Review

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ARID1B-mediated disorders: Mutations and possible mechanisms

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Summary **Mutations in the gene encoding AT-rich interactive domain-containing protein 1B (ARID1B) were recently associated with multiple syndromes characterized by developmental delay and intellectual disability, in addition to nonsyndromic intellectual disability. While the majority of *ARID1B* mutations identified to date are predicted to result in haploinsufficiency, the underlying pathogenic mechanisms have yet to be fully understood. ARID1B is a DNA-binding subunit of the Brahma-associated factor chromatin remodelling complexes, which play a key role in the regulation of gene activity. The function of remodelling complexes can be regulated by their subunit composition, and there is some evidence that ARID1B is a component of the neuron-specific chromatin remodelling complex. This complex is involved in the regulation of stem/progenitor cells exiting the cell cycle and differentiating into postmitotic neurons. Recent research has indicated that alterations in the cell cycle contribute to the underlying pathogenesis of syndromes associated with *ARID1B* haploinsufficiency in fibroblasts derived from affected individuals. This review describes studies linking *ARID1B* to neurodevelopmental disorders and it summarizes the function of *ARID1B* to provide insights into the pathogenic mechanisms underlying ARID1B-mediated disorders. In conclusion, ARID1B is likely to play a key role in neurodevelopment and reduced levels of wild-type protein compromise normal brain development. Additional studies are required to determine the mechanisms by which impaired neural development contributes to the intellectual disability and speech impairment that are consistently observed in individuals with *ARID1B* haploinsufficiency.**

Keywords: Intellectual disability, chromatin remodelling, Coffin-Siris syndrome, ARID1B mutation, cell cycle, haploinsufficiency

1. Introduction

Intellectual disability (ID) is an incapacitating condition that imposes a significant burden on affected individuals and their families. ID affects approximately 0.5% of all newborns and the overall incidence of ID is estimated to be 2-3% (*1*). Studies of X-linked, autosomal-recessive, syndromic, and sporadic cases of ID have resulted in the identification of several hundred genes associated with ID. In general, the relative incidence of mutations in each gene appears to be quite low. The latest findings have indicated that mutations in chromatin remodelling genes can cause ID in nonsyndromic and syndromic individuals.

The control of gene expression is an intricately regulated process that requires many multi-protein complexes. Chromatin remodelling regulates gene expression by modulating the access of transcription machinery proteins to the condensed genomic DNA *via* dynamic modification of the chromatin architecture. This modification is mediated by either covalent histone modifications *via* specific enzymes such as histone acetyltransferases or ATP-dependent alteration of DNA-nucleosome topology (*2*). The latter mode of modification is mediated by a class of protein complexes called ATP-dependent chromatin-remodelling complexes, which are known to regulate gene expression in specific cellular contexts or at

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defined time points (*3*). Mutations in the genes encoding subunits of these complexes have recently been linked to both developmental disorders and cancer (*4*).

