Neurodevelopmental and other phenotypes recurrently associated with heterozygous BAZ2B loss-of-function variants

Sewani, S.; Azamian, M.S.; Mendelsohn, B.A.; Mau-Them, F.T.; Réda, M.; Nambot, S.; ... ; Scott, D.A.

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Neurodevelopmental and other phenotypes recurrently associated with heterozygous *BAZ2B* loss-of-function variants

Soha Sewani[1] | Mahshid S. Azamian[1,2] | Bryce A. Mendelsohn[3] | Frederic Tran Mau-Them[4,5] | Manon Réda[6,7,8,9] | Sophie Nambot[10,11] | Bertrand Isidor[12,13] | Jasper J. van der Smagt[14] | Joseph J. Shen[15] | Amelle Shillington[16,17,18] | Lori White[16] | Houda Zghal Elloumi[19] | Peter R. Baker 2nd[20] | Shayna Svihovec[20] | Kathleen Brown[20] | Yvonne Koopman-Keemink[21] | Mariette J. V. Hoffer[22] | Inge M. M. Lakeman[22] | Elise Brischoux-Boucher[23] | Maria Kinali[24] | Xiaonan Zhao[1,25] | Seema R. Lalani[1,2] | Daryl A. Scott[1,2,26]

Correspondence
Daryl A. Scott, Department of Molecular Physiology and Biophysics, Baylor College of Medicine, R813, One Baylor Plaza, BCM225, Houston, TX 77030, USA.
Email: dscott@bcm.edu

Abstract

The bromodomain adjacent to zinc finger 2B (*BAZ2B*) gene encodes a chromatin remodeling protein that has been shown to perform a variety of regulatory functions. It has been proposed that loss of *BAZ2B* function is associated with neurodevelopmental phenotypes, and some recurrent structural birth defects and dysmorphic features have been documented among individuals carrying heterozygous loss-of-function *BAZ2B* variants. However, additional evidence is needed to confirm that these phenotypes are attributable to *BAZ2B* deficiency. Here, we report 10 unrelated individuals with heterozygous deletions, stop-gain, frameshift, missense, splice junction, indel, and start-loss variants affecting *BAZ2B*. These included a paternal intragenic deletion and a maternal frameshift variant that were inherited from mildly affected or asymptomatic parents. The analysis of molecular and clinical data from this cohort, and that of individuals previously reported, suggests that *BAZ2B* haploinsufficiency causes an autosomal dominant neurodevelopmental syndrome that is incompletely penetrant. The phenotypes most commonly seen in association with loss of *BAZ2B* function include developmental delay, intellectual disability, autism spectrum disorder, speech delay—with some affected individuals being non-verbal—behavioral abnormalities, seizures, vision-related issues, congenital heart defects, poor fetal growth, and an indistinct pattern of dysmorphic features in which epicanthal folds and small ears are particularly common.

KEYWORDS
autism spectrum disorder, BAZ2B, developmental delay, genetic syndrome, intellectual disability, neurodevelopmental disorder

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1 | INTRODUCTION

The bromodomain adjacent to zinc finger 2B (*BAZ2B*) gene, located on chromosome 2, is a member of the bromodomain gene family. It has been shown to have a variety of related regulatory functions and has specificity for the acetylated 14th lysine residue of the H3 histone (H3K14ac) whose presence at promoter regions is generally associated with gene activation (Charlop-Powers et al., 2010; Karmodiya et al., 2012; Ntranos & Casaccia, 2016; Philpott et al., 2011; Pokholok et al., 2005; Wang et al., 2008). The acetylation and deacetylation of lysine residues within the tail of histones plays a crucial role in regulating gene expression (Verdone et al., 2006). Lysine acetylation removes a positive charge, leading to a decreased interaction between the N-termini of histones and the negatively charged phosphates of DNA. This decrease in interaction leads to an increase in DNA accessibility. Acetylated lysines also function to increase transcription by interacting with the bromodomains of various activating transcription factors (Ntranos & Casaccia, 2016).

Initial studies identified *BAZ2B* as a potential candidate gene for autism spectrum disorder (ASD) (De Rubeis et al., 2014; Fischbach & Lord, 2010; Guo et al., 2019). Scott et al. corroborated these findings through bioinformatic analyses that demonstrated a high level of functional convergence between *BAZ2B* and genes known to cause autism spectrum disorder and neurodevelopmental disorder during fetal cortical development (Scott et al., 2020). They went on to identify an excess of de novo *BAZ2B* loss-of-function variants within previously published cohorts of individuals with ASD, intellectual disability (ID), or developmental disorders and subsequently identified seven additional individuals with heterozygous deletions, stop-gain, or de novo missense variants affecting *BAZ2B*. All of these individuals had developmental delay (DD), ID, and/or ASD. Although some recurrent structural birth defects and dysmorphic features were noted among individuals carrying *BAZ2B* loss-of-function variants, they concluded that the identification of additional affected individuals would be needed to determine whether these phenotypes were attributable to *BAZ2B* deficiency.

Several metrics suggest that *BAZ2B* is haploinsufficient. Specifically, *BAZ2B* has a loss-of-function intolerance (pLI) score of 0.98, a loss-of-function observed/expected upper bound fraction (LOEUF) score of 0.29, and a probability of haploinsufficiency (pHaplo) score of 0.94 (Collins et al., 2022; Lek et al., 2016). However, Scott et al. noted that there were multiple individuals carrying heterozygous high confidence loss-of-function variants and missense variants with high CADD scores affecting *BAZ2B* cataloged in the Genome Aggregation Database version 2.1.1 (gnomAD v2.1.1) (Karczewski et al., 2020; Scott et al., 2020). Since subjects in this database were not assessed for neurodevelopmental phenotypes, they hypothesized that these individuals might be mildly affected or that *BAZ2B* haploinsufficiency may be incompletely penetrant.

Based on the results reported by Scott et al. (2020), *BAZ2B* has been added to some commercially available neurodevelopmental and autism gene panels. However, the relative paucity of reported affected individuals, and the prevalence of putatively damaging *BAZ2B* variants in control databases, suggests the need to confirm that *BAZ2B* is a bona fide human disease gene whose haploinsufficiency is associated with neurodevelopmental and other phenotypes. Here, we describe 10 additional unrelated individuals, 6 males and 4 females, with putatively deleterious heterozygous *BAZ2B* variants. Molecular and clinical data from this cohort, and previously reported individuals, provide evidence that haploinsufficiency of *BAZ2B* causes an autosomal dominant neurodevelopmental syndrome with incomplete penetrance whose primary features include DD, ID, ASD, speech delay with some individuals being non-verbal, behavioral abnormalities, seizures, vision-related issues, congenital heart defects, poor fetal growth, and an indistinct pattern of dysmorphic features in which epicanthal folds and small ears are particularly common.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

Subjects were identified through personal communications, through GeneMatcher (Subjects S1, S2, and S4–S9), and through the DECIPHER database (Subjects S3 = DECIPHER 391176 and S10 = DECPHER 503075) (Firth et al., 2009; Sobreira et al., 2015). Research consent was obtained for each subject using protocols approved by resident institutional review boards or coded/anonymized data is being presented as authorized by the institutional review board of Baylor College of Medicine (protocol H-47546).

In the case of subjects identified through the DECIPHER database, contact was made with each of the submitting centers who then approved the publication of their patient's clinical and molecular data.

All research was conducted in accordance with the ethical standards of Baylor College of Medicine's committee on human research and international standards.

