observed in other ASD mouse models, especially in regard to PV-positive interneurons.

**Molecular insights of ARID1B function**

ARID1B participates in ATP-dependent chromatin remodeling as the largest subunit in certain BAF complexes. BAF complexes, sometimes referred to as mammalian SWI/SNF complexes, regulate chromatin organization by ejecting, sliding, and rearranging nucleosomes in order to regulate gene transcription. Over 20% of human cancers are caused by a mutation to a BAF complex subunit. All BAF complexes are composed of multiple subunits, and the composition of each multi-subunit complex is determined in a cell type-specific manner. ARID1B contains a helix-turn-helix AT-rich interactive domain (ARID) DNA-binding domain, which recognizes and binds to linear duplex DNA, and, despite the name, does not preferentially bind to AT-rich DNA regions in humans. ARID1B is more than 60% identical with another BAF complex subunit, ARID1A, and their incorporation in BAF complexes is mutually exclusive. Recent structural analyses showed that ARID1A and ARID1B display opposing roles in regulating cell-cycle progression, with ARID1A repressing the cell-cycle and ARID1B driving the expression of pro-proliferation genes. In addition, cell-cycle arrest is not disrupted in ARID1B-depleted cells, but cell-cycle re-entry is delayed in a parental pre-osteoblast cell line. These results suggest that ARID1B haploinsufficiency may be due to dysregulation of the cell-cycle, potentially leading to aberrant neuronal precursor proliferation.

Considering the role ARID1B plays in epigenetic regulation, it is no surprise that ARID1B haploinsufficiency leads to large-scale changes in gene expression. Shibutani et al. utilized RNA-sequencing to compare the Arid1b+/− brain transcriptome with microarray data from patients with ASD and Chd8 haploinsufficient mice. They reported widespread overlap in gene expression between Arid1b+/− mice and both ASD patients and Chd8 mutant mice, but they did not further explore any mechanistic explanations for these similarities, beyond mentioning that CHD8 and ARID1B are both chromatin remodeling factors. The authors did, however, perform a further RNA expression level comparison between Arid1b+/− brains and mouse fast-spiking neonatal neurons, presumably PV-expressing inhibitory interneurons, and reported that Arid1b haploinsufficiency generates a gene-expression profile more...
similar to immature fast-spiking cells, a hallmark of ASD brains. Celen et al. also performed RNA-sequencing and determined widespread gene expression differences in the hippocampus of Arid1b+/− mice compared to wild-type mice, including differential regulation of 14 autism risk genes. They also showed that plasma IGF1 level and liver Igf1 mRNA expression are lower in Arid1b+/− mice compared to control animals, and suggested that this IGF1 deficiency may explain the smaller stature of Arid1b+/− mice and some human patients with ARID1B haploinsufficiency. The authors failed to suggest any direct mechanistic link between IGF1 levels and ARID1B. However, they did report that conditional, brain-specific, heterozygous knockout of Arid1b leads to reduced mouse size and IGF1 deficiencies, while liver-specific Arid1b manipulations influence neither stature nor IGF1 levels. This implies that ARID1B deficits within the brain are, in large part, responsible for growth impairments and brain dysfunction in Arid1b haploinsufficient mice.

In addition to chromatin remodeling, ARID1B is involved in gene regulation via the posttranslational epigenetic modification of histones, though this too may be attributed to increased physical access for histone modifying enzymes to nucleosome-depleted DNA regions created by BAF complex activity. In their mouse model of Arid1b haploinsufficiency, Jung et al. showed that histone acetylation and methylation are decreased in Arid1b+/− mice, compared with wild type littermates. ARID1B modulates histone acetyltransferase (HAT) and histone deacetyltransferase (HDAC) activity in the periphery and in cell lines, but Jung and colleagues did not detect any changes in the level or activity of HAT or HDAC in the brains of Arid1b haploinsufficient mice. However, they reported that heterozygous deletion of Arid1b leads to decreased acetylation of histone H3 at lysine 9 (H3K9ac), a marker of transcriptional activation, in the promoter region of the Pvalb gene, which encodes PV. Accordingly, Jung et al. also reported a decrease in phosphorylation of the (ser5)-carboxy-terminal domain of RNA polymerase II in the Pvalb promoter region, which indicates decreased transcriptional initiation of the gene (Figure 2).