A DNA-binding subunit of the Brahma-associated factor (BAF, also referred to as switching defective and sucrose non-fermenting SWI/SNF-α) chromatin remodelling complex named AT-rich interactive domain-containing protein 1B (ARID1B) was recently found to cause ID in both nonsyndromic and syndromic individuals. The first report of an individual with a phenotype likely attributable to a mutation in *ARID1B* was in 1998 (*5*). A large heterozygous deletion of 26 genes (including *ARID1B*) was identified in an individual with ID and agenesis of the corpus callosum. In 2009, Nagamani *et al*. reported heterozygous interstitial deletions affecting 6q.25.2-q25.3 (spanning *ARID1B*) in three individuals with developmental delay, microcephaly, facial characteristics, and hearing and speech impairments (*6*). Backx *et al*. subsequently documented a balanced translocation t(6;14)(q25.3;q13.2) that led to reciprocal fusion transcripts of *ARID1B* and *MRPP3* in an individual with ID and agenesis of the corpus callosum (*7*) and Nord *et al*. described an individual with autism who had a deletion of three exons in *ARID1B* (*8*). In the following year, haploinsufficiency of *ARID1B* was identified in four individuals with ID, autism, and corpus callosum abnormalities (*9*). Similarly, Michelson *et al*. reported an interstitial 1.19 Mb deletion of 6q25.2 including *ARID1B* and *ZDHHC14* in an individual with global developmental delay, facial characteristics, dysgenesis of the corpus callosum, limb anomalies, and genital hypoplasia (*10*). The phenotypic spectrum of *ARID1B*-mediated disorders was further broadened when Hoyer *et al*. noted haploinsufficiency for *ARID1B* in eight nonsyndromic/unselected individuals (approximately 1% of cases analyzed) with unexplained ID (*11*). In addition, mutations in *ARID1B* leading to haploinsufficiency were later identified in Coffin-Siris syndrome (CSS), which is characterized by ID, severe speech impairment, coarse facial features, microcephaly, developmental delay, and hypoplastic nails of the fifth digits (MIM 135900) (*12-14*). Mutations in other genes within the BAF complex have also been found to cause CSS, but *ARID1B* mutations account for approximately 70% of cases (*15*). In 2014, the phenotypic spectrum of CSS was further broadened when an individual with CSS with a *de novo* frameshift mutation in ARID1B presented with extreme obesity, macrocephaly, hepatomegaly, hyperinsulinism, and polycystic ovarian syndrome (*16*). Sim *et al*. reported a heterozygous 1.2 Mb deletion of 6q25.3, which contains *ARID1B*, *ZDHHC14*, and *TMEM242*, in an individual with a phenotype overlapping CSS but with distinctive features including plantar fat pads and facial dysmorphism (*17*). Additional analysis identified heterozygous *de novo ARID1B* frameshift and nonsense mutations in four additional affected individuals with a strikingly similar phenotype (*17*). Most recently, an individual with an apparently balanced, *de novo* translocation [t(5;6)(q11;q?24)], that resulted in the heterozygous loss of *ARID1B* and *ADAMTS6* was described. The phenotype included developmental delay, speech impairment and mild ID, hypotonia, hypermetropia, and microstrabismus (*18*). Dysmorphic features included thin upper lip vermilion, single transverse palmar creases, a funnel chest, brachydactyly, clinodactyly, fragile and grooved nails, and skewed flat feet.

Collectively, the heterozygous deletions and mutations of *ARID1B* are predicted to cause haploinsufficiency of ARID1B, leading to the aforementioned disorders. What is striking is the considerable clinical variability associated with reduced levels of ARID1B. A recent review identified the major features associated with ARID1B haploinsufficiency to be ID, speech delay, coarse facies, and hypertrichosis. Minor features, present in a smaller but significant proportion of individuals, included finger/toe abnormalities, feeding difficulties, agenesis of the corpus callosum, seizures, myopia, and growth delay (*15*). However, the data were primarily from individuals with a prior clinical diagnosis of CSS and therefore there is likely to be significant ascertainment bias. Although a range of clinical features have been mentioned here, the clinical features of nonsyndromic individuals with mutations in *ARID1B* may broaden the phenotypic spectrum considerably.

2. What is ARID1B?

ARID1B is a large, ubiquitous nuclear-localized protein of approximately 250 kDa. To date, the Consensus Coding Sequence (CCDS) database has reported that *ARID1B* encodes a large isoform of 2,249 amino acids (CCDS55072.1) and a smaller isoform of 2,236 amino acids (CCDS5251.2). The first functional studies of Arid1b analyzed the *Drosophila* protein (initially termed eyelid and subsequently renamed Osa), which was found to be important in embryonic segmentation, development of the notum and wing margin, and photoreceptor differentiation in flies (*19*). Subsequent studies using genetic and biochemical approaches indicated that the protein binds to DNA without sequence specificity and that the protein is a subunit of BAF complexes containing a core ATP-dependent helicase called Brahma (BRM) (*20,21*).

In humans, there are two paralogues of both Osa [AT-rich interactive domain-containing protein 1A (ARID1A) and ARID1B] and Brahma [BRM and Brahma Related Gene 1 (BRG1)]. ARID1B was found to bind to DNA without sequence specificity and is a component of BAF complexes containing either BRM or BRG1 (*22,23*). However, ARID1B and ARID1A are

mutually exclusive in BAF complexes (*22,24*).