2.2 | CNV and sequence variant analyses

CNVs and sequence variants were identified using chromosome analyses or exome/genome sequencing studies performed in CLIA- or ISO 15189-certified laboratories.

Throughout the manuscript, all CNV data are reported based on hg19, and all *BAZ2B* sequence variants are reported based on *BAZ2B* transcript variant 1 (NM_013450.4). Sequence variants were classified as pathogenic, likely pathogenic, or variants of unknown significance (VUS) according to ACMG 2015 guidelines (Richards et al., 2015).

3 | RESULTS

Here, we describe 10 individuals who carry CNVs ($n = 3$) or putatively deleterious stop-gain, frameshift, missense, splice junction, start-loss, and indel variants ($n = 7$) in *BAZ2B*. Molecular and clinical data from this cohort is summarized below, in Table 1, and in Figures 1 and 2.

TABLE 1 Clinical and molecular data from Subjects S1 to S10.

Patient identifier, sex, age	*BAZ2B* deletion (hg19) or variant [NM_013450.4]	Inheritance; variant classification (criteria)[b]	Neurologic phenotypes	Brain MRI	Speech and language abilities	Eye/vision problems	Other medical problems and dysmorphic features
S1, female, 5y	1.23 Mb deletion, chr2:159,844,069–161,073,462[a]	De novo	DD, ASD, hyperactivity	Normal	First words at 3y, currently speaks in short sentences	None	Relative microcephaly
S2, male, 6y	127 kb deletion, chr2:160,229,645–160,357,102	Unknown; pathogenic (PVS1, PM2, PP3)	DD, mild ID, ASD, behavioral abnormalities	N/D	Vocabulary of ~500 words, 3-word phrases	Pseudo-strabismus verses intermittent accommodative esotropia of left eye, mild myopia right eye, mild hyperopia left eye, moderate bilateral astigmatism	AV canal, mildly high bitemporal hairline, hypoplastic nipples, 5th finger clinodactyly
S3 (DECIPHER 391176), male, 8y 3m	217 kb deletion, chr2:160,294,883–160,511,552	Paternal; likely pathogenic (PVS1, PM2, PP1, PP3)	DD, moderate ID, seizures	Normal	Expressive language delay, 50 words at 32 months, speaks in simple sentences	Unilateral strabismus and hypermetropia	Arachnodactyly, xerosis
S4, female, 6y	c.1435del, p.(His479Thrfs*6)	De novo; pathogenic (PVS1, PS2, PM2)	GDD, ID hypertonia	Atlantoaxial subluxation	Said words but lost this ability between 12 and 18m, currently nonverbal	Cerebral visual impairment, blepharophimosis, microphthalmia, high myopia, strabismus, photophobia	High arched palate, PDA, PFO, bicuspid aortic valve, dairy intolerance, constipation, hand-to-mouth behavior, hypertelorism, epicanthal folds, small ears with folded superior helix, small philtrum, tented upper lip, underdeveloped and depressed nasal bridge, hypoplastic midface, long toes, persistent fetal finger pads, vitiligo
S5, male, 14y 4m	c.2105dup, p.(Ser703Leufs*9)	Maternal; likely pathogenic (PVS1, PM2)	DD, learning disabilities	Normal	Speech delay, current speech is normal	Strabismus, hyperopia	Muscular torticollis, plagiocephaly, arched eyebrows, high arched palate, recurrent otitis media, epicanthal folds, small low-set ears, bulbous nasal tip, excess hair on lower limbs, macrocephaly, recurrent otitis media

(Continues)

TABLE 1 (Continued)

Patient identifier, sex, age	*BAZ2B* deletion (hg19) or variant [NM_013450.4]	Inheritance; variant classification (criteria)[b]	Neurologic phenotypes	Brain MRI	Speech and language abilities	Eye/vision problems	Other medical problems and dysmorphic features
S6, female, 16y	c.502G>A, p.(Gly166Ser); abnormal splicing	Not maternal; likely pathogenic (PS3, PP3)	DD, ID, behavioral abnormalities, gross hypotonia, clumsy lordotic gait, seizures	Lateral and third ventricle enlargement, central white matter and mild cerebellar volume loss, small corpus callosum, small areas of gliosis, gray matter heterotopias	First words at 3y, currently speaks in sentences	None	Aggression and irritability, hyperphagia with antipsychotic medication, dental caries, hypothyroidism, diarrhea, rashes, bulbous nasal tip, microcephaly, hypotelorism, short philtrum
S7, female, 6y 10 m	c.2152C>T, p.(Leu718Phe)	De novo; likely pathogenic (PS2, PM2, PP3)	DD, balance issues, motor weakness, ataxia of upper limbs, action and postural tremor, clonus, dysmetria, postural tremor, astasia abasia, fear of falling, rigidity of thinking, obsessive-compulsive symptoms, hyperacusis, misophonia	Macrocephaly, ventriculomegaly, paucity of cerebral white matter	Normal	Congenital cataracts	Obstructive hydrocephalus status post third ventriculostomy, PDA, GERD in infancy, café au lait macules, epicanthal folds, low-set ears, short hands, pes planus, hypermobility, fibrous histiocytoma, acute immune thrombocytopenia
S8, male, 9y	c.3075+3_3075+6del, p.(?)	De novo; likely pathogenic (PS2, PP3)	DD, mild ID, ASD,	N/D	Delayed speech development	None	Repetitive behaviors, needs support for daily activities; small ears, flat eyebrows, long slender fingers
S9, male, 7y	c.2 T>C, p.(Met1?)	De novo; pathogenic (PVS1, PS2, PM2, PP3)	DD, hypotonia, suspected ASD, behavioral abnormalities	Suspected vascular abnormality at mesencephalon level	Delayed speech development	Improving vertical gaze palsy, Marcus Gunn jaw winking synkinesis	Behavioral abnormalities
S10 (DECIPHER 503075), male, 4y 6 m	c.1910_1927del, p.(Ser637_Asp642del)	Not maternal; VUS (PM2)	Speech delay, suspected ASD	N/D	First words at 1y, stopped talking at 2y, and currently only uses seven words	None	Recurrent otitis media, gastroenteritis, broad forehead, pointed chin, mildly hypoplastic 5th fingernails

Abbreviations: ASD, autism spectrum disorder; AV, atrioventricular; DD, developmental delay; GDD, global developmental delay; GERD, gastroesophageal reflux disease; ID, intellectual disability; m, months; N/D, not done; PDA, patent ductus arteriosus; VUS, variant of unknown significance; y, years.

[a]In addition to *BAZ2B* (pLI = 0.98), this deletion includes *TANC1* (pLI = 0, *WDSUB1* (pLI = 0), *MARCHF7* (pLI = 0.66), *CD302* (pLI = 0), *LY75I* (pLI = 0), *PLA2R1I* (pLI = 0), *ITGB6* (pLI = 0).

[b]ACMG 2015 guidelines (Richards et al., 2015).

