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ORIGINAL ARTICLE

Proximal Deletions of 14q32.2 Result in Severe Neurodevelopmental Outcomes, Congenital Anomalies, and Dysmorphic Features

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ABSTRACT

Deletions of chromosome 14q32.2 often involve the imprinted region of chromosome 14, giving rise to paternal or maternal UPD(14)-like phenotypes. A few individuals with deletions that spare the imprinted region have been reported, with significant variability in deletion size and gene involvement. Four patients with proximal deletions of 14q32.2 were gathered from the primary authors' clinic or through the DECIPHER database. Informed consent for inclusion in this study was obtained from all participants. A retrospective chart review was performed, and medical history records were compiled and analyzed. We report four patients with similar deletions of 14q32.2, three of whom do not involve the imprinted region. These deletions overlapped for 13 different genes, three of which are associated with autosomal dominant conditions: *BCL11B*, *CCNK*, and *YY1*. All four patients presented with prenatal and/or postnatal growth restriction, feeding problems, congenital urogenital anomalies, hypotonia, severe intellectual and developmental disability, and similar dysmorphic features. We propose that deletions involving *BCL11B*, *CCNK*, and *YY1* result in a discrete clinical entity entailing a severe neurodevelopmental phenotype, characteristic facial features, and congenital anomalies. We propose the nomenclature of proximal 14q32.2 deletion syndrome.

1 | Introduction

More than 100 annotated genes reside in the human 14q32.2 locus, a few of which are associated with human disease. Within this region is a cluster of imprinted genes, including the paternally expressed *DLK1* (OMIM #176290) and *RTL1* (OMIM #611896) genes, and the maternally expressed *MEG3* (OMIM #605636) and *MEG8* (OMIM #613648) genes. Loss of function of the paternal or maternal locus by various mechanisms results in Temple syndrome (OMIM #616222) or Kagami-Ogata syndrome

(OMIM #608149), respectively. Shared phenotypes for these conditions include growth restriction, feeding problems, developmental delay, intellectual disability, and dysmorphic features (Prasasya et al. 2020).

Deletions of 14q32.2 are typically reported in the context of their association with the known imprinting disorders of this region. Patients with proximal deletions of 14q32.2 (~88,550,163–101,126,789) have been included in larger cohorts with single nucleotide variants (SNVs) involving genes in this region, such

as *CCNK* (OMIM #603544) and *YY1* (OMIM #600013) to further define their function and phenotype (Gabriele et al. 2017; Fan et al. 2018). In many instances, detailed clinical information on these patients is not available. Gabriele et al. (2017) collected a cohort of patients with missense variants and deletions including *YY1* and concluded that there was no significant difference in phenotype between patients with missense mutations and deletions. For those with larger, multi-gene deletions, the authors proposed that other genes in the 14q32.2 region may contribute to overlapping phenotypes seen in those with *YY1* missense variants. For example, both the intragenic pathogenic variants in the *YY1* gene and uniparental disomy of chromosome 14 (UPD(14)) cause intrauterine growth restriction.

We present detailed clinical information on four patients with comparable deletions of 14q32.2, including two patients for whom only limited tabular data was provided in a previous study (Gabriele et al. 2017) and two patients who have not been reported in the literature. All deletions included *BCL11B* (OMIM #606558) and *CCNK*; three deletions included *YY1*, and the fourth included several promoter/enhancer regions of *YY1* evidenced by an abnormal methylation pattern consistent with disrupted *YY1* function.

2 | Methods

2.1 | Patients

Patients 1 and 4 were identified through routine clinical genetics workup, and patients 2 and 3 were subsequently recruited for inclusion in this study by initiating contact and collaborating through the DECIPHER database (deciphergenomics.org).

All patients' specimens were evaluated via chromosomal microarray of various platforms, according to manufacturer instructions. Patients 1 and 3 were evaluated on SNP arrays (High-Density Cytoscan Platform from Applied Biosystems (ThermoFisher) and Affymetrix GeneChip Human Mapping 262K (ThermoFisher), respectively), and patients 2 and 4 were evaluated on oligonucleotide arrays (CytoChip v.3.01 (BlueGnome) and SignatureChipOSTM (Signature Genomics), respectively).

Patient 4 underwent EpiSign Methylation analysis (Greenwood Genetics) using the Infinium MethylationEPIC BeadChip (Illumina).

2.1.1 | Editorial Policies and Ethical Considerations

Informed consent was obtained from all parties, including for inclusion of photographs (Figure 1). This study was deemed IRB exempt by the IRB at Upstate University Hospital.