Like Osa in *Drosophila* development, both ARID1A and ARID1B are important in mammalian embryogenesis. Haploinsufficiency for ARID1A was found to cause late embryonic lethality, whereas complete loss of ARID1A arrested development at E6.5 without formation of a primitive streak and mesoderm in mice (*25*). Deficiency of ARID1A was also reported to disrupt the pluripotency of mouse embryonic stem (ES) cells by inhibiting their self-renewal capacity and by promoting their differentiation into primitive endoderm-like cells. Similarly, ARID1B deficiency also reduced the self-renewal capacity of ES cells (*26*). In addition, ARID1B-deficient ES cells displayed features of differentiated cells, such as reduced expression of several pluripotency-related genes and increased expression of some differentiation-related genes.

Functional studies by Nagl *et al*. suggested that ARID1A and ARID1B are important to mammalian development by regulating the cell cycle during differentiation. Their studies indicated that ARID1A deficiency delayed the cell cycle arrest of mouse MC3T3-E1 pre-osteoblasts during osteogenic differentiation induced by ascorbic acid, while ARID1B deficiency had no impact on the kinetics of cell cycle arrest (*27*). Subsequent analyses of the kinetics of the cell cycle using serum deprivation and replenishment indicated that ARID1A and ARID1B have important and opposing roles in regulating cell cycle. ARID1A-deficient MC3T3 cells displayed delayed cell cycle arrest induced by serum starvation, whereas ARID1B deficiency had no impact on serum-starved cells (*28*). However, ARID1B deficiency delayed cell cycle entry of serum-starved cells during serum replenishment. Conversely, ARID1A-deficient cells shared similar kinetics of cell cycle entry with parental cells. The current authors also observed delayed cell cycle entry of serum-starved human fibroblasts derived from an individual with *ARID1B* haploinsufficiency and fibroblasts with ARID1B deficiency mediated by shRNAmir (*17*), a finding that coincides with the results of previous studies.

Molecular analysis using chromatin immunoprecipitation (ChiP) indicated that ARID1B regulates cell cycle entry by mediating the expression of *c-Myc*. ARID1B deficiency prevented the association of BAF complexes containing the subunits BAF155 or BAF170 with the *c-Myc* promoter. Therefore, the expression of *c-Myc* was not upregulated when serum-starved MC3T3 cells were replenished with serum, leading to delayed cell cycle entry (*28*). Conditional deletion of *c-Myc* is embryonically lethal in mice and has been found to decrease the size of the brain by disrupting the development of forebrain and hindbrain (*29,30*). Consistent with these findings, microcephaly has been noted in some individuals with *ARID1B* haploinsufficiency (*6,12,13*).

Both BAF155 and BAF170 are also important for correct neural development. BAF155 was reported to drive chromatin restructuring in mouse ES cells during neural differentiation induced by retinoic acid (*31*). Down-regulation of BAF155 resulted in reduced chromatin compaction and prolonged expression of self-renewal genes such as *Nanog* and *Oct4*, resulting in delayed neural differentiation of ES cells. In addition, heterozygous deletion of *Baf155* is embryonic lethal in mice and results in defective neural tube closure leading to exencephaly (*32,33*). BAF170 has been found to be an intrinsic factor that controls cortical size. Conditional deletion of *Baf170* was found to promote indirect neurogenesis by increasing the pool of intermediate progenitors and in turn result in an enlarged cortex (*34*). Similarly, overexpression of Baf170 promoted direct neurogenesis and resulted in the development of a smaller cortex. Collectively, these findings suggest that *ARID1B* haploinsufficiency partially impairs the function(s) of BAF complexes containing BAF155 and/or BAF170. This leads to dysregulation of the expression of *C-MYC*, delaying cell cycle entry of developmentally arrested cells, such as neural progenitors. These deficits may explain why