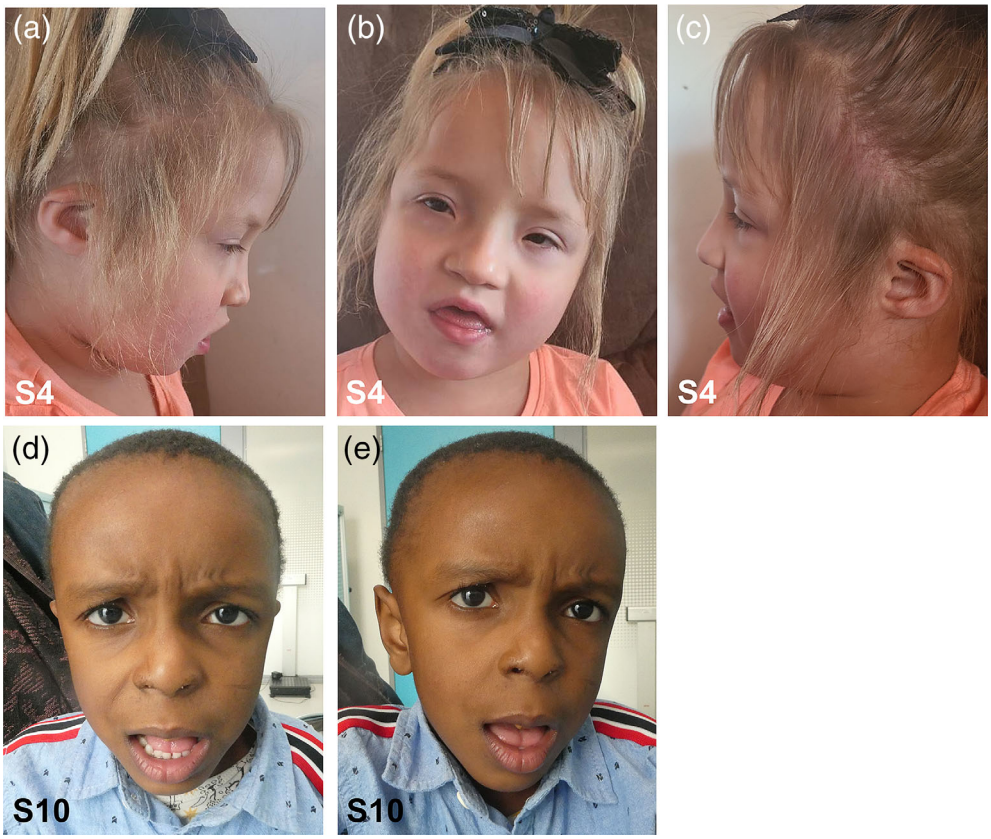

FIGURE 1 Photographs of individuals with putatively deleterious variants in *BAZ2B*. (a–c) Photographs of Subject S4 at 6 years of age. She has small ears with folded over superior helices (Lidding deformity), an underdeveloped and depressed nasal bridge, hypoplastic midface, hypertelorism, epicanthal folds, blepharophimosis, microphthalmia, strabismus, a small philtrum, and a tented upper lip. (d, e) Photographs of Subject S10. He has a broad forehead and a pointed chin.

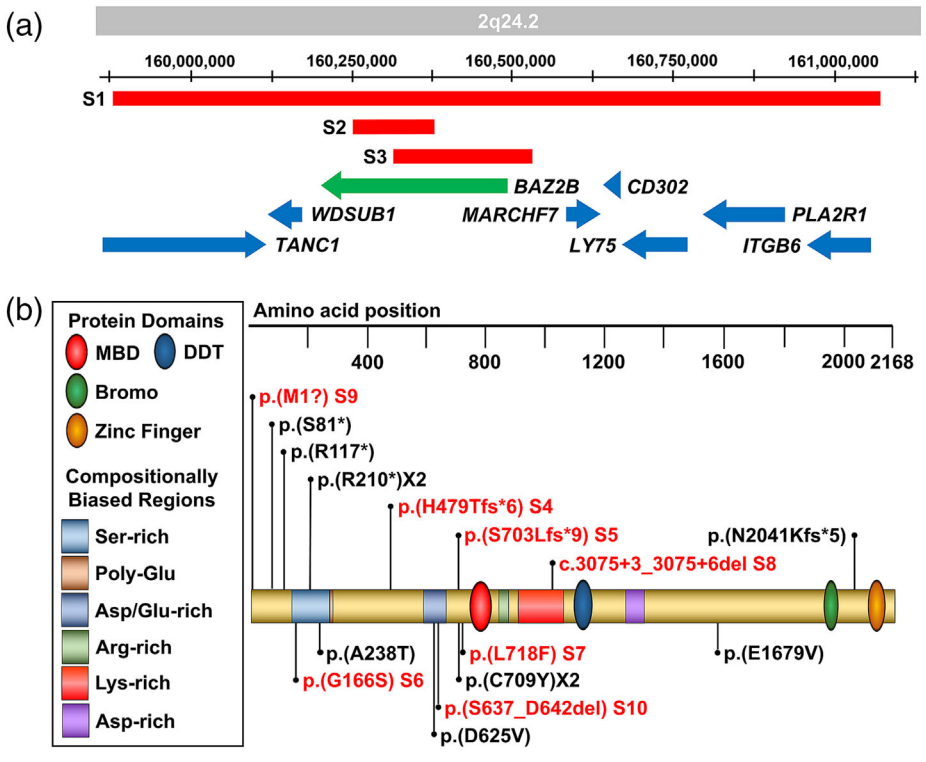

FIGURE 2 Copy number and sequence variants affecting *BAZ2B*. (a) Schematic showing the relative locations of the deletions found in Subject S1–S3 in relation to *BAZ2B* and surrounding genes on chromosome 2q24.2. (b) Schematic representation of the predicted protein changes associated with the *BAZ2B* variants identified in Subject S4–S10 (red) and previously reported variants (black) in relation to various BAZ2B protein domains. Figure was adapted from Scott et al. (2020).

The CNVs and *BAZ2B* sequence variants identified in these individuals arose de novo in five cases and were inherited from mildly affected or asymptomatic parents in two cases (S3 and S5). The inheritance patterns of the other three variants could not be determined because one individual was adopted (S2) and DNA was available from only one parent for two individuals (S6 and S10).

To determine the features most commonly associated with loss of BAZ2B function, we summarized the phenotypes seen in our cohort and fully phenotyped individuals previously reported by Scott et al. (Table S1). The phenotypes most commonly described in these individuals included neurodevelopmental phenotypes (16/16, 100%), CNS anomalies revealed by brain MRI (4/10, 40%), vision problems (11/16, 69%), congenital heart defects (3/16, 19%), gastrointestinal issues (4/16, 25%), abnormalities of the male genitalia (2/11, 18%), musculoskeletal problems (9/16, 56%), and growth-related phenotypes (6/16, 38%). A variety of dysmorphic features were also documented among individuals, but a clinically recognizable pattern was not apparent.

3.1 | Patient reports

3.1.1 | Subject S1

Subject S1 is a 5-year-old white female who carries a de novo 1.23 Mb deletion (chr2: 159,844,069–161,073,462; hg19) that includes *BAZ2B* and seven other protein coding genes *TANC1*, *WDSUB1*, *MARCHF7*, *CD302*, *LY75*, *PLA2R1*, *ITGB6*. All of these other genes, with the exception of *MARCHF7*, have pLI scores of 0 in gnomAD v2.1.1, making their deletion unlikely to be causative (Karczewski et al., 2020; Lek et al., 2016). *MARCHF7* (pLI = 0.66), has not been associated with a human disease. *Marchf7*$^{-/-}$ mice are viable and fertile but have agenesis of the corpus callosum and degeneration of substantia gelatinosa lamina II axons in adulthood (Metcalfe et al., 2005). Hence, we cannot rule out the possibility that haploinsufficiency of *MARCHF7* is contributing to S1's phenotypes. No additional genetic testing beyond chromosomal microarray analysis with FISH confirmation was obtained.