3 | Patients

Patient 1, a male, was born at 39 weeks gestation via cesarean section due to loss of fetal heart tones, to a 21-year-old primigravida mother and a 21-year-old father. The pregnancy was

complicated by ventriculomegaly, intrauterine growth restriction (IUGR) first noted at 32 weeks, and hydronephrosis. The birth weight was 2.319 kg (< 3rd percentile), length was 45.7 cm (5th percentile), and head circumference was 32 cm (4th percentile). The neonatal period was complicated by feeding problems, hypoglycemia, hypotonia, bilateral cryptorchidism, and unilateral hydronephrosis. His newborn metabolic screen was positive for severe combined immunodeficiency syndrome (SCID) with T-cell receptor excision circles (TRECs) levels of 0, 0, and 98; follow-up molecular testing for 20 genes associated with SCID was negative. The family history contributes a congenital heart defect in a maternal aunt and autism in a paternal first cousin.

The medical history is significant for T-cell lymphopenia with recurrent respiratory infections and rashes that resolved by 12 months of age, unilateral hydronephrosis that resolved by 3.5 years of age, profound hypotonia, spastic quadriplegia Gross Motor Function Classification System (GMFCS) level 5, dysphagia requiring supplemental nasogastric tube feedings when sick, failure to thrive, bilateral cryptorchidism, chronic constipation, strabismus, hyperopia, scoliosis (38° thoracic spine and 66° lumbar spine dextroscoliosis), and global developmental delay. A brain magnetic resonance imaging (MRI) at 4 years of age was normal save slightly prominent ventricles. At 6.5 years old, his height was 111.8 cm (7th percentile), weight was 15.1 kg (< 1st percentile), and head circumference was 49.5 cm (6th percentile). He has dysmorphic features, as presented in Table 1 and seen in Figure 1A.

The patient could track, smile, and roll over by 7 months of age but achieved no other motor or speech milestones. At 9 years of age, he is nonambulatory, nonverbal, and incontinent. He is able to communicate in simple sentences via an eye gaze communication device and is responsive to verbal prompts from parents. He can operate toys with simple switches but otherwise has limited use of his hands. He is enrolled in a mainstream school and is in a special education classroom.

Chromosome analysis revealed an interstitial deletion (46,XY,del(14)(q32.2q32.2)); follow-up chromosomal microarray revealed a *de novo* 3.125 Mb deletion of 14q32.2 (98,029,521-101,154,362); hg19. Fluorescence in situ hybridization (FISH) for 22q11.2 deletion/duplication syndrome was negative. Chromosome analysis and microarray for both parents were normal.

Patient 2, a male, was born at 41 weeks gestation via a cesarean section due to fetal distress, to a 42-year-old gravida 2 para 1 > 2 mother and a 46-year-old father. The pregnancy was complicated by IUGR. The birth weight was 2.12 kg (1st percentile), length was 50 cm (50th percentile), and head circumference was 35 cm (50th percentile). The neonatal period was complicated by feeding problems, hypotonia, and glandular hypospadias. The family history was noncontributory.

The medical history is significant for undescended testicles and hypospadias, hypotonia, poor feeding requiring a percutaneous endoscopic gastrostomy, and global developmental delay. A brain MRI at 14 months of age revealed ventricular enlargement and increased cerebral spinal fluid (CSF) space, indicative of cerebral atrophy. Nerve conduction studies and creatinine kinase



FIGURE 1 | (A) Patient 1 at (from left to right) 1 month old, 14 months old, 4 years old, and 6.5 years old. (B) Patient 3 at (from left to right) 12 months old, 9 years old, 14 years old, and 19 years old. (C) Patient 4 at 12 years old.

levels were normal. At 8 months old, his height was 66 cm (< 1st percentile), weight was 5.7 kg (< 3rd percentile), and head circumference was 42 cm (2nd percentile). He has dysmorphic features, as presented in Table 1.

Patient 2 showed very early signs of global developmental delay. He started smiling at 4 months of age. He was making good eye contact, and he was fixing and following at 10 months of age. He rolled over at about 12 months of age. He achieved independent

sitting and crawling at 18 months. He started standing in a frame at 6 years of age. His first words emerged at 6 years, and by 8 years, he occasionally used two-word sentences. Despite these milestone achievements, he was mostly nonverbal. At 8 years, he was incontinent and required a wheelchair for mobility, although he could ambulate with support using a walking frame.

Chromosomal microarray analysis identified a *de novo* 3.9 Mb deletion at 14q32.2q32.31 (98,890,898-102,783,552; hg19).

