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## RESEARCH ARTICLE

# Speech and language in *DDX3X*-neurodevelopmental disorder: A call for early augmentative and alternative communication intervention

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## Abstract

Pathogenic variants in *DDX3X* are associated with neurodevelopmental disorders. Communication impairments are commonly reported, yet specific speech and language diagnoses have not been delineated, preventing prognostic counseling and targeted therapies. Here, we characterized speech and language in 38 female individuals, aged 1.69–24.34 years, with pathogenic and likely pathogenic *DDX3X* variants (missense,  $n = 13$ ; nonsense,  $n = 12$ ; frameshift,  $n = 7$ ; splice site,  $n = 3$ ; synonymous,  $n = 2$ ; deletion,  $n = 1$ ). Standardized speech, language, motor, social, and adaptive behavior assessments were administered. All participants had gross motor deficits in infancy (34/34), and fine motor deficits were common throughout childhood (94%; 32/34). Intellectual disability was reported in 86% (24/28) of participants over 4 years of age. Expressive, receptive, and social communication skills were, on average, severely impaired. However, receptive language was significantly stronger than expressive language ability. Over half of the assessed participants were minimally verbal (66%; 22/33; range = 2 years 2 months–24 years 4 months;

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mean = 8 years;  $SD = 6$  years) and augmented speech with sign language, gestures, or digital devices. A quarter of the cohort had childhood apraxia of speech (25%; 9/36). Despite speech and language impairments, social motivation was a relevant strength. Many participants used augmentative and alternative communication (AAC), underscoring the need for early, tailored, and comprehensive AAC intervention.

#### KEYWORDS

*DDX3X*, developmental delay, intellectual disability, language, neurodevelopment, speech

## 1 | INTRODUCTION

Pathogenic variants in *DDX3X* are consistently reported to cause developmental delay and/or intellectual disability (DD/ID), referred to as *DDX3X*-neurodevelopmental disorder (*DDX3X*-NDD, also known as *DDX3X* syndrome). As an X-linked disorder, *DDX3X*-NDD has emerged as one of the most common genetic causes of ID/DD in females, accounting for 1%–3% of cases and typically resulting from de novo variants (McRae et al., 2017; Snijders Blok et al., 2015). The *DDX3X*-NDD phenotype has been associated with autism spectrum disorder (henceforth, autism), attention-deficit/hyperactivity disorder (ADHD), self-injurious behavior, epilepsy and structural brain abnormalities (Beal et al., 2019; Lennox et al., 2020; Ruzzo et al., 2019; Snijders Blok et al., 2015; Takata et al., 2018; Tang et al., 2021; Wang et al., 2018; Yuen et al., 2017). Movement disorders, congenital heart defects, vision and hearing impairments are also reported (Lennox et al., 2020; Snijders Blok et al., 2015; Wang et al., 2018).

Persistent speech (i.e., the ability to produce sounds) and/or language (i.e., the ability to understand and use words and sentences/grammar, as distinct from speech production) deficits are frequently reported features of *DDX3X*-NDD (Hildebrand et al., 2020; Kaspi et al., 2023; Kellaris et al., 2018; Lennox et al., 2020; Scala et al., 2019; Wang et al., 2018). Fifty-two percent of females over 5 years of age with *DDX3X*-NDD are reported to be minimally verbal; defined here as having <40 spoken words and not combining words (Brady et al., 2021; Lennox et al., 2020). Yet despite this high prevalence of limited verbal output, there has been no deep systematic examination of nonverbal, alternative, or augmentative communication abilities in minimally verbal individuals with *DDX3X*-NDD to guide therapy recommendations (Levy et al., 2023). In terms of predicting speech and language outcomes associated with this condition, recent genotype–phenotype correlational data indicates that missense variants or in-frame deletions are associated with poorer speech and language outcomes than protein-truncating variants (Tang et al., 2021).

Despite the common and pervasive communication deficits reported in *DDX3X*-NDD, a prospective systematic evaluation of speech and language phenotypes has not been undertaken. Understanding communication in *DDX3X*-NDD expands genotype–phenotype knowledge more broadly and lays the foundation for tailored speech and language interventions (e.g., St John et al., 2023). While speech and language research reveals insights into neurological systems affected by genetic disruptions, a literature gap exists in

understanding these variations from social and behavioral genetics perspectives (Eising et al., 2019; Hildebrand et al., 2020; Kaspi et al., 2023; Peter, 2023). Further phenotypic knowledge of *DDX3X*-NDD could also help elucidate the underlying biological mechanisms of the disorder, for instance, *DDX3X*'s role in gene splicing regulation is critical for speech development (Kaspi et al., 2023). Here, we comprehensively phenotype communication in individuals with pathogenic or likely pathogenic *DDX3X* variants. We examined speech production, receptive, expressive, written, and social language ability. Communication profiles were also considered relative to other neurodevelopmental and health characteristics.

