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BAZ2B haploinsufficiency as a cause of developmental delay, intellectual disability and autism spectrum disorder

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Abstract

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DATA AVAILABILITY STATEMENT

Variant data have been submitted to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/).

CONFLICT OF INTEREST STATEMENT

The authors do not report any individual conflict of interests. The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from clinical laboratory testing conducted at Baylor Genetics Laboratories, which provides exome sequencing on a clinical basis. The Greenwood Genetic Center (GGC) receives revenue from diagnostic testing performed in the GGC Molecular Diagnostic Laboratory.

The bromodomain adjacent to zinc finger 2B gene (*BAZ2B*) encodes a protein involved in chromatin remodeling. Loss of BAZ2B function has been postulated to cause neurodevelopmental disorders. To determine whether BAZ2B deficiency is likely to contribute to the pathogenesis of these disorders, we performed bioinformatics analyses that demonstrated a high level of functional convergence, during fetal cortical development, between *BAZ2B* and genes known to cause autism spectrum disorder and neurodevelopmental disorder. We also found an excess of de novo *BAZ2B* loss-of-function variants in exome sequencing data from previously published cohorts of individuals with neurodevelopmental disorders. We subsequently identified seven additional individuals with heterozygous deletions, stop-gain, or de novo missense variants affecting *BAZ2B*. All of these individuals have developmental delay, intellectual disability and/or autism spectrum disorder. Taken together, our findings suggest that haploinsufficiency of *BAZ2B* causes a neurodevelopmental disorder whose cardinal features include developmental delay, intellectual disability and autism spectrum disorder.

Keywords

BAZ2B; developmental delay; intellectual disability; autism spectrum disorder; neurodevelopmental disorder

MANUSCRIPT

The bromodomain adjacent to zinc finger (BAZ) gene family consists of four members: *BAZ1A* [MIM# 605680], *BAZ1B* [MIM# 605681], *BAZ2A* [MIM# 605682] and *BAZ2B* [MIM# 605683] (Jones, Hamana, Nezu, & Shimane, 2000). None of these genes are currently associated with a specific human disease. However, BAZ1A has been shown to act as a regulator of cellular senescence in both normal and cancer cells (Li et al., 2019), BAZ1A and BAZ1B each promote survival after DNA damage (Oppikofer et al., 2017), and BAZ2A is involved in epigenetic alterations in prostate cancer and its overexpression predicts disease recurrence (Gu et al., 2015). BAZ1A may also play a role in neurodevelopment (Zaghlool et al., 2016), and *BAZ1B* haploinsufficiency contributes to Williams syndrome-related phenotypes through transcriptional dysregulation of neurodevelopmental pathways (Lalli et al., 2016).

Members of the BAZ gene family encode proteins that are integral components of chromatin remodeling complexes, which have been implicated in the disruption and reformation of nucleosomal arrays resulting in modulation of transcription, DNA replication, and DNA repair (Clapier & Cairns, 2009). Although the molecular function of BAZ2B has not been fully defined, it has been postulated to function similarly to the *Drosophila* Acf1 protein, which regulates nucleosome mobilization through the ATP-dependent chromatin remodeling factor ISWI (Eberharter, Vetter, Ferreira, & Becker, 2004). Additionally, the BAZ2B bromodomain has been shown to bind to acetylated H3K14 (H3K14ac), whose presence at promoter regions is generally associated with gene activation (Charlop-Powers, Zeng, Zhang, & Zhou, 2010; Philpott et al., 2011; Pokholok et al., 2005; Wang et al., 2008). This suggests a potential role for BAZ2B in transcriptional activation.

Data from the genome aggregation database (gnomAD v2.1.1; https://gnomad.broadinstitute.org/) suggests that *BAZ2B* is likely to be loss-of-function intolerant (pLI = 0.98) with 109.2 loss-of-function variants expected but only 22 observed (observed (o)/expected (e) score = 0.2 [90% CI 0.14–0.29]) (Karczewski et al., 2019). This is consistent with *BAZ2B*'s revised residual variation intolerance score (RVIS) of −1.0079, which places it amongst the top 13.1% of the most functional-variation-intolerant of human genes (Petrovski et al., 2015; Petrovski, Wang, Heinzen, Allen, & Goldstein, 2013).

BAZ2B was recently prioritized as a potential candidate gene for autism spectrum disorder (ASD) by Guo et al. based on the analysis of exome sequencing data from large, family-based, exome sequencing studies (De Rubeis et al., 2014; Fischbach & Lord, 2010; Guo et al., 2019). Loss of BAZ2B function has also been postulated to contribute to the development of neurodevelopmental disorders in humans (Deciphering Developmental Disorders, 2017; Iossifov et al., 2014; Krupp et al., 2017; Lelieveld et al., 2016) based on the identification of de novo and mosaic *BAZ2B* variants in individuals with these disorders.