TABLE 1 | Physical exam findings of patients in this study compared to those with *BCL11B*, *CCNK*, and *YY1* single nucleotide variants (SNVs) or deletions. (+) present, (–) absent, (ND) not disclosed, (NA) not applicable.

	Patient 1	Patient 2	Patient 3	Patient 4	Total			
					14q32.2 deletions	BCL11B SNVs (n = 28)	CCNK SNVs and deletions (n = 6)	YY1 SNVs (n = 31)
Age at observation	6.5 years	8 years	21 years	14 years				
Sex	Male	Male	Male	Female				
Deletion coordinates (hg19)	14q32.2 (98,029,521–101,154,362)	14q32.2q32.31 (98,890,898–102,783,552)	14q32.2 (98,534,687–101,064,183)	14q32.2 (98,849,926–100,695,237)			14q32.2 (98,058,263–100,498,578)	
Height	7th percentile	10th percentile	< 1st percentile	13th percentile				
Weight	< 1st percentile	< 3rd percentile	32nd percentile	26th percentile				
Head circumference	6th percentile	2nd percentile	47th percentile	ND				
High prominent forehead	+	+	–	+	3/4	2/28	0/6	0/31 (25/31 broad)
Temporal thinning of hair	+	–	–	+	2/4	0/28	0/6	0/31
Low-set ears	+	+	+	+	4/4	5/28	4/6	At least 2/31; ear abnormality 25/31
Short/small palpebral fissures	+	+	+	+	4/4	7/28	ND	1/31
Upward-slanted palpebral fissures	+	–	+	+	3/4	5/28	ND	5/31
Epicanthal folds	–	+	+	+	3/4	4/28	0/6	0/31
Sparse eyebrows	+ (laterally)	+	–	+	3/4	1/28	0/6	1/31
Wide nasal bridge	+	+	+	+	4/4	0/28	1/6	0/31
Small nasal passages	+	+	+	–	3/4	0/28	0/6	0/31

(Continues)

TABLE 1 | (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Total		CCNK SNVs and deletions (<i>n</i> = 6)	YY1 SNVs (<i>n</i> = 31)
					14q32.2 deletions	BCL11B SNVs (<i>n</i> = 28)		
Prominent smooth philtrum	+	+	–	+	3/4	0/28	0/6	6/31
Microstomia	+	+	+	+	4/4	4/28	0/6	1/31
Thin upper and/or lower vermillion border	+	–	–	+	2/4	7/28	5/6	6/31
High arched palate	+	+	–	–	2/4	3/28	0/6	2/31
Micrognathia	+	+	+	+	4/4	1/28	0/6	6/31
Micropenis	+	–	+	NA	2/3	0/28	0/6	0/31
Pes planus	+	+	–	–	2/4	0/28	1/6	0/31
Toe camptodactyly	+	–	–	+	2/4	0/28	0/6	0/31
Overlapping toes	+	–	+	–	2/4	0/28	0/6	0/31
Long fingers and toes	– (long feet)	+	–	+	2/4	0/28	0/6	0/31
Spasticity	+	+	– (motoric restlessness)	+	3/4	0/28	4/6	2/31
Other	High anterior hairline	Thick eyelashes	Left single transverse palmar crease	Bifid uvula		Hypertelorism (15/29)	Hypertelorism (6/6)	Facial asymmetry
	Hypotelorism	Anteverted nares	Valgus deformity of ankles	Hypoplastic lower teeth		Long philtrum (15/29)	Thin eyebrows (5/6)	Broad nasal tip
	Hypoplastic nipples	Depressed nasal bridge	Occipital flattening	Oligodontia		Thin eyebrows (7/29)	Narrow jaw (5/6)	Depressed nasal bridge (5/6)
		Abnormal hair whorls	Hemangioma of neck and right heel	Wide-set breasts		Pointed chin (6/29)	Thick lower lip	Pointed chin

Note: Cases included in the literature review: BCL11B – Che et al. (2022), Gaillard et al. (2021), Goos et al. (2019), Lessel et al. (2018), Lu et al. (2021), Prasad et al. (2020), Punwani et al. (2016), Qiao et al. (2019), Yan et al. (2020), Yang et al. (2020), Zhao et al. (2022); CCNK – Dai et al. (2023), Fan et al. (2018); YY1 – Balakrishnan and Ranganath (2021), Carminho-Rodrigues et al. (2020), Cherik et al. (2022), Santos et al. (2022), Gabriele et al. (2017), Khamirani et al. (2022), Koruga et al. (2023), Morales-Rosado et al. (2018), Tan et al. (2021), Yang et al. (2024), Zorzi et al. (2021).