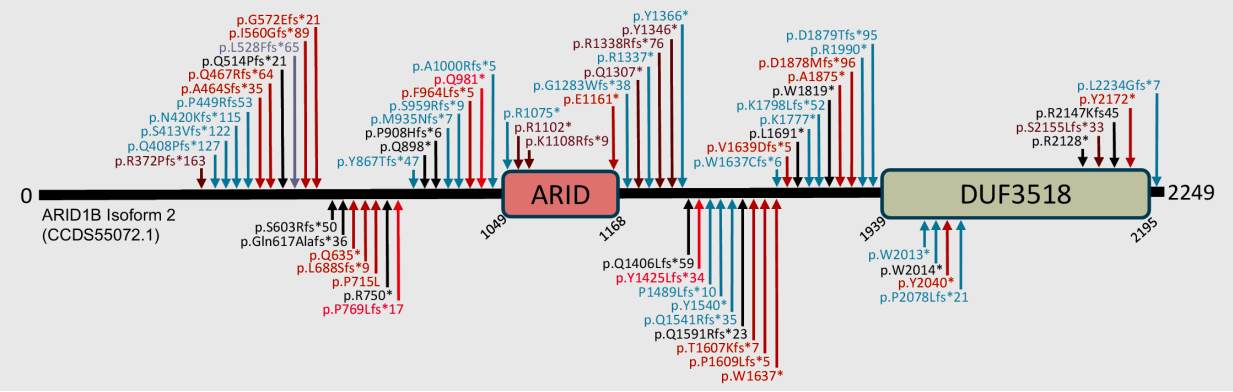

Figure 1. The protein domain organization of ARID1B and the distribution of ARID1B mutations associated with intellectual disability. Mutations in brown were identified by Hoyer *et al*. (*11*), those in blue were identified by Santen *et al*. (*12*), those in orange were identified by Tsurusaki *et al*. (*13*), those in black were identified by Wieczorek *et al*. (*14*), those in red were identified by Sim *et al*. (*17*), and those in purple were identified by Vals *et al*. (*16*).

Table 1. Summary of individuals with deletions affecting *ARID1B* and neighboring genes