## 2 | MATERIALS AND METHODS

### 2.1 | Participants

Caregivers of participants were recruited by advertising to international *DDX3X*-associated support groups, clinical geneticists, and genetic organizations. GenIDA—Genetic forms of Intellectual Disability and Autism (<https://genida.unistra.fr/>), Association Française *DDX3X*, Rare Chromosome Disorder Support Group (Unique) and Association *Xtraordinaire* contributed to study recruitment. Inclusion criteria were a pathogenic or likely pathogenic variant in *DDX3X* confirmed by a genetics report from the participant's clinical genetics team and age  $\geq 6$  months. There was no upper limit on the age of participants. Caregivers provided informed consent. Participant information statements were available in the language spoken by the participant. Ethical approval was obtained by the Human Research Ethics Committees at the Royal Children's Hospital, Melbourne (HREC 37353). All caregivers completed measures online, while English-speaking caregivers were additionally invited to attend a telehealth appointment, detailed below.

### 2.2 | Health and development

Caregivers completed a detailed (>20 pages) health questionnaire on behalf of the participant (Beal et al., 2019; Kellaris et al., 2018) ( $n = 30$ ) or a similar GenIDA health survey for six families (see Table S1). The questionnaires surveyed participants' birth, medical, and developmental history (Table 1). Health professional reports (e.g., neurologist, speech pathologist, occupational therapist,

**TABLE 1** Genetic variants in 38 individuals with *DDX3X*-related neurodevelopmental disorder.

ID	Age of participant (years; months)	Age range participant is in (years)	Country	Coding DNA <sup>a</sup>	Protein	Inheritance <sup>b</sup>	Variant and pathogenicity
1	4; 11	3–5	US	c.1206_1208delCTT	p.Phe402del	De novo	Deletion <i>P</i>
2	5; 11	3–5	AU	c.1437_1438delTA	p.Asp479Glufs*38	De novo	Frameshift <i>P</i>
3	5; 4	3–5	BE	c.749_750insGCCTC	p.Leu251Profs*3	De novo	Frameshift <i>P</i>
4	7; 2	6–8	AU	c.623dupA	p.His209Alafs*86	De novo	Frameshift <i>P</i>
5	2; 10	0–2	FR	c.1535_1536delAT	p.His512Argfs*5	Unknown	Frameshift <i>P</i>
6	18; 2	18–20	FR	c.67_71dupTC TTC	p.Asp25Leufs*21	Unknown	Frameshift <i>P</i>
7	8; 2	6–8	NL	c.1535_1536delAT	p.His512Argfs*5	De novo	Frameshift <i>P</i>
8	1; 8	0–2	US	c.1535_1536delAT	p.His512Argfs*5	De novo	Frameshift <i>P</i>
9	14; 7	12–14	FR	c.704T>A	p.Leu235Gln	Unknown	Missense <i>LP</i>
10	3; 3	3–5	AU	c.1051C>T	p.Arg351Trp	De novo	Missense <i>LP</i>
11	2; 6	0–2	CA	c.976C>T	p.Arg326Cys	De novo	Missense <i>P</i>
12	15; 11	15–17	FR	c.1084C>A	p.Arg362Ser	De novo	Missense <i>LP</i>
13	5; 11	3–5	FR	c.1126C>T	p.Arg376Cys	Unknown	Missense <i>P</i>
14	7; 4	6–8	US	c.544T>G	p.Phe182Val	De novo	Missense <i>LP</i>
15	9; 10	9–11	ES	c.572T>A	p.Ile191Asn	De novo	Missense <i>P</i>
16	5; 8	3–5	ES	c.1208T>G	p.Leu403Trp	De novo	Missense <i>LP</i>
17	22; 6	21–23	FR	c.1463G>A	p.Arg488His	De novo	Missense <i>P</i>
18	8; 5	6–8	FR	c.1541T>C	p.Ile514Thr	De novo	Missense <i>P</i>
19	7; 10	6–8	UK	c.1382T>C	p.Leu461Ser	De novo	Missense <i>LP</i>
20	8; 8	6–8	ES	c.1279A>C	p.Lys427Gln	De novo	Missense <i>P</i>
21	11; 8	9–11	FR	c.1438A>G	p.Arg480Gly	De novo	Missense <i>P</i>
22	4; 8	3–5	FR	c.1331delC	p.Leu445*	De novo	Nonsense <i>P</i>
23	6; 5	6–8	FR	c.869C>G	p.Ser290*	De novo	Nonsense <i>