Additional evaluations, including chromosome analysis, FISH for 22q11.2 deletion/duplication syndrome, methylation studies for Prader-Willi/Angelman syndromes, white cell enzyme analysis, and very long chain fatty acids, were all normal.

Patient 3, a male, was born at 36 weeks, 4 days gestation via spontaneous vaginal delivery to a 31-year-old primigravid mother and 32-year-old father. The pregnancy was complicated by preterm premature rupture of membranes. The birth weight was 2.330 kg (< 3rd percentile). The neonatal period was complicated by small for gestational age, feeding problems, hypoglycemia, and hypotonia. The family history contributes to an intrauterine fetal demise at 5 months gestation in the maternal grandmother and intellectual disability and blindness in a paternal first cousin once removed.

The medical history is significant for congenital visual impairment (light perception only) with strabismus and horizontal nystagmus of unknown cause (non-corrected visual acuity of 3% using Teller Acuity cards), craniosynostosis of all sutures and metopic ridging, bilateral cryptorchidism, hyperthyroidism, failure to thrive, dysphagia requiring gastrostomy tube placement, constipation, pyelectasia, nephroliths, axial hypotonia, motoric restlessness, global developmental delay, and recurrent upper respiratory tract infections which resolved with adenoidectomy at 3 years of age. Type 1 diabetes was diagnosed at 3 years of age and controlled with an insulin pump. Surgical correction of scoliosis (left-sided convex large angle of about 85°) was completed at 13 years of age. At 17 years of age, three seizures were noted; an electroencephalogram (EEG) at 17 years of age and brain MRI at 3 years of age were normal. At 21 years old, his height was 150 cm (10th percentile), weight was 65 kg (32nd percentile), and head circumference was 55 cm (2nd percentile). He has dysmorphic features as presented in Table 1 and seen in Figure 1B.

The patient can smile and partially roll over but cannot track. He did not achieve other motor or speech milestones. At 21 years old, he was at the developmental level of a 3–6-month-old and was nonambulatory, nonverbal, and incontinent. He is reactive to his surroundings and alert, but unable to communicate.

Chromosomal microarray revealed a *de novo* 2.5 Mb deletion of 14q32.2 (98,534,687–101,064,183); hg19. Additional evaluations included chromosome analysis, FISH for 22q11.2 deletion/duplication syndrome, DNA testing for Pelizaeus-Merzbacher disease, and trio whole exome sequencing, all of which were normal. Chromosome analysis and microarray for both parents were normal.

Patient 4, a female, was born at 38 weeks gestation via spontaneous vaginal delivery, to a 26-year-old gravida 6 para 4014 > 5 Caucasian mother and 44-year-old Caucasian father. The pregnancy was complicated by polyhydramnios. The birth weight was 2.58 kg (10th percentile), and length was 48 cm (25th percentile). The neonatal period was complicated by feeding problems. The family history was noncontributory.

The medical history is significant for submucosal cleft palate, uterine didelphys with longitudinal vaginal septum,

strabismus, feeding difficulties requiring a gastrostomy tube, severe constipation, scoliosis (upper thoracic apex right scoliosis of 3°, apex left thoracolumbar scoliosis of 7°, lower lumbar apex right scoliosis of 20°) poor growth, hypotonia, spastic diplegic cerebral palsy GMFCS level 2, global developmental delay, and intellectual disability. Recurrent infections persist at 14 years of age. Hypothyroidism (Hashimoto's thyroiditis) was diagnosed at eight months of age and evolved to hyperthyroidism (Graves') at 12 years of age, which was treated by thyroidectomy at 14 years of age. Behavioral concerns include aggression, autism spectrum disorder, and severe insomnia. An EEG at six years of age revealed generalized background slowing. A brain MRI at 12 years of age was normal. At 11 years of age, evaluation for severe and chronic constipation returned a normal endoscopy, colonoscopy, and colon mucosa biopsy. At 14 years old, her height was 142.2 cm (23rd percentile), weight was 44.5 kg (29th percentile), and head circumference was unavailable (50.8 cm at 7 years; 31st percentile). She has dysmorphic features as presented in Table 1 and seen in Figure 1C.

The patient sat independently at 16 months of age and walked independently at three years of age; she has a persistent crouched gait with femoral anteversion and uses a transport stroller for longer distances. She had her first words at seven years of age and spoke occasional two-word sentences at 10 years of age; she will vocalize briefly when prompted but is mostly nonverbal at 14 years of age. She is continent for urine only, which was achieved around 11 years of age. She is enrolled in a mainstream school and is in a special education classroom.