There were no known complications during pregnancy. However, she was small for gestational age. She was subsequently diagnosed with developmental delay and autism spectrum disorder. She began walking at 24 months of age and spoke her first words at 3 years of age. Currently, she can only speak in short sentences. She is hyperactive.

At 3 years and 10 months of age, her weight and height were in the normal range, but she had relative microcephaly. Her brain MRI and neurological exam were normal.

3.1.2 | Subject S2

Subject S2 is a 6-year-old male who carries a 127 kb partial deletion (chr2:160,229,645–160,357,102; hg19) of *BAZ2B* detected by chromosomal microarray analysis. This deletion encompasses exons 3–27. No additional genetic testing was obtained. He was adopted at a young age and his ethnic origins are unknown. The pregnancy was complicated by late prenatal care and maternal use of alcohol, marijuana, and methamphetamine. A prenatal ultrasound revealed the presence of an atrioventricular canal defect. He was born at 39 weeks gestation.

Over time he was found to have developmental delay, a mild form of intellectual disability, and autism spectrum disorder. His current language ability is limited to 500 words and 3-word phrases. Behavioral abnormalities include boundary issues, affinity for rigid routines, an apparent lack of empathy, being a picky eater, and sleeping poorly despite the use of melatonin. Ophthalmologic evaluations revealed pseudostrabismus verses intermittent accommodative esotropia of the left eye, mild myopia of the right eye, mild hyperopia of the left eye, and moderate bilateral astigmatism.

His most recent physical examination was at 6 years of age. His weight was 21.5 kg (61st centile, +0.27 SD) and his height was 111 cm (20th centile, −0.83 SD). His neurological exam was normal. Notable dysmorphic features include a mildly high bitemporal hairline, hypoplastic nipples, and mild 5th finger clinodactyly.

3.1.3 | Subject S3 (DECIPHER 391176)

Subject S3 is an 8-year, 3-month-old white male who carries a 217 kb partial deletion (chr2:160,294,883–160,511,552; hg19) of *BAZ2B* that encompasses exons 1–7, and part of exon 8. This deletion was identified by array comparative genomic hybridization and confirmed by qPCR. He inherited this deletion from his father who has a mild learning disability but is otherwise asymptomatic and has a normal head circumference. His family history is also significant for a maternal uncle with intellectual disability who is unavailable for genetic testing. A Laboratory of Gent University, Belgium Intellectual Disability and Epilepsy Panel revealed that Subject S3 also carries a maternally inherited c.2179C>T, p.(Arg727Trp) [NM_004606.4] variant of unknown significance in *TAF1*. Pathogenic *TAF1* variants are associated with intellectual developmental disorder, X-linked syndromic 33 (MIM# 300966). The cardinal phenotypes of this neurodevelopmental syndrome include dysmorphic features not documented in Subject S3.

There were no pregnancy complications, but he was born prematurely at 35 weeks gestation. His Apgar scores were 10 and 10. At birth, he weighed 2.41 kg (10th centile, −1.27 SD), had a length of 46 cm (15th centile, −1.03 SD), and an OFC of 32.5 cm (20th centile, −0.83 SD). He was later diagnosed with developmental delay, expressive language delay, and moderate intellectual disability. He sat at 8 months of age, walked at 16 months of age, knew 50 words at 32 months of age, and currently speaks in simple sentences. He has bilateral tonic–clonic seizures. A brain MRI was normal. Other medical problems included poor feeding, unilateral strabismus, hypermetropia, and xerosis.

At 8 years, 3 months of age his height was 117.5 cm (7th centile, −1.5 SD), his weight was 17.9 kg (1st centile, −2.5 SD), his head circumference was 49 cm (< 1st centile, −3 SD), and he had a BMI of 13.1 (1st centile, −2.5 SD). On exam, he was noted to have arachnodactyly. His neurologic exam was normal.

3.1.4 | Subject S4

Subject S4 is a 6-year-old white female who carries a de novo c.1435del, p.(His479Thrfs*6) frameshift variant in *BAZ2B* identified on a GeneDx Autism/IDXpanded trio panel. No other variants of interest were reported. Previous genetic testing had included a normal chromosome analysis and a normal chromosomal microarray analysis. She was born at 37 weeks gestation. At birth, she weighed 1.673 kg (<1st centile, −2.99 SD) and had a length of 43.18 cm (4th centile, −1.75 SD). The pregnancy was complicated by blood pressure concerns due to maternal influenza. After birth she was admitted to the NICU due to poor feeding and poor weight gain and remained there for 1 month. Other neonatal findings included congenital heart defects—a patent foramen ovale, patent ductus arteriosus, and a bicuspid aortic valve—microcephaly, and a high arched palate. Shortly after being discharged from the hospital, she returned to the NICU due to influenza.

S4 was ultimately diagnosed with global developmental delay and cerebral visual impairment. She was able to sit at 7 months of age but did not walk until she was 4 years old. Notably, she was able to say a few words including "mama" and "dada" but lost this skill at 12–18 months of age and is currently nonverbal. She has not been formally evaluated for autism. A brain MRI was normal, but she was noted to have C2 subluxation and instability. Other issues include dairy intolerance and constipation.

At approximately 4 years, 6 months of age, she had a height of 98 cm (8th centile), weight of 14 kg (6th centile, −1.55 SD), and a head circumference of 45.8 cm (<1st centile, −2.7 SD). She was noted to have small ears with folded over superior helices (Lidding deformity), an underdeveloped and depressed nasal bridge, hypoplastic midface, hypertelorism, epicanthal folds, blepharophimosis, microphthalmia, high myopia, strabismus, photophobia requiring her to wear tinted glasses, a small philtrum, a tented upper lip, and persistent fetal finger pads. A neurological exam revealed that she was hypertonic in her lower extremities, making extension difficult. Other notable characteristics include hand-to-mouth behavior, long toes, and hypopigmented skin consistent with vitiligo around her eyes, mouth, elbows, and knees.

3.1.5 | Subject S5

Subject S5 is a 14-year, 4-month-old white male who carries a c.2105dup, p.(Ser703Leufs*9) frameshift variant in *BAZ2B*. This variant was inherited from his asymptomatic mother. The family history is negative for other individuals with neurodevelopmental issues, and no segregation studies were undertaken in family members beyond his parents. He is also hemizygous for a ≥31 kb de novo deletion of Xq28 (chrX:154,290,107–154,321,772; hg19) that involves *MTCP1* (pLI = 0.45), *CMC4* (pLI = 0.16), and *BRCC3* (pLI = 0.01). X chromosome deletions involving *MTCP1* and *BRCC3* have been implicated in the development of an X-linked syndrome characterized by moyamoya angiopathy, short stature, and facial dysmorphisms including and a long philtrum (Miskinyte et al., 2011). Hypergonadotropic hypogonadism, hypertension, dilated cardiomyopathy, premature coronary heart disease, premature hair graying, and early bilateral acquired cataracts have also been documented among affected individuals.

S5 was born at 38 weeks gestation with a birth length of 52 cm (88th centile, 1.2 SD), weight of 3.76 kg (90th centile, 1.3 SD), and head circumference of 36 cm (92nd centile, 1.4 SD). His Apgar scores were 10 and 10. He was later diagnosed with congenital muscular torticollis and plagiocephaly. He began walking at 18 months of age. He had recurrent ear infections with serous otitis media that were treated with an adenoidectomy and pressure equalization tubes at 1 year of age and tonsillectomy at age 3. He was followed for strabismus and hyperopia.