Reference	Case	Approximate Deleted Region (Hg19)	Genes Affected
Pirola *et al.*, 1998	1	chr6:151,225,045-158,663,897	*MTHFD1L, AKAP12, ZBTB2, RMND1, C6orf211, ESR1, SYNE1, MYCT1, VIP, FBXO5, MTRF1L, RGS17, OPRM1, IPCEF1, CNKSR3, SCAF8, TIAM2, TFB1M, CLDN20, NOX3, ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2, SERAC1, GTF2H5*
Nagamani *et al*., 2009	1	chr6:155,085,617-158,876,467	*SCAF8, TIAM2, TFB1M, CLDN20, NOX3, ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2, SERAC1, GTF2H5, TULP4*
	2	chr6:154,841,486-161,623,426	*SCAF8, TIAM2, TFB1M, CLDN20, NOX3, ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2, SERAC1, GTF2H5, TULP4, TMEM181, DYNLT1, SYTL3, EZR, OSTCP1, RSPH3, C6orf99, TAGAP, FNDC1, SOD2, WTAP, ACAT2, TCP1, SNORA20, SNORA29, MRPL18, PNLDC1, MAS1, IGF2R, AIRN, SLC22A1, SLC22A2, SLC22A3, LPAL2, LPA, PLG, MAP3K4, AGPAT4-IT1*
	3	chr6:149,951,406-160,276,072	*KATNA1, LATS1, NUP43, PCUMT1, LRP11, RAET1E, RAET1G, ULBP2, ULBP1, RAET1K, RAET1L, ULBP3, PPR1R14C, IYD, PLEKHG1, MTHFD1L, AKAP12, ZBTB2, RMND1, C6orf211, ESR1, SYNE1, MYCT1, VIP, FBXO5, MTRF1L, RGS17, OPRM1, IPCEF1, CNKSR3, SCAF8, TIAM2, TFB1M, CLDN20, NOX3, ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2, SERAC1, GTF2H5, TULP4, TMEM181, DYNLT1, SYTL3, EZR, OSTCP1, RSPH3, C6orf99, TAGAP, FNDC1, SOD2, WTAP, ACAT2, TCP1, SNORA20, SNORA29, MRPL18, PNLDC1*
	4	chr6:155,336,861-169,178,124	*TIAM2, TFB1M, CLDN20, NOX3, ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2, SERAC1, GTF2H5, TULP4, TMEM181, DYNLT1, SYTL3, EZR, OSTCP1, RSPH3, C6orf99, TAGAP, FNDC1, SOD2, WTAP, ACAT2, TCP1, SNORA20, SNORA29, MRPL18, PNLDC1, MAS1, IGF2R, AIRN, SLC22A1, SLC22A2, SLC22A3, LPAL2, LPA, PLG, MAP3K4, AGPAT4-IT1, PARK2, PACRG, CAHM, QKI, C6orf118, PDE10A, LINC00473, LINC00602, T, PRR18, SFT2D1, MPC1, RPS6KA2, RNASET2, FGFR1OP, CCR6, GPR31, TCP10L2, UNC93A, TTLL2, TCP10, MLLT4, HGC6.3, KIF25, FRMD1, DACT2, SMOC2*
Nord *et al*., 2011	1	chr6:157,250,871-157,462,426	*ARID1B*
Halgren *et al.*, 2012	2	chr6:157,210,495-157,467,930	*ARID1B*
	3	chr6:157,079,676-157,806,675	*ARID1B, TMEM242, ZDHHC14*
	4	chr6:156,190,443-158,076,922	*ARID1B, TMEM242, ZDHHC14*
	5	chr6:155,797,565-158,517,307	*ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2*
	6	chr6:152,497,968-157,996,910	*SYNE1, MYCT1, VIP, FBXO5, MTRF1L, RGS17, OPRM1, IPCEF1, CNKSR3, SCAF8, TIAM2, TFB1M, CLDN20, NOX3, ARID1B, TMEM242, ZDHHC14*
	7	chr6:151,019,422-159,187,660	*PLEKHG1, MTHFD1L, AKAP12, ZBTB2, RMND1, C6orf211, ESR1, SYNE1, MYCT1, VIP, FBXO5, MTRF1L, RGS17, OPRM1, IPCEF1, CNKSR3, SCAF8, TIAM2, TFB1M, CLDN20, NOX3, ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2, SERAC1, GTF2H5, TULP4, TMEM181, DYNLT1, SYTL3, EZR*
	8	chr6:153,073,486-167,754,128	*VIP, FBXO5, MTRF1L, RGS17, OPRM1, IPCEF1, CNKSR3, SCAF8, TIAM2, TFB1M, CLDN20, NOX3, ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2, SERAC1, GTF2H5, TULP4, TMEM181, DYNLT1, SYTL3, EZR, OSTCP1, RSPH3, C6orf99, TAGAP, FNDC1, SOD2, WTAP, ACAT2, TCP1, SNORA20, SNORA29, MRPL18, PNLDC1, MAS1, IGF2R, AIRN, SLC22A1, SLC22A2, SLC22A3, LPAL2, LPA, PLG, MAP3K4, AGPAT4-IT1, PARK2, PACRG, CAHM, QKI, C6orf118, PDE10A, LINC00473, LINC00602, T, PRR18, SFT2D1, MPC1, RPS6KA2, RNASET2, FGFR1OP, CCR6, GPR31, TCP10L2, UNC93A, TTLL2*
Santen *et al.*, 2012	5	chr6:157,079,676-157,806,675	*ARID1B, TMEM242, ZDHHC14*
	6	chr6:157,144,644-158,028,969	*ARID1B, TMEM242, ZDHHC14*
Hoyer *et al.*, 2012	1	chr6:155,364,154-157,681,073	*TIAM2, TFB1M, CLDN20, NOX3, ARID1B*
	2	chr6:157,299,982-157,474,352	*ARID1B*
Wieczorek *et al.*, 2013	K2428	chr6:157,402,040-157,460,542	*ARID1B*
	K2438	chr6:156,960,439-158,889,653	*ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2, SERAC1, GTF2H5, TULP4*
Santen *et al*., 2014	24	not available	*Deleted ARID1B exons 1-20*
	47	not available	*Deleted ARID1B exons 6-9*
Sim *et al*., 2014	1	chr6:156,897,183-158,222,240	*ARID1B, TMEM242, ZDHHC14*
Vengochea *et al*., 2014	1	chr6:155,538,131-158,756,793	*TIAM2, TFB1M, CLDN20, NOX3, ARID1B, TMEM242, ZDHHC14, SNX9, SYNJ2, SERAC1, GTF2H5, TULP4*

Case 1 reported by Pirola *et al*. (*5*) has a heterozygous deletion between FISH loci D6S1496 and D6S437. Case 1 described by Sim *et al*. (*17*) has a heterozygous deletion between (Hg18) chr6:156938875-158142228. For both individuals, the deleted region was converted to Hg19 coordinates using UCSC genome browser.