An oligomicroarray revealed a *de novo* 1.8 Mb deletion of 14q32.2 (98,849,926–100,695,237); hg19. Methylation analysis via EpiSign revealed an abnormal DNA methylation in a pattern consistent with the *YY1* gene-associated epigenetic signature, consistent with Gabriele-de Vries syndrome (Cherik et al. 2022). Trio whole exome sequencing revealed two variants of uncertain significance (*CHD3* c.5950T>A p.(Y1984N), and *KAT6B* c.418A>G, p.(T140A)); both were inherited from her asymptomatic mother. Of note, the methylation profiles for *KAT6B* were specifically reviewed via EpiSign and were normal. Additional evaluations included chromosome analysis, FISH for 22q11.2 deletion/duplication syndrome and Williams syndrome (7q11.23), and methylation for Prader-Willi/Angelman syndromes, all of which were normal. The chromosomal microarray for both parents was negative.

4 | Discussion

Proximal deletions of 14q32.2 are rarely reported and often do not provide detailed clinical information. We present four cases with proximal 14q32.2 deletions, including the *BCL11B* and *CCNK* genes, and either the entire *YY1* gene (patients 1, 2, and 3) or the promoter/enhancer region of *YY1* (patient 4) (Figure 2). Though these deletions overlap significantly, there is considerable variability in the breakpoints among all patients described. It, therefore, stands to reason that recurrent low-copy repeats were absent from any of the breakpoints in these patients, per evaluation of segmental duplications identified in the UCSC genome browser.

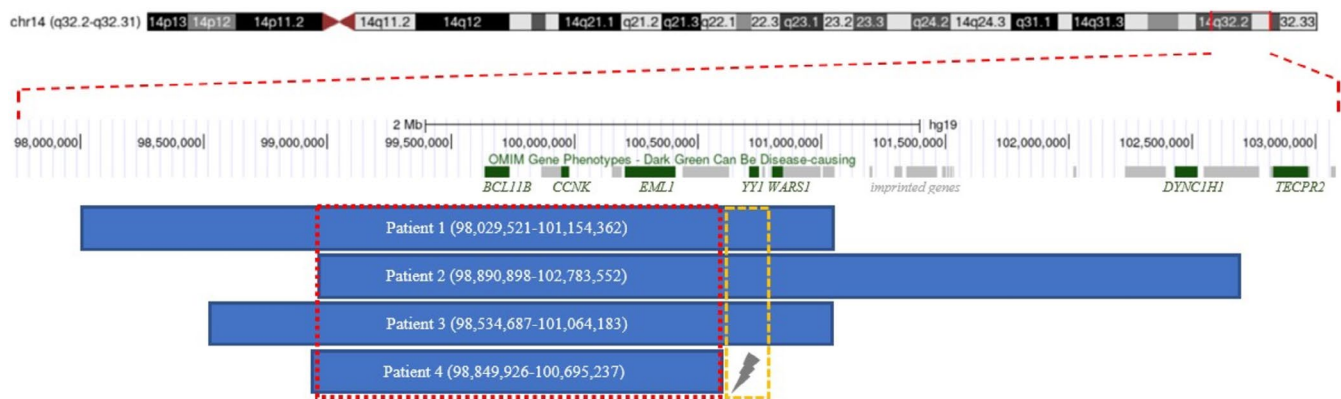


FIGURE 2 | Schematic of the 14q32.2 chromosomal region, adapted from UCSC genome browser. Blue boxes indicate each patient's deletion, with overlapping deleted region highlighted with red dashed lines. The yellow dashed lines indicate further region of functional overlap for the four patients, when accounting for the abnormal methylation analysis of *YY1* for patient 4 (depicted with gray lightning bolt).

The *BCL11B* gene (OMIM #606558; position 99,635,624–99,738,534) encodes a transcription factor involved in T-cell development, neuronal development, and other organ systems (Kominami 2012). Germline variants are reported in association with neurologic disorders with/without immunologic deficits and craniosynostosis less frequently, while somatic variants are associated with T-cell acute lymphoblastic leukemia. Efforts to delineate a genotype–phenotype correlation for germline variants have been initiated, but deletions were not included in this cohort (García-Aznar et al. 2024). Only three patients with full gene deletions of *BCL11B* are reported, described in an investigation of patients with *CCNK*-related phenotypes (Fan et al. 2018).

The *CCNK* gene (position 99,947,746–99,978,777) encodes a cyclin-dependent kinase involved in the cell cycle and transcription regulation. Germline variants are seldom reported in association with cognitive impairment and autism (Dai et al. 2023). Full gene deletions encompassing *CCNK* and *BCL11B* are associated with more severe impairment than SNVs, though the sample size is small in these studies.