He has been diagnosed with learning disabilities and speech delay. His current language abilities are considered normal, and a speech and language assessment revealed appropriate vocabulary, good language and writing skills, and good auditory verbal memory. A brain MRI, echocardiogram, and abdominal ultrasound were normal.

At 13 years, 1 month of age, he had a height of 147 cm (14th centile, −1.1 SD) a weight of 41 kg (27th centile, −0.6 SD), and a head circumference of 57.6 cm (99th centile, +2.3 SD). Other notable features include epicanthal folds, arched eyebrows, high arched palate, small low-set ears, a bulbous nose tip, thick lips, down-turned corners of mouth, and excess hair on the upper and lower limbs that has been present since childhood.

3.1.6 | Subject S6

Subject S6 is a 16-year-old white female who carries a non-maternal c.502G>A, p.(Gly166Ser) *BAZ2B* variant identified on a Prevention Genetics Comprehensive Developmental Disorders Panel. Targeted RNA studies performed by Labcorp MNG Laboratories revealed three aberrations associated with the presence of the c.496G>A variant; 1) inclusion of intron 5 with the c.496G>A variant located at the last nucleotide of exon 5 (less than 10% of transcripts), 2) skipping of exons 4 and 5 with the junction extending from the splice donor site of exon 3 to the acceptor splice site of exon 6 (noted in tissue-matched controls but at a smaller proportion), and 3) skipping of exons 4 and 5 with the junction extending from a novel aberrant donor splice junction within intron 3 (utilizing GT sequence at chr2:161,172,318–61,172,319; hg19) to the acceptor splice site of exon 6. These abnormal transcripts comprised approximately 50% of reads suggesting that the c.496G>A variant disrupts the adjacent canonical donor splice site and that the majority of the reads associated with this allele are abnormally spliced. The overall expression of *BAZ2B* was comparable with tissue-matched controls.

S6 was also found to be a carrier of a maternally inherited heterozygous c.1730dup, p.(Leu578Thrfs*35) likely pathogenic variant in *PIGT*. This variant has been reported in the compound heterozygous state in multiple individuals with autosomal recessive PIGT-related multiple congenital anomalies-hypotonia-seizures syndrome, but a second variant was not identified. A chromosomal microarray analysis was normal.

The pregnancy was complicated by intrauterine growth restriction. She was born at 36 weeks gestation with a weight of 1.8 kg (3rd centile, −1.96 SD), resulting in a 2-week NICU stay. She was subsequently diagnosed with developmental delay and intellectual disability. She began sitting at 2 years of age, walking at 2.5 years of age, and speaking at 3 years of age. Currently, she can speak in sentences.

She started experiencing seizures before 1 year of age. She has been seizure free for 2 years on medication. A brain MRI revealed enlargement of the lateral and third ventricles, central white matter volume loss, mild cerebellar volume loss without abnormal cerebellar signal, a corpus callosum that was abnormally narrow in caliber with poor development of the splenium and rostrum, and gray matter heterotopias with multiple nodules bordering the occipital horns, right greater than left, and additional nodules in the left frontal horn. There were also small foci of increased signal intensity within the subcortical white matter of both hemispheres with a frontal lobe predominance. These foci were thought to most likely represent small areas of gliosis.

She has behavioral issues including aggression and irritability. She also had hyperphagia while on antipsychotic medication for behavioral management. Other medical problems include dental caries, hypothyroidism, diarrhea, and occasional rashes.

Her most recent clinic visit was at 17 years, 4 months of age. She had a height of 153 cm (5th centile, −1.51 SD), a weight of 62.5 kg (76th centile, 0.72 SD), and a head circumference of 49.5 cm (<1st centile, −4.5 SD). At the time, she was noted to have hypotonia, lordotic posture, a wide-based gait, hypotelorism, a bulbous nasal tip, and a short philtrum.

3.1.7 | Subject S7

Subject S7 is a 6-year, 10-month-old female who carries a de novo c.2152C>T, p.(Leu718Phe) *BAZ2B* variant. A mitochondria DNA genome, mitochondria DNA depletion studies on muscle, an ataxia repeat expansion panel, and fragile X testing were normal. There were no complications in pregnancy. Her mother used escitalopram which is considered safe during pregnancy.

She began sitting at 5 months of age, walked at 21 months of age, and spoke her first words at 18 months of age. Her current language abilities are on par for her age. She has been diagnosed with developmental delay and had gastroesophageal reflux disease in infancy. Other medical problems include congenital cataracts, a patent ductus arteriosus, obstructive hydrocephalus status post third ventriculostomy, ataxia of upper limbs with frank dysmetria but no dysarthria, action and postural tremors, balance issues, hypermobility, and motor weakness. She has developed multiple café au lait spots and a fibrous histiocytoma on the leg. At 2 years, 9 months of age she developed acute immune thrombocytopenia with bone marrow cellularity more than 90% that is now resolved. She has a history of astasia abasia and fear of falling. She was prescribed low dose propranolol starting at 5 years, 3 months of age which has resulted in improvement in her tremors, balance, and astasia abasia. She has a friendly predisposition, rigidity of thinking, and obsessive-compulsive symptoms. She has recently developed hyperacusis and misophonia.

A brain MRI obtained at 1 year, 7 months of age revealed macrocephaly, ventriculomegaly, dilation of all 4 ventricles, and paucity of the cerebral white matter. A repeat surveillance brain MRI at 6 years of age showed stable ventriculomegaly. Muscle biopsy with routine histopathology at 3.5 years of age years was essentially within normal limits. Muscle respiratory chain enzyme analysis showed only evidence of a loss of complex IV activity with a low ratio of 0.011 (normal = 0.013–0.039). Electromyography and nerve conduction velocity studies were normal. A prolonged video EEG at 3 years of age showed no specific diagnostic features.

Her most recent examination was at 6 years, 3 months of age. She had a height of 116.5 cm (25th centile, −6.7 SD), weighed of 22 kg (48th centile, −0.04 SD), had an occipitofrontal circumference of 63 cm (>99th centile, 7.18 SD), and a BMI of 16.2 (64th centile, 0.42 SD). A neurological examination revealed improved postural tremor and hyperreflexia of the lower limbs with three to four beats of clonus on the left and two beats on the right. She has low-set ears, epicanthal folds, short hands, pes planus, and café au lait macules.

3.1.8 | Subject S8

Subject S8 is a 9-year, 2-month-old South Asian male who carries a de novo c.3075+3_3075+6del, p.(?) *BAZ2B* variant identified on a GeneDx Autism/IDXpanded trio panel. No additional variants of interest were reported. Fragile X testing was normal, and a chromosomal microarray analysis revealed a heterozygous Xq28/Yq12 deletion (chrX:154,941,868–155,233,781; chrY:59,044,874–59,336,737; hg19) of unknown significance.

S8 was born prematurely and was small for gestational age. The pregnancy was complicated by early twin loss. He was ultimately diagnosed with language, social, and cognitive delays, mild intellectual disability, and autism spectrum disorder. No motor delays were apparent. He is in special education classes. He has repetitive behaviors and requires significant support to accomplish daily activities.

At his most recent physical examination, his height and weight were normal. He was also noted to have flat eyebrows, small ears, and long slender fingers.