In accordance with prior research demonstrating the role of ARID1B in cell-cycle regulation, Jung et al. showed that Arid1b haploinsufficiency-induced loss of PV-positive interneurons is due to impaired proliferation of interneuron precursors in the ganglionic eminences. They reported that Wnt/β-catenin signaling-related genes, including Lef1, c-Myc, Cyclin D1 and others, are downregulated in the ventral telencephalon of Arid1b+/− mice (Figure 2). ARID1B was previously shown in vitro to enable access for the BAF chromatin remodeling complex to the c-Myc promoter and activating c-Myc gene expression, a well-established β-catenin target. The same report also showed that ARID1B associates with repressive transcription factors at the c-Myc promoter, but concluded that ARID1B is not essential for repressing cell-cycle activity via c-Myc. Another study reported, however, that ARID1B represses the expression of Wnt/β-catenin target genes in a BRG1-dependent manner. ARID1B does not directly interact with β-catenin, rather BRG1 complexes with β-catenin, and ARID1B influences β-catenin’s transcriptional regulation via its interaction with BRG1. Initially, the physical interaction between BRG1 and β-catenin was shown to promote the expression of β-catenin target genes, but the specific BAF complex subunits recruited to the BRG1-β-catenin complex appear to determine whether expression of a specific target gene is promoted or repressed.
transcriptional regulation in HEK293T cells, and that this regulation is indeed dependent on BRG1-β-catenin interaction. They further showed that knockout of Arid1b in a mouse chondrogenic cell line impedes cell proliferation and reduces the expression level of downstream β-catenin target genes, however, Arid1b/ARID1B knockout in undifferentiated chondrogenic cells and in HEK293 cells upregulates β-catenin target gene expression.

They concluded that the growth deficits they and others observe in human patients with ARID1B haploinsufficiency, as well as in their own zebrafish arid1b knockdown model, are likely due to impaired Wnt/β-catenin activity. These findings provide perhaps a more complete explanation for the causative role of ARID1B in regulating growth. Overall, due to the physical interaction between β-catenin and BRG1/ARID1B and ARID1B’s upstream regulation of Wnt/β-catenin gene expression, it is likely that the effects of ARID1B haploinsufficiency on Wnt/β-catenin signaling will largely come down to specific cell-types and developmental timepoints.

Research into the direct and indirect roles of ARID1B in brain development and neuronal function is still in its nascent stages. Future elucidation of the epigenetic and signaling regulatory roles of ARID1B will contribute to the development of more targeted therapies. Furthermore, a new human embryonic stem cell (hESC) heterozygous ARID1B line could allow for more investigation of the molecular function of ARID1B in human cells, though it is vital to remember that different cell-types utilize distinct BAF complex conformations, which can have an extreme influence on the apparent molecular function of ARID1B.

Development of clinical readiness and outcome assessment for ARID1B disorders

One hurdle to addressing the treatment of ARID1B-RD and other neurodevelopmental disorders, is the lack of reliable clinical endpoints for treatment, or targeted outcome measurements indicating therapeutic success. In a recent report, Kruizinga and colleagues grappled with the specific challenges in assessing the efficacy of therapeutic interventions to treat ARID1B-RD. They recruited 12 patients with pathogenic ARID1B mutations and performed a battery of non-invasive tests to determine appropriate clinical endpoints that could be incorporated into a clinical trial testing potential ARID1B-RD treatments. The authors argued that the tolerability, accuracy, stability, and significance of each test needs to be evaluated to determine its efficacy for use as a clinical endpoint. Specifically, they demonstrated that cognitive assessments (such as the animal fluency test), eye tracking measurements, executive function tests, and EEG analyses were all found to effectively differentiate between individuals with an ARID1B-RD and a control group. They also equipped subjects with smart watches that tracked their step count, heart rate and sleep patterns, and report that these may be an effective and well-tolerated tool for evaluating clinical outcomes for ARID1B-RD and similar rare neurodevelopmental disorders.