Finally, the *YY1* gene (position 100,705,481–10,749,125) encodes a transcription factor that regulates gene expression. Germline variants are associated with Gabriele-de Vries syndrome (OMIM #600013), characterized by cognitive impairment, growth restriction, and congenital abnormalities.

The *EML1* gene (OMIM #602033), which encodes a microtubule-binding protein involved in planar cell polarity, and the *WARS1* gene (OMIM #191050), which encodes the tryptophanyl-tRNA synthetase involved in translation, are also included in these patients' deletions. Both genes are associated with autosomal recessive neurologic conditions (subcortical band heterotopia with *EML1* [OMIM #600348], and a neurodevelopmental disorder with *WARS1* [OMIM #620317]), and therefore a deletion of one copy of the gene should not cause this molecular phenotype.

While the *WARS1* gene is also associated with a dominant form of distal hereditary motor neuronopathy (OMIM #617721), available literature suggests that pathogenic variants associated with the dominant phenotype result in a dominant-negative effect, rather than a loss of function as would be the case with a

full gene deletion. Further, it would be expected that any phenotypic presentation of this disorder would be impossible to distinguish from the severe neuromuscular features resulting from deletions of the other genes in the three males whose deletions involve this gene.

The four patients presented in this study possess both characteristics of others with exon-level loss-of-function SNVs in the *BCL11B*, *CCNK*, and/or *YY1* genes, as well as their own set of unique phenotypes (Table 2, Figure 3). While all previously published cohorts had developmental delays, patients with 14q32.2 deletions had more severe delays—motor and speech milestones were met less often and, when achieved, it usually occurred at a significantly later age than those with *BCL11B* or *YY1* SNVs (Table 2). Importantly, despite two of our patients achieving first words, they are still described as nonverbal at 8 and 14 years old.

Some features occurred more frequently in our cohort, such as spasticity, genitourinary abnormalities, constipation, and thyroid abnormalities (Table 2). Feeding problems, growth restriction, and vision problems occurred at a similar frequency to those with *YY1* SNVs. Other features, such as behavioral concerns, were observed more frequently in those with SNVs and deletions of *BCL11B* and *CCNK*; while this may partly be related to the inability to clinically assess behaviors in our cohort with severe delays, note that all three patients with severe ID and *BCL11B* and *CCNK* deletions had autism spectrum disorder.

Regarding the clinical features expressed in these four patients, it is interesting to note that genitourinary abnormalities, growth restriction, and thyroid abnormalities were not observed in any patients with *BCL11B* or *CCNK* involvement. These features were seen in some patients with *YY1* SNVs, albeit at a lower frequency than the currently reported patients. It is likely that these phenotypes are at least partly related to the involvement of the *YY1* gene in these deletions, though additional research is needed. The dysmorphic features seen in our cohort overlap those with loss-of-function variants in *BCL11B*, *CCNK*, and *YY1*, including low-set ears, short and upward-slanted palpebral fissures, a smooth philtrum, thin lips, and micrognathia. Some features were seen more frequently or exclusively in our cohort, including sparse eyebrows, a wide nasal bridge, and small nasal

TABLE 2 | Phenotypes of patients from this study with proximal 14q32.2 deletions, patients with germline *BCL11B* single nucleotide variants (SNVs), *CCNK* SNVs, *BCL11B* and *CCNK* deletions, and *YY1* SNVs. When calculating the average age of first words and independent ambulation, individuals without a specific time for first words (i.e., provided age for sentences or unspecified delays) were excluded from the analysis.