To further evaluate *BAZ2B* as a candidate gene for neurodevelopmental disorders, we performed bioinformatics analyses to determine whether *BAZ2B* is co-expressed with known ASD or neurodevelopmental disability (NDD) genes (Supporting Information Materials and Methods) (Basu, Kollu, & Banerjee-Basu, 2009; Stessman et al., 2017). First, using the developing human brain RNA-Seq data (Kang et al., 2011), we found that *BAZ2B* exhibits higher expression in prenatal cortical samples than in postnatal cortical samples (fold change = 1.6; P = 2.2e-24; one-sided Wilcoxon rank sum test), suggesting that *BAZ2B* might play a more important role during prenatal cortical development than post-natal function (Figure 1A).

We then calculated the Spearman's correlation with genes associated with ASD for all genes expressed in prenatal cortex, and found that *BAZ2B* is highly positively correlated with ASD genes (Figure 1B and Supp. Table S1). Similarly, *BAZ2B* is also highly positively correlated with genes associated with NDD (Figure 1C and Supp. Table S2). As expected, ASD genes are highly correlated with each other, NDD genes are highly correlated with each other, and these gene sets are distinguishable from the other prenatal cortex-expressed genes with area under the receiver operating characteristic curve (AUC) values of 0.71 and 0.73 respectively (data not shown). These results indicate that *BAZ2B* is a highly promising ASD and NDD candidate gene.

To find additional evidence in support of BAZ2B's role in neurodevelopmental disorders, we leveraged data from large-scale, next generation sequencing studies. Among 10,927 individuals with ASD, intellectual disability (ID) or developmental disorders, we identified five individuals with de novo germline mutations affecting the coding region of *BAZ2B*; three individuals with loss-of-function variants, and two individuals with conserved missense variants (Supp. Table S3, Supp. Figure S1) (Deciphering Developmental Disorders Study, 2017; Iossifov et al., 2014; Lelieveld et al., 2016; Turner et al., 2017). Some of these individuals carry variants in other genes that may represent alternative explanations for their neurodevelopmental phenotypes—particularly the *CTCF* c.1102C>T, p.(Arg368Cys) [NM_006565.3] variant in DDD4K.00342—or modifiers. Using a statistical model (O'Roak

et al., 2012) and denovolyzeR (Samocha et al., 2014; Ware, Samocha, Homsy, & Daly, 2015), we found an excess of de novo *BAZ2B* loss-of-function variants within this cohort ($p = 0.00045$ and $p = 0.0032$, respectively) based on a single, hypothesis-driven test. However, this finding did not meet the criteria for genome-wide significance.

As a next step, we searched a clinical database of >80,000 array-based copy number variant (CNV) analyses performed at Baylor Genetics. We found two individuals (Subjects D1 and D2) who carried small (<1 Mb) deletions involving *BAZ2B* (Figure 2A, Supp. Table 4). The minimal deletion in Subject D1 affects the entire *BAZ2B* coding region, and the minimal deletion in Subject D2 includes exons that code for both the bromodomain and zing finger domain of BAZ2B (Figure 2B). Population data suggest that it is unlikely that the effects of these deletions on *WDSUB1* and *TANC1* expression are contributing significantly to the ASD and ID documented in these individuals (Supp. Table S4), although that possibility cannot be excluded.

We then used GeneMatcher (Sobreira, Schiettecatte, Valle, & Hamosh, 2015) to identify six individuals (Subjects V1-V6) who carry rare, *BAZ2B* stop-gain or conserved missense variants with high Combined Annotation Dependent Depletion (CADD) scores (26.7–27.7) (Supp. Table S4, Supp. Figure S1) identified in exome/genome sequencing studies. All *BAZ2B* variants in this manuscript are described based on *BAZ2B* transcript variant 1 (GenBank: NM_013450.4). One of these individuals, Subject V1, was previously reported by Lelieveld et al. (Patient 418) without detailed clinical information (Lelieveld et al., 2016). All of these individuals had developmental delay (DD), ID and/or ASD (Supplemental Information Case Reports). Developmental regression was clearly documented in Subjects V4-V6. These subjects were diagnosed with ASD, and the timing of their developmental regression is consistent with the regression that has been described in association with ASD (Ozonoff & Iosif, 2019; Rogers, 2004; Tammimies, 2019).