3.1.9 | Subject S9

Subject S9 is a 7-year-old male who carries a de novo c.2T>C, p.(Met1?) *BAZ2B* variant. He is also hemizygous for a maternally inherited c.489T>G, p.(Asn163Lys) variant of unknown significance in *PHKA1*, a gene associated with X-linked recessive muscle glycogenosis (MIM# 300559). He also carries a maternally inherited c.1486C>T, p.(Arg496*) variant in *RBBP8*, the gene associated with autosomal recessive Jawad syndrome and Seckel syndrome 2 (MIM# 606744). Information about his pregnancy and birth is unavailable.

S9 has been diagnosed with developmental delay, particularly affecting his speech, gross motor delay due to severe axial hypotonia which has improved over time, and behavioral abnormalities. Although not formally tested, his intelligence likely lies within the low normal to mild intellectual disability range. He is suspected of having autism spectrum disorder but has not received a formal diagnosis. A brain MRI revealed an elongated and slightly dilated superior cerebellar artery on the left side, which could indicate a vascular abnormality at the level of the mesencephalon. His other medical conditions include improving vertical gaze palsy and Marcus Gunn jaw winking synkinesis.

3.1.10 | Subject S10 (DECIPHER 503075)

Subject S10 is a 4-year, 6-month-old male who carries a c.1910_1927del, p.(Ser637_Asp642del) *BAZ2B* variant that was not inherited from his mother. Pregnancy was complicated by preeclampsia. No other putatively damaging variants were identified by exome sequencing or chromosome microarray analysis. He was born via emergency Caesarean section at 37 3/7 weeks. Apgar scores were 3, 5, and 9. He weighed 2.91 kg (39th centile, −0.25 SD). Although gross motor development was normal and he said his first words at 1 year of age, he stopped talking at 2 years of age, and currently only uses seven words. He was noted to have autistic behavior and a diagnosis of autism spectrum disorder was suspected but has not been confirmed. Additional diagnoses include chronic otitis media requiring the placement of pressure equalization tubes, and gastroenteritis. His heart was found to be structurally normal. Currently, his height is 104.2 cm (35th centile, −0.38 SD) and his weight is 16 kg (24th centile, −0.73 SD). Other dysmorphic features noted on physical examination include a broad forehead, a pointed chin, and mildly hypoplastic 5th fingernails.

4 | DISCUSSION

Haploinsufficiency of many human disease genes is associated with a wide phenotypic spectrum (Chowdhury et al., 2021; Muroya et al., 2001). This is likely due, at least in part, to variability in the function of the "unaffected" allele or to the effects of modifying loci whose identities are often unknown. The association of haploinsufficiency with seemingly disparate low-penetrance phenotypes may ultimately be confirmed though statistical analyses performed on large numbers of affected individuals or in animal models (Beck et al., 2013; Hardcastle et al., 2022; Jordan, Fregeau, et al., 2018; Scott et al., 2021). Alternatively, unusual phenotypic presentations may be due to mutational modes of action other than haploinsufficiency that manifest themselves in specific phenotype/genotype correlations (Jordan, Beck, et al., 2018). Hence, there can be great value in reporting the detailed phenotypic descriptions of individuals who are haploinsufficient for genes that may play a role in human disease.

Including Subjects S1–S10, detailed phenotypic descriptions have been reported for 16 individuals with putatively deleterious *BAZ2B* variants (Scott et al., 2020). Based on their common symptoms, we assume that these variants are associated with a loss of *BAZ2B* function, although other deleterious effects cannot be excluded. The most common phenotypes—seen in all 16 of these individuals (100%)—are neurodevelopmental. This data corroborates previous findings suggesting that developmental delay, intellectual disability, and/or autism spectrum disorder are recurrent phenotypes associated with *BAZ2B* haploinsufficiency (Scott et al., 2020).

Across all 16 individuals, developmental delay was identified in 13 (81%), intellectual disability in 7 (44%), autism spectrum disorder or suspected autism in 10 (63%), and speech delay or mixed receptive-expressive language disorder in 10 (63%). Of the 10 patients reported with speech delay, two were non-verbal (20%). Behavioral issues were also identified in five individuals (31%). Seizures were reported in two subjects (13%). Brain MRIs were performed for 10 individuals and were normal in six cases (60%). No clear pattern of brain anomalies was observed in the four brain MRIs (40%) in which an abnormality was identified.

Vision-related issues were identified in 11 individuals (69%) with strabismus being the most common (31%). This high frequency underscores the importance of ophthalmologic screening in individuals with *BAZ2B* haploinsufficiency.

Congenital heart defects were not described in the six cases reported by Scott et al. but were reported in three individuals in our cohort (3/16, 19%) (Scott et al., 2020). These included atrioventricular canal defect in Subject S2, bicuspid aortic valve and patent foramen ovale (PFO) in Subject S4, and patent ductus arteriosus (PDA) in Subjects S4 and S7.

No discernable pattern of dysmorphic features was evident among individuals. However, the most common dysmorphic features described were epicanthal folds (38%) and small ears (25%). Intrauterine growth restriction and/or being small for gestational age was documented in five individuals (31%).

Among the *BAZ2B* variants identified in this cohort, the inheritance pattern could not be determined in three cases due to an inability to obtain one or both parental samples. In the seven cases for which the inheritance pattern could be defined, five arose de novo, and two were inherited, one from a father with a mild learning disability, and one from an asymptomatic mother (Table 1). Scott et al. previously hypothesized that some individuals carrying heterozygous loss-of-function variants in *BAZ2B* would be mildly affected or asymptomatic based on the presence of multiple individuals in the gnomAD v2.1.1 database who carried *BAZ2B* loss-of-function variants (Karczewski et al., 2020; Scott et al., 2020). Our data supports this hypothesis.

Molecular and clinic data from our cohort, and that of individuals previously reported in the literature, suggest that *BAZ2B* haploinsufficiency causes an autosomal dominant neurodevelopmental syndrome that is incompletely penetrant. Phenotypes recurrently associated with heterozygous loss-of-function *BAZ2B* variants include DD, ID, ASD, speech delay with some individuals being non-verbal, behavioral abnormalities, seizures, vision-related issues, congenital heart defects, poor fetal growth, and an indistinct pattern of dysmorphic features in which epicanthal folds and small ears are particularly common.

AUTHOR CONTRIBUTIONS

Soha Sewani: formal analysis, writing – original draft, and writing – review and editing. **Mahshid S. Azamian**: data curation and writing – review and editing. **Bryce A. Mendelsohn**: data curation, and writing – review and editing. **Frederic Tran Mau-Them**: data curation, and writing – review and editing. **Manon Réda**: data curation, and writing – review and editing. **Sophie Nambot**: data curation, and writing – review and editing. **Bertrand Isidor**: data curation, and writing – review and editing. **Jasper J. van der Smagt**: data curation, and writing – review and editing. **Joseph J. Shen**: data curation, and writing – review and editing. **Amelle Shillington**: data curation, and writing – review and editing. **Lori White**: data curation, and writing – review and editing. **Houda Zghal Elloumi**: data curation, and writing – review and editing. **Peter R. Baker 2nd**: data curation, and writing – review and editing. **Shayna Svihovec**: data curation, and writing – review and editing. **Kathleen Brown**: data curation, and writing – review and editing. **Yvonne Koopman-Keemink**: data curation, and writing – review and editing. **Mariette J. V. Hoffer**: data curation, and writing – review and editing. **Inge M. M. Lakeman**: data curation, and writing – review and editing. **Elise Brischoux-Boucher**: data curation, and writing – review and editing. **Maria Kinali**: data curation, and writing – review and editing. **Xiaonan Zhao**: variant calling, and writing – review and editing. **Seema R. Lalani**: data curation, and writing – review and editing. **Daryl A. Scott**: conceptualization, formal analysis, data curation, writing – original draft, writing – review and editing.