Overall, this study demonstrates an important first step toward the effective evaluation of pharmacological agents for treating ARID1B-RD. Due to the relatively small sample size, and the necessary exclusion of patients with severe ID, it is possible that additional tests may be more effective in evaluating outcomes in some cases.
Reversing E/I imbalance as a treatment tool for ARID1B haploinsufficiency-induced neurodevelopmental conditions

Developing pharmacological interventions for neurodevelopmental and neuropsychiatric disorders has proved challenging, but as preclinical and clinical tools for measuring the underlying causes of these disorders improve, the opportunity for targeted therapies is expanding. For instance, new research suggests that the gut/brain axis may play a role in the pathogenesis of ASD and other neurological disorders, which intimates that guided repopulation of the gut microbiome could be a viable treatment option in the future. In 2012, Han et al. demonstrated that treatment with a low dose of the GABA_A receptor positive allosteric modulator, clonazepam, is effective in reversing several ASD-like behaviors in the Scn1A haploinsufficiency mouse model of autism. The same group later showed that the low-dose clonazepam treatment is effective in another ASD mouse model, BTBR mice. As Jung et al. detected a marked decrease in the number of PV-expressing interneurons in Arid1b+/− mice, they examined the efficacy of clonazepam in reversing ID- and ASD-like behavior in this model. Acute clonazepam treatment produced a significant improvement in social behavior, anxiety-like behavior, and recognition memory, but was unable to rescue all aberrant behavioral phenotypes. It is likely that that some of these behaviors would benefit from interventions during a particular developmental window, but it is promising that positive GABA modulation is effective in treating some behavioral aspects in multiple ASD mouse models.

A benzodiazepine, clonazepam is a potent sedative and patients who take clonazepam can develop dependence and undergo withdrawal following treatment cessation. In addition to its function as a positive allosteric modulator of the GABA_A receptor, clonazepam also has serotonergic effects and is commonly prescribed to treat panic disorder and seizures. On a promising note, the doses commonly used in animal models for ASD, including Arid1b haploinsufficient mice, are much lower than those typically required to treat other neurological disorders. This implies that clonazepam may be effective in treating ARID1B-RD without the complications and side effects associated with higher doses. Nevertheless, there is still work to be done in developing more targeted treatments.

One potential avenue for future exploration is developing GABA modulators that specifically target interneuron subtypes. As discussed above, Jung et al. showed that Arid1b haploinsufficient mice display a significant reduction in PV-expressing interneurons and, in a follow-up study, Smith et al. demonstrated that conditional deletion of Arid1b in PV- or SST-expressing interneurons yields divergent behavioral outcomes. Due to the heterogeneity of ARID1B-RD, and of ID and ASD in general, developing specific drugs targeting a small subset of affected cells would allow for a more personalized treatment regimen. Achieving this level of specificity, however, will require a concerted effort. Due to the rise of chemogenetic and optogenetic technologies in preclinical research, it is getting easier to manipulate specific neurons in real-time in rodents, but there is currently limited potential for translation into clinical use. On the other hand, cortical PV- and SST-positive GABAergic interneurons may have distinct surface receptors, as is the case with nicotinic acetylcholine receptors, that could be targeted individually to improve
specific symptoms. Characterizing and utilizing the intrinsic diversity present in neuronal subtypes, will hopefully lead to effective and targeted therapies.