	This report (<i>n</i> = 4)	<i>BCL11B</i> SNVs (<i>n</i> = 28)	<i>BCL11B</i> and <i>CCNK</i> deletions (<i>n</i> = 3)	<i>CCNK</i> SNVs (<i>n</i> = 3)	<i>YY1</i> SNVs (<i>n</i> = 31)
Developmental delay	4/4	25/28	3/3	3/3	31/31
Achieved independent ambulation (average age)	1/4 (36 m)	14/19 (22.6 m)	ND; moderate–extremely severe delays	ND; mild–moderate delays	25/27 (33.8 m)
No independent ambulation (average age)	3/4 (152 m)	5/19 (59.2 m)	ND; moderate–extremely severe delays	ND; mild–moderate delays	2/27 (23.5 m)
Achieved first words (average age)	2/4 (78 m)	7/14 (34.9 m)	ND; extremely severe delays	ND; mild–moderate delays	14/17 (21.2 m)
No words (average age)	2/4 (180 m)	7/14 (54 m)	1/3 (48 m)	ND	3/17 (79 m)
Intellectual disability	4/4	12/12; borderline-moderate	3/3; severe	3/3; mild–moderate	23/29; mild–severe
Behavioral problems	1/4	6/28	3/3	0/3	19/31
Feeding problems	4/4	6/28	0/3	0/3	22/31
Growth restriction	3/4	0/28	0/3 (overgrowth in 2/3)	0/3 (overgrowth in 1/3)	6/31
Constipation	3/4	1/28	0/3	0/3	4/31
Hypotonia	4/4	8/28	0/3	0/3	11/31
Spasticity	3/4	2/28	0/3	0/3	2/31
Abnormal gait	1/4	1/28	0/3	0/3	5/31
Seizure(s)	1/4	5/18	0/3	0/3	4/31
Frequent infections	3/4	8/28	0/3	0/3	5/31
Vision problems	3/4	9/28	0/3	0/3	19/31
Genitourinary abnormalities	4/4	ND	0/3	0/3	7/31
Thyroid abnormalities	2/4	0/28	0/3	0/3	4/31
Craniosynostosis	1/4	5/28	0/3	0/3	0/31
Scoliosis	3/4	0/28	0/3	0/3	6/31
Dental abnormalities	1/4	9/28	0/3	0/3	3/31

Note: Cases included in the literature review: *BCL11B* SNVs – Che et al. (2022), Gaillard et al. (2021), Goos et al. (2019), Lessel et al. (2018), Lu et al. (2021), Prasad et al. (2020), Punwani et al. (2016), Qiao et al. (2019), Yan et al. (2020), Yang et al. (2020), Zhao et al. (2022); *BCL11B* and *CCNK* deletions – Dai et al. (2023); *CCNK*-Dai et al. (2023), Fan et al. (2018); *YY1* – Balakrishnan and Ranganath (2021), Carminho-Rodrigues et al. (2020), Cherik et al. (2022), Santos et al. (2022), Gabriele et al. (2017), Khamirani et al. (2022), Koruga et al. (2023), Morales-Rosado et al. (2018), Tan et al. (2021), Yang et al. (2024), Zorzi et al. (2021). Abbreviation: ND, Not disclosed.

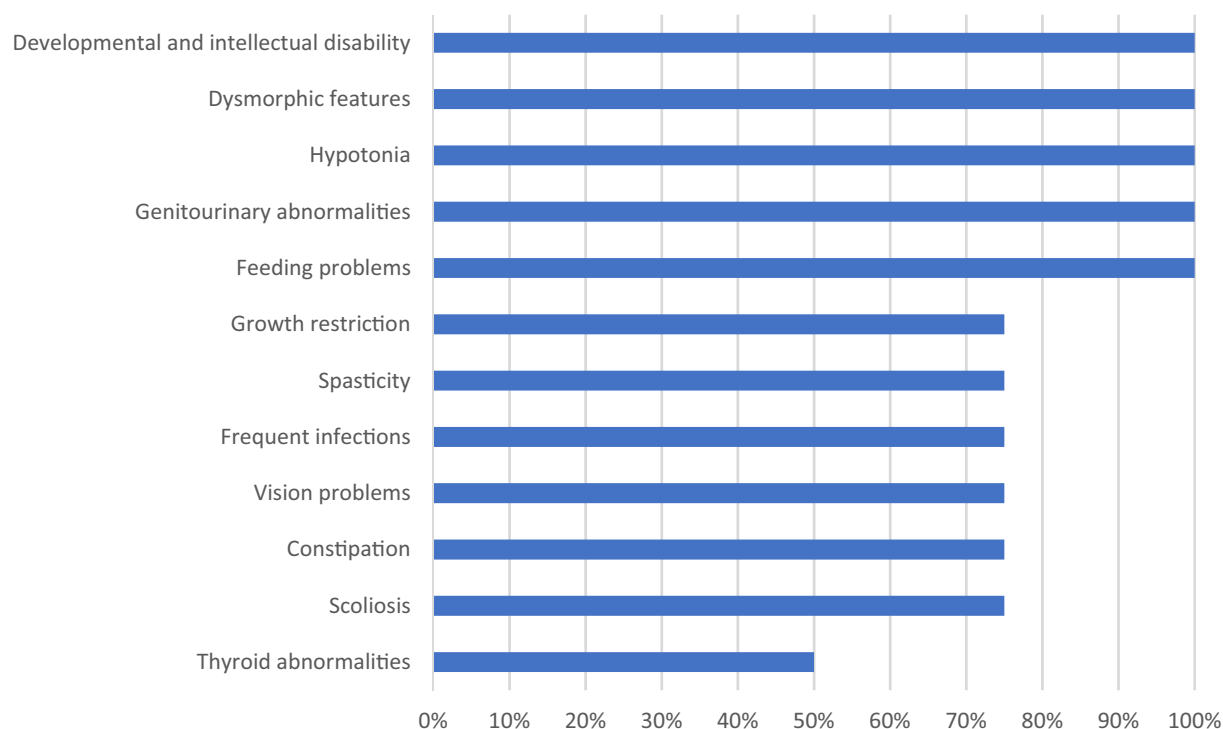


FIGURE 3 | Frequency of shared features in the four people with 14q32.2 deletion in this study. Only features seen in two or more individuals were included in this figure.