AFFILIATIONS

[1]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA
[2]Texas Children's Hospital, Houston, Texas, USA
[3]Department of Medical Genetics, Kaiser Permanente Oakland Medical Center, Oakland, California, USA
[4]UF6254 Innovation en Diagnostic Genomique des Maladies Rares, Dijon, France
[5]Équipe Génétique des Anomalies du Développement (GAD), Dijon, France
[6]Department of Medical Oncology, Georges François Leclerc Cancer Center – UNICANCER, Dijon, France
[7]Platform of Transfer in Cancer Biology, Georges François Leclerc Cancer Center – UNICANCER, Dijon, France
[8]Université Bourgogne Franche-Comté, Dijon, France
[9]Genomic and Immunotherapy Medical Institute, Dijon, France
[10]Unité Fonctionnelle Innovation en Diagnostic génomique des maladies rares, FHU-TRANSLAD, Dijon, France
[11]Centre de Référence Maladies Rares "Anomalies du Développement et Syndromes Malformatifs", Centre de Génétique, FHU-TRANSLAD, Dijon, France
[12]Centre Hospitalier Universitaire de Nantes, Service de Génétique Médicale, Nantes, France
[13]INSERM, CNRS, UNIV Nantes, l'institut du thorax, Nantes, France
[14]Department of Genetics, University Medical Center Utrecht, Utrecht, The Netherlands
[15]Division of Genomic Medicine, Department of Pediatrics, MIND Institute, University of California, Davis, Sacramento, California, USA
[16]Cincinnati Children's Hospital Medical Center, Department of Human Genetics, Cincinnati, Ohio, USA
[17]Cincinnati Children's Hospital Medical Center Department of Psychiatry, Cincinnati, Ohio, USA
[18]University of Cincinnati College of Medicine Department of Pediatrics, Cincinnati, Ohio, USA
[19]Clinical Genomics Program, GeneDx, Gaithersburg, Maryland, USA
[20]Department of Pediatrics, University of Colorado, Aurora, Colorado, USA
[21]Department of Paediatrics, Juliana Children's Hospital, HAGA Medical Center, the Hague, The Netherlands
[22]Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands
[23]Centre de Genetique Humaine, Universite de Bourgogne Franche-Comte, France
[24]Department of Brain Sciences, Imperial College London and Portland Hospital HCA International, London, United Kingdom
[25]Baylor Genetics, Houston, Texas, USA
[26]Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas, USA

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CONFLICT OF INTEREST STATEMENT

The authors do not report any individual conflicts of interest. Baylor Genetics and GeneDx provide clinically based genetic testing. The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from clinical copy number variant analyses and exome sequencing studies performed at Baylor Genetics.

DATA AVAILABILTY STATEMENT

The data generated during this study can be found within the published article and its supplementary files. All variants not reported in DECIPHER have been submitted to the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/).

ORCID

Joseph J. Shen https://orcid.org/0000-0002-5604-7639
Amelle Shillington https://orcid.org/0000-0002-7447-8117
Seema R. Lalani https://orcid.org/0000-0003-0707-657X
Daryl A. Scott https://orcid.org/0000-0003-1460-5169

REFERENCES

Beck, T. F., Veenma, D., Shchelochkov, O. A., Yu, Z., Kim, B. J., Zaveri, H. P., van Bever, Y., Choi, S., Douben, H., Bertin, T. K., Patel, P. I., Lee, B., Tibboel, D., de Klein, A., Stockton, D. W., Justice, M. J., & Scott, D. A. (2013). Deficiency of FRAS1-related extracellular matrix 1 (FREM1) causes congenital diaphragmatic hernia in humans and mice. *Human Molecular Genetics*, *22*(5), 1026–1038. https://doi.org/10.1093/hmg/dds507

Charlop-Powers, Z., Zeng, L., Zhang, Q., & Zhou, M. M. (2010). Structural insights into selective histone H3 recognition by the human polybromo bromodomain 2. *Cell Research*, *20*(5), 529–538. https://doi.org/10.1038/cr.2010.43

Chowdhury, F., Wang, L., Al-Raqad, M., Amor, D. J., Baxova, A., Bendova, S., Biamino, E., Brusco, A., Caluseriu, O., Cox, N. J., Froukh, T., Gunay-Aygun, M., Hancarova, M., Haynes, D., Heide, S., Hoganson, G., Kaname, T., Keren, B., Kosaki, K., … Balci, T. B. (2021). Haploinsufficiency of PRR12 causes a spectrum of neurodevelopmental, eye, and multisystem abnormalities. *Genetics in Medicine*, *23*(7), 1234–1245. https://doi.org/10.1038/s41436-021-01129-6

Collins, R. L., Glessner, J. T., Porcu, E., Lepamets, M., Brandon, R., Lauricella, C., Han, L., Morley, T., Niestroj, L. M., Ulirsch, J., Everett, S., Howrigan, D. P., Boone, P. M., Fu, J., Karczewski, K. J., Kellaris, G., Lowther, C., Lucente, D., Mohajeri, K., … Talkowski, M. E. (2022). A cross-disorder dosage sensitivity map of the human genome. *Cell*, *185*(16), 3041–3055 e3025. https://doi.org/10.1016/j.cell.2022.06.036

De Rubeis, S., He, X., Goldberg, A. P., Poultney, C. S., Samocha, K., Cicek, A. E., Kou, Y., Liu, L., Fromer, M., Walker, S., Singh, T., Klei, L., Kosmicki, J., Shih-Chen, F., Aleksic, B., Biscaldi, M., Bolton, P. F., Brownfeld, J. M., Cai, J., … Buxbaum, J. D. (2014). Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*, *515*(7526), 209–215. https://doi.org/10.1038/nature13772

Firth, H. V., Richards, S. M., Bevan, A. P., Clayton, S., Corpas, M., Rajan, D., Van Vooren, S., Moreau, Y., Pettett, R. M., & Carter, N. P. (2009). DECIPHER: Database of chromosomal imbalance and phenotype in humans using Ensembl resources. *American Journal of Human Genetics*, *84*(4), 524–533. https://doi.org/10.1016/j.ajhg.2009.03.010

Fischbach, G. D., & Lord, C. (2010). The Simons simplex collection: A resource for identification of autism genetic risk factors. *Neuron*, *68*(2), 192–195. https://doi.org/10.1016/j.neuron.2010.10.006

Guo, H., Bettella, E., Marcogliese, P. C., Zhao, R., Andrews, J. C., Nowakowski, T. J., Gillentine, M. A., Hoekzema, K., Wang, T., Wu, H., Jangam, S., Liu, C., Ni, H., Willemsen, M. H., van Bon, B. W., Rinne, T., Stevens, S. J. C., Kleefstra, T., Brunner, H. G., … Eichler, E. E. (2019). Disruptive mutations in TANC2 define a neurodevelopmental syndrome associated with psychiatric disorders. *Nature Communications*, *10*(1), 4679. https://doi.org/10.1038/s41467-019-12435-8

Hardcastle, A., Berry, A. M., Campbell, I. M., Zhao, X., Liu, P., Gerard, A. E., Rosenfeld, J. A., Sisoudiya, S. D., Hernandez-Garcia, A., Loddo, S., Di Tommaso, S., Novelli, A., Dentici, M. L., Capolino, R., Digilio, M. C., Graziani, L., Rustad, C. F., Neas, K., Ferrero, G. B., … Scott, D. A. (2022). Identifying phenotypic expansions for congenital diaphragmatic hernia plus (CDH+) using DECIPHER data. *American Journal of Medical Genetics. Part A*, *188*(10), 2958–2968.