**Concluding remarks**

It has now been 10 years since the first reported case of ID caused by ARID1B haploinsufficiency was published 1. In the intervening decade, our collective understanding of the role of ARID1B in normal brain development and function has rapidly expanded. With the development of Arid1b haploinsufficiency mouse models 9, 19, 52 and, now, a heterozygous ARID1B knockout hESC line 14, the requisite tools are in place to develop novel therapies to treat ARID1B-RD. The discovery that Arid1b haploinsufficiency leads to E/I imbalance in the mouse brain due to a significant loss of PV-positive interneurons, and that treatment with a GABA positive allosteric modulator effectively rescues several ASD- and ID-like behaviors 9, could have a large impact on future drug development to treat ARID1B-RD and other neurological disorders with a convergent E/I imbalance root. Moreover, as we continue to disentangle the apparently complex interaction between ARID1B and the Wnt/β-catenin signaling cascade in different cell-types, we stand to receive fresh insight into epigenetic regulation of the cell-cycle, with potentially outsized roles in neurodevelopmental and emotional disorders and cancer. Finally, the initiative to test ARID1B-RD patients for suitable clinical endpoints 15, will help to ensure that clinical trials provide an accurate accounting of drug efficacy.

Looking forward, the future is bright in the sphere of ARID1B-RD research, and the next 10 years have great promise to produce new breakthroughs. As technologies and computational strategies are developed and improved, the potential to untangle the complicated molecular roles of ARID1B, on its own and within BAF complexes, will continue to grow, as will the prospect of translating these molecular insights into clinical treatments.

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Figure 1: Abnormal epigenetics and gene expression related to inhibitory neurons

Arid1b haploinsufficiency leads to a reduction in body size and impaired inhibitory synaptic function, including decreased GAD, VGAT, and Gephyrin levels. Inhibitory synaptic cleft width is also increased. The resulting shift in E/I balance leads to ASD- and ID-like behaviors.
ARID1B, as a member of the BAF complex, maintains HAT activity in the Pvalb promoter region, leading to increased gene expression. ARID1B also interacts with β-catenin to up- or down-regulate β-catenin target gene expression in a cell-type specific manner.

Figure 2: Abnormal epigenetics and gene expression related to inhibitory neurons

ARID1B, as a member of the BAF complex, maintains HAT activity in the Pvalb promoter region, leading to increased gene expression. ARID1B also interacts with β-catenin to up- or down-regulate β-catenin target gene expression in a cell-type specific manner.
### Table 1

Summary of human genetic studies examining *ARID1B* haploinsufficiency

| STUDY REFERENCE   | TOTAL NUMBER OF INDIVIDUALS | INDIVIDUALS WITH ARID1B HAPLOINSUFFICIENCY | KEY FINDINGS                                                                                                                                 |
|-------------------|-----------------------------|--------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| PIROLA ET AL. 1998 | 1                           | 1                                          | Agenesis of the corpus callosum in a patient with a deletion including *ARID1B*                                                            |
| NAGAMANI ET AL. 2009 | 4                           | 4                                          |                                                                                                                                             |
| BACKX ET AL. 2011  | 1                           | 1                                          |                                                                                                                                             |
| NORD ET AL. 2011   | 41                          | 1                                          |                                                                                                                                             |
| HALGREN ET AL. 2012 | 8                           | 7                                          |                                                                                                                                             |
| HOYER ET AL. 2012  | 887                         | 2                                          |                                                                                                                                             |
| SANTEN ET AL. 2012 | 2000                        | 3 (6)                                      | 6 patients with deletions including *ARID1B*. 3 individuals with only *ARID1B* haploinsufficiency.                                           |
| TSURUSAKI ET AL. 2012 | 22                         | 5                                          | Mutations affecting different BAF complex subunits lead to divergent phenotypes                                                            |
| SANTEN ET AL. 2013  | 63                          | 28                                         |                                                                                                                                             |
| TSURUSAKI ET AL. 2012 | 52                         | 15                                         | *ARID1B* mutations account for 76% of the 21 identified mutations leading to Coffin-Siris syndrome and 43% of the 7 mutations detected in patients with Nicolaides-Baraitser syndrome |
| WIECZOREK ET AL. 2013 | 46                         | 19                                         |                                                                                                                                             |
| SIM ET AL. 2014     | 1                           | 1                                          | Evidence of dysregulated cell-cycle in patient-derived cells                                                                             |
| VENGOECHEA ET AL. 2014 | 1                           | 1                                          |                                                                                                                                             |
| WRIGHT ET AL. 2015  | 271                         | 11                                         | *ARID1B* haploinsufficiency is a chief cause of corpus callosum defects in individuals with ID                                               |
| MIGNOT ET AL. 2016  | 99                          | 10                                         | Severity of corpus callosum defects may be used to predict other symptoms                                                                  |
| DEMILY ET AL. 2019  | 8                           | 8                                          |                                                                                                                                             |
| GOROKHOVA ET AL. 2019 | 44                         | 44                                         |                                                                                                                                             |
| VAN DER SLUIJS ET AL. 2019 | 143                        | 143                                        | *ARID1B*-related disorders exist on a spectrum and should be treated as such                                                                |
| KRUIZINGA ET AL. 2020 | 24                         | 12                                         | Suggestions on tests and clinical endpoints to be used in treating patients with *ARID1B*-related disorders                                      |