passages. Other features that were common to those with SNVs were not seen in our cohort, including a pointed chin or narrow jaw. Characteristic finger and toe abnormalities and micropenis were seen only in those with 14q32.2 deletions (Table 1).

Several patients with deletions encompassing at least the *YY1* gene were reported by Gabriele and colleagues, including four patients (RUMC1, 249,213, SA1, SA2) with deletions including at least *BCL11B*, *CCNK*, and *YY1*. Reported features were similar to those seen in the currently reported cases but again occurred at lower frequencies and included IUGR (2/4), intellectual disability (2/4), dysmorphic features (2/4), feeding problems (2/4), craniosynostosis (2/4), hypotonia (2/4), genitourinary abnormalities (2/4), congenital heart defects (2/4), and other features. Importantly, the deletions for two of these cases, RUMC1 and 249,213, are significantly larger than those seen in the currently reported patients (13.3 Mb and 9.2 Mb, respectively) and also include the UPD(14) cluster; therefore, it is difficult to determine if these features are truly related to the deletion of the current genes in question or if they might be related to a UPD(14) phenotype.

In the DECIPHER database, there are only three entries of deletions that involve at least *BCL11B*, *CCNK*, and *YY1*. Two of these entries are presented for the first time in this manuscript (patient 2 [case 250,486] and patient 3 [case 254,518]). The third (266323) presents with similar features, including cognitive impairment, IUGR, feeding problems, hypotonia, micropenis, and dysmorphic features (Gabriele et al. 2017). Three other cases (296,462, 296,477, 260,834) involve only *BCL11B* and *CCNK* but involve a promoter and/or enhancer region for *YY1*, which would result in abnormal *YY1* function in a similar mechanism to that seen in patient 4 in our group. Phenotypic information is limited and

includes cognitive impairment (in 3 patients) and microcephaly (in 2 patients).

Deletion size and gene content did not correlate with disease severity in our cohort. Patient 2 had the largest deletion and the fewest medical comorbidities, while patient 4 had the smallest deletion and exhibited numerous medical problems diagnosed from an early age. Patient 2 was also the only male in this cohort to achieve motor milestones beyond rolling over, and he also had language skills comparable to patient 4. Gabriele and colleagues demonstrated a similar phenomenon, whereby the case with the largest deletion (identifier RUMC1;13.3 Mb) and the case with the smallest multi-gene deletion that resulted in a viable birth (identifier 263,711; 1.1 Mb) both presented with IUGR, hypotonia, feeding problems, recurrent infections, and dysmorphic features (Gabriele et al. 2017). The latter patient additionally manifested congenital anomalies of the heart and kidney. It is important to note, however, that this patient also has a 36 kb deletion of chromosome 8, which is classified as likely benign in DECIPHER. Therefore, deletion size of 14q32.2 likely is not an indicator of disease severity.

In conclusion, we present four patients with deletions of the proximal region 14q32.2 involving *BCL11B*, *CCNK*, and *YY1*. The clinical features of these deletions include severe global developmental delay, hypotonia, spasticity, feeding difficulty, genitourinary abnormalities, skeletal abnormalities, and characteristic facial features. We propose that 14q32.2 proximal deletions should be considered in the differential diagnosis for patients undergoing workup for Prader-Willi syndrome in the neonatal period, and cerebral palsy and other neurodevelopmental disorders later in life. We propose that 14q32.2 proximal deletions should be considered in the differential diagnosis for

patients undergoing workup for Prader-Willi syndrome in the neonatal period, and cerebral palsy and other neurodevelopmental disorders later in life. Further, we propose that the presence of these deletions results in an entity that is clinically distinct from known single-gene disorders in the region.

Author Contributions

Contributors J.B., R.R.L., M.K., and H.G. collected and provided clinical information. C.R. and S.C.S. contributed to the molecular analysis of the deletions. J.B. wrote the initial draft, with SS writing the methods section. All authors revised and edited the final draft and approved it for publication.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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