Jordan, V. K., Beck, T. F., Hernandez-Garcia, A., Kundert, P. N., Kim, B. J., Jhangiani, S. N., Gambin, T., Starkovich, M., Punetha, J., Paine, I. S., Posey, J. E., Li, A. H., Muzny, D., Hsu, C. W., Lashua, A. J., Sun, X., Fernandes, C. J., Dickinson, M. E., Lally, K. P., … Scott, D. A. (2018). The role of FREM2 and FRAS1 in the development of congenital diaphragmatic hernia. *Human Molecular Genetics*, *27*(12), 2064–2075. https://doi.org/10.1093/hmg/ddy110

Jordan, V. K., Fregeau, B., Ge, X., Giordano, J., Wapner, R. J., Balci, T. B., Carter, M. T., Bernat, J. A., Moccia, A. N., Srivastava, A., Martin, D. M., Bielas, S. L., Pappas, J., Svoboda, M. D., Rio, M., Boddaert, N., Cantagrel, V., Lewis, A. M., Scaglia, F., … Scott, D. A. (2018). Genotype-phenotype correlations in individuals with pathogenic RERE variants. *Human Mutation*, *39*(5), 666–675. https://doi.org/10.1002/humu.23400

Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alfoldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., … MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*, *581*(7809), 434–443. https://doi.org/10.1038/s41586-020-2308-7

Karmodiya, K., Krebs, A. R., Oulad-Abdelghani, M., Kimura, H., & Tora, L. (2012). H3K9 and H3K14 acetylation co-occur at many gene regulatory elements, while H3K14ac marks a subset of inactive inducible promoters in mouse embryonic stem cells. *BMC Genomics*, *13*, 424. https://doi.org/10.1186/1471-2164-13-424

Lek, M., Karczewski, K. J., Minikel, E. V., Samocha, K. E., Banks, E., Fennell, T., O'Donnell-Luria, A. H., Ware, J. S., Hill, A. J., Cummings, B. B., Tukiainen, T., Birnbaum, D. P., Kosmicki, J. A., Duncan, L. E., Estrada, K., Zhao, F., Zou, J., Pierce-Hoffman, E., Berghout, J., … Exome Aggregation, C. (2016). Analysis of protein-coding genetic variation in 60,706 humans. *Nature*, *536*(7616), 285–291. https://doi.org/10.1038/nature19057

Metcalfe, S. M., Muthukumarana, P. A., Thompson, H. L., Haendel, M. A., & Lyons, G. E. (2005). Leukaemia inhibitory factor (LIF) is functionally linked to axotrophin and both LIF and axotrophin are linked to regulatory immune tolerance. *FEBS Letters*, *579*(3), 609–614. https://doi.org/10.1016/j.febslet.2004.12.027

Miskinyte, S., Butler, M. G., Herve, D., Sarret, C., Nicolino, M., Petralia, J. D., Bergametti, F., Arnould, M., Pham, V. N., Gore, A. V., Spengos, K., Gazal, S., Woimant, F., Steinberg, G. K., Weinstein, B. M., & Tournier-Lasserve, E. (2011). Loss of BRCC3 deubiquitinating enzyme leads to abnormal angiogenesis and is associated with syndromic moyamoya. *American Journal of Human Genetics*, *88*(6), 718–728. https://doi.org/10.1016/j.ajhg.2011.04.017

Muroya, K., Hasegawa, T., Ito, Y., Nagai, T., Isotani, H., Iwata, Y., Yamamoto, K., Fujimoto, S., Seishu, S., Fukushima, Y., Hasegawa, Y., & Ogata, T. (2001). GATA3 abnormalities and the phenotypic spectrum of HDR syndrome. *Journal of Medical Genetics*, *38*(6), 374–380. https://doi.org/10.1136/jmg.38.6.374

Ntranos, A., & Casaccia, P. (2016). Bromodomains: Translating the words of lysine acetylation into myelin injury and repair. *Neuroscience Letters*, *625*, 4–10. https://doi.org/10.1016/j.neulet.2015.10.015

Philpott, M., Yang, J., Tumber, T., Fedorov, O., Uttarkar, S., Filippakopoulos, P., Picaud, S., Keates, T., Felletar, I., Ciulli, A., Knapp, S., & Heightman, T. D. (2011). Bromodomain-peptide displacement assays for interactome mapping and inhibitor discovery. *Molecular BioSystems*, *7*(10), 2899–2908. https://doi.org/10.1039/c1mb05099k

Pokholok, D. K., Harbison, C. T., Levine, S., Cole, M., Hannett, N. M., Lee, T. I., Bell, G. W., Walker, K., Rolfe, P. A., Herbolsheimer, E., Zeitlinger, J., Lewitter, F., Gifford, D. K., & Young, R. A. (2005). Genome-wide map of nucleosome acetylation and methylation in yeast. *Cell*, *122*(4), 517–527. https://doi.org/10.1016/j.cell.2005.06.026

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H. L., & Committee, A. L. Q. A. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*, *17*(5), 405–424. https://doi.org/10.1038/gim.2015.30

Scott, T. M., Guo, H., Eichler, E. E., Rosenfeld, J. A., Pang, K., Liu, Z., Lalani, S., Bi, W., Yang, Y., Bacino, C. A., Streff, H., Lewis, A. M., Koenig, M. K., Thiffault, I., Bellomo, A., Everman, D. B., Jones, J. R., Stevenson, R. E., Bernier, R., … Scott, D. A. (2020). BAZ2B

haploinsufficiency as a cause of developmental delay, intellectual disability, and autism spectrum disorder. *Human Mutation*, *41*(5), 921–925. https://doi.org/10.1002/humu.23992

Scott, T. M., Campbell, I. M., Hernandez-Garcia, A., Lalani, S. R., Liu, P., Shaw, C. A., Rosenfeld, J. A., & Scott, D. A. (2021). Clinical exome sequencing data reveal high diagnostic yields for congenital diaphragmatic hernia plus (CDH+) and new phenotypic expansions involving CDH. *Journal of Medical Genetics*, *59*(3), 270–278. https://doi.org/10.1136/jmedgenet-2020-107317

Sobreira, N., Schiettecatte, F., Valle, D., & Hamosh, A. (2015). GeneMatcher: A matching tool for connecting investigators with an interest in the same gene. *Human Mutation*, *36*(10), 928–930. https://doi.org/10.1002/humu.22844

Verdone, L., Agricola, E., Caserta, M., & Di Mauro, E. (2006). Histone acetylation in gene regulation. *Briefings in Functional Genomics & Proteomics*, *5*(3), 209–221. https://doi.org/10.1093/bfgp/ell028

Wang, Z., Zang, C., Rosenfeld, J. A., Schones, D. E., Barski, A., Cuddapah, S., Cui, K., Roh, T. Y., Peng, W., Zhang, M. Q., & Zhao, K. (2008). Combinatorial patterns of histone acetylations and methylations in the human genome. *Nature Genetics*, *40*(7), 897–903. https://doi.org/10.1038/ng.154

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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