Individuals carrying heterozygous, high confidence, loss-of-function *BAZ2B* variants and *BAZ2B* missense variants with high CADD scores (NM_013450.4) have also been reported in the gnomAD v2.1.1 database. Since subjects included in this database were not assessed for neurological phenotypes, it is possible that these individuals have milder versions of the phenotypes reported here. Alternatively, the DD, ID and ASD associated with *BAZ2B* haploinsufficiency may be incompletely penetrant. Indeed, it seems likely that genetic, environmental and/or stochastic factors play a role in determining the type and severity of neurodevelopmental phenotypes seen in individuals with reduced levels of BAZ2B function. It follows, that some of the copy number and sequence variants identified in previously published individuals in Supp. Table S3 and the subjects described here (Supp. Table S4) may be acting as modifiers of their *BAZ2B*-related phenotypes.

While neurodevelopmental issues were documented in all subjects, brain anomalies were noted in only one of the four (25%) subjects who had a brain MRI. Similarly, no consistent pattern of additional medical problems was seen among subjects, with the possible exception of vision problems which were seen in 5/6 (83%) of the individuals who were fully phenotyped (Supp. Table S4). Epicanthal folds (3/6, 50%) and macrocephaly (2/6, 33%) were the only recurrently reported dysmorphic features that were found in subjects from

different families. The identification of additional affected individuals will be needed in order to determine whether these features are truly associated with BAZ2B deficiency.

Taken together, our findings suggest that haploinsufficiency of *BAZ2B* causes a neurodevelopmental disorder whose cardinal features include DD, ID and ASD. The phenotype associated with this disorder is not sufficiently distinct to be suspected on clinical grounds alone. The identification of additional individuals with *BAZ2B* haploinsufficiency may help to clarify the spectrum of neurodevelopmental phenotypes and additional medical problems associated with this disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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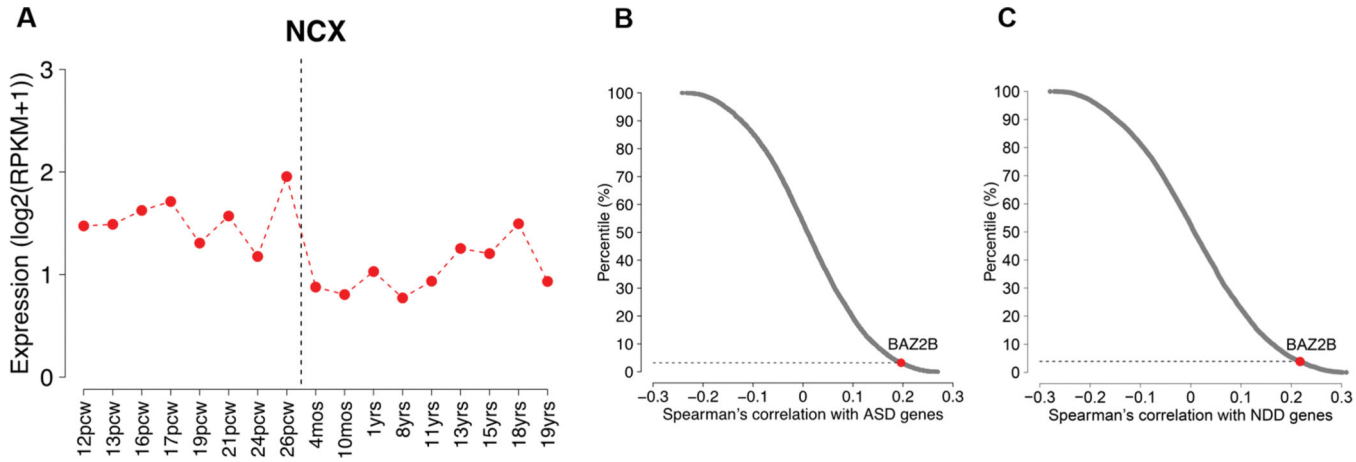

Figure 1: Functional convergence of BAZ2B with ASD and NDD genes during human fetal neocortical development.

A) The expression of *BAZ2B* during human neocortical development. The expression values of *BAZ2B* across cortical samples were grouped and sorted by developmental time points. NCX, neocortex; pcw, post-conceptional weeks; mos, months; yrs, years. B) Scatter plot shows the distribution of Spearman's correlation with ASD genes in prenatal cortical samples for all prenatal cortex-expressed genes. Dots represent individual genes. The dashed horizontal line at 3.2% indicates the top percentile among which the correlation between ASD genes and *BAZ2B* is ranked. C) Scatter plot shows the distribution of Spearman's correlation with NDD genes in fetal cortical samples for all the prenatal cortex-expressed genes. Dots represent individual genes. The dashed horizontal line at 3.9% indicates the top percentile among which the correlation between NDD genes and *BAZ2B* is ranked.