ID is consistently found in individuals with *ARID1B*-mediated disorders.

3. Impact of ARID1B mutations

Despite being a protein of over 2,000 amino acid residues, ARID1B has only two defined protein domains, an AT-rich Interactive Domain (ARID) and Domain of Unknown Function 3518 (DUF3518) (Figue 1). ARID consists of approximately 100 amino acid residues and has been found to bind to DNA without sequence specificity (*22,23*). Missense mutations in this domain are likely to disrupt the DNA-binding ability of ARID1B and compromise the function of the BAF complex. DUF3518 is approximately 260 amino acids long and biochemical studies have indicated that the domain interacts with the helicase subunits BRG1 and BRM in BAF complexes (*24,35*). Therefore, missense mutations in DUF3518 are likely to disrupt the interaction between ARID1B, BRG1, and BRM. Collectively, missense mutations in either domain would presumably have a negative impact by rendering BAF complexes dysfunctional (if the resulting mutant ARID1B protein was stable). However, a striking feature of studies investigating *ARID1B*-mediated disorders is that there is only a single reported missense mutation (p.Pro715Leu) in comparison to more than 60 nonsense or frameshift mutations (Figure 1). However, this may reflect ascertainment bias in the clinical cohorts studied to date, as was mentioned earlier. Most nonsense and frameshift mutations activate nonsense-mediated mRNA decay (NMD) because the mutation causes premature termination of translation that results in incomplete displacement of exon junction protein complexes by the ribosomes (*36*). Thus, these mutations are likely to cause NMD of the *ARID1B* transcript rather than the expression of mutant ARID1B protein. Truncating mutations that avoid NMD usually cause a distinct and more severe phenotype than that observed in NMD due to the dominant negative effects of the mutant protein (*37*).

The other major class of *ARID1B* mutations observed to date involves copy number variations (CNV), and particularly heterozygous deletions (Table 1). In most affected individuals, the additional genes lost could potentially contribute to phenotypic variability. However, no obvious correlation between variable clinical phenotypes and specific types of *ARID1B* mutations has been observed thus far. Moreover, there are several individuals with deletion of *ARID1B* and multiple additional genes that present with a phenotype indistinguishable from individuals with truncating and frameshift *ARID1B* mutations (*11,12,17,38*). In a recent study by the current authors, affected individuals with frameshift and truncating *ARID1B* mutations had a phenotypic presentation very similar to that of an affected individual with a heterozygous deletion of *ARID1B*, *ZDHHC14*, and *TMEM242* (*17*). Therefore, the clinical presentation appears likely to manifest predominantly from *ARID1B* haploinsufficiency rather than the deletion of other genes. Collectively, these findings indicate that the primary pathogenic mechanism in most individuals with an *ARID1B*-mediated disorder who have been described thus far is the result of *ARID1B* haploinsufficiency. Additional studies are required to delineate the mechanisms underlying phenotypic variability associated with *ARID1B* haploinsufficiency and a consortium has recently been established to address this issue (*15*).

4. Conclusions

The predominant mechanism underlying *ARID1B*-mediated disorders appears to be *ARID1B* haploinsufficiency. Why the phenotypic presentation is so variable is a question that has yet to be answered, although there is evidence from *in vitro* studies and animal models that reduced levels of ARID1B can disrupt regulation of the cell cycle. Given that the BAF complex consists of over 25 core and interchangeable protein subunits that give rise to functionally distinct and cell-type specific complexes, variation in these components is likely to contribute to the observed phenotypic variability of *ARID1B*-mediated disorders (*39*). Nonetheless, ID and speech impairment are consistently observed. Although a specific role for ARID1B in early brain development has yet to be identified, the gene is predominantly expressed in neural tissues in the developing mouse embryo (*40*). Thus, *ARID1B* is likely to be important to development of the brain when multipotent neuroepithelial cells are actively proliferating. Future studies will need to investigate if impaired neural development contributes to the ID and speech impairment that characterize individuals with *ARID1B* haploinsufficiency.

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