List of human studies including references to *ARID1B* discussed in this review. The total number of cases, individuals with *ARID1B*-RD, and key findings are given for each study, where applicable.
Table 2
Summary of behavioral phenotypes observed in *Arid1b* haploinsufficient mice

| BEHAVIOR                | BEHAVIORAL ASSAY       | CELEN ET AL. 2017 | JUNG ET AL. 2017 | SHIBUTANI ET AL. 2017 |
|-------------------------|------------------------|-------------------|------------------|-----------------------|
| SPATIAL REFERENCE MEMORY| Morris Water Maze      | –                 | †                | N/A                   |
| SPATIAL REFERENCE MEMORY| T Maze                 | N/A               | †                | –                     |
| RECOGNITION MEMORY      | Novel Object Recognition| N/A               | †                | N/A                   |
| MOTOR LEARNING          | Rotarod Test           | N/A               | †                | N/A                   |
| FEAR LEARNING           | Fear Conditioning      | –                 | N/A              | †                     |
| SOCIABILITY             | Open Field Social Interaction | †             | †                | –                     |
| SOCIABILITY             | Home-Cage Social Interaction | N/A           | N/A              | †                     |
| SOCIABILITY             | 3-Chamber Test         | N/A               | †                | –                     |
| SOCIAL NOVELTY          | 3-Chamber Test         | N/A               | †                | –                     |
| COMMUNICATION           | Ultrasonic Vocalizations| Altered Communication | N/A             | N/A                   |
| REPETITIVE BEHAVIOR     | Grooming               | †                 | †                | –                     |
| ANXIETY                 | Elevated Plus Maze     | †                 | †                | †                     |
| ANXIETY                 | Open Field             | †                 | †                | Unclear               |
| ANXIETY                 | Light-Dark Box         | †                 | N/A              | –                     |
| DEPRESSION              | Forced Swim            | N/A               | †                | Unclear               |
| DEPRESSION              | Tail Suspension        | N/A               | †                | N/A                   |

Comparison between the three published mouse models of global *Arid1b* heterozygous knockout.
Table 3
Summary of behavioral deficits in global and conditional *Arid1b* heterozygous mice

| BEHAVIOR                    | ARID1B s/− | F/+;PV-CRE | F/+;SST-CRE |
|-----------------------------|------------|------------|------------|
| SOCIAL BEHAVIOR             | ↓          | ↓          | –          |
| REPETITIVE BEHAVIOR         | ↑          | –          | ↑          |
| ANXIETY                     | ↑          | ↑          | –          |
| DEPRESSION-LIKE BEHAVIOR    | ↑          | ↑          | –          |
| RECOGNITION MEMORY          | ↓          | –          | ↓          |
| MOTOR LEARNING              | ↓          | –          | ↓          |
| SPATIAL REFERENCE MEMORY    | ↓          | –          | ↓          |

Comparison between global, PV-Cre conditional, and SST-Cre conditional heterozygous *Arid1b* knockout mice. ↓ = a decrease in a particular behavior; ↑ = an increase in a particular behavior; − = no change in behavior.