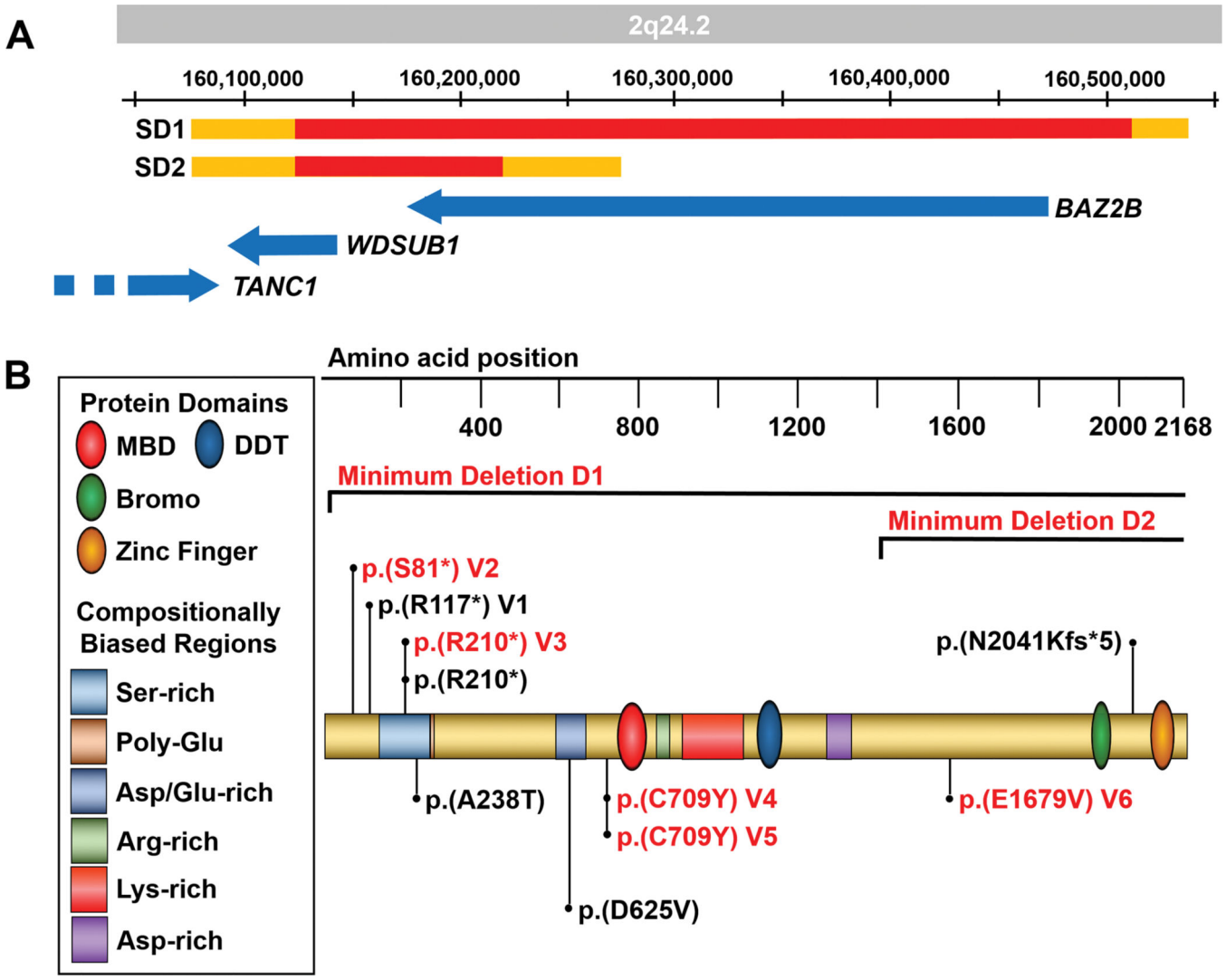

Figure 2: Molecular changes in individuals with *BAZ2B* deletions and deleterious variants.

A) Schematic representing the minimum (red) and maximum (orange) deletions seen in Subjects D1 and D2. *BAZ2B* and other genes in the region are represented by blue arrows whose direction indicates the direction of transcription. B) The predicted locations of domains within BAZ2B are presented along with the locations of the BAZ2B changes predicted to occur in previously reported individuals (black) and additional subjects described here (D1-D2, V2-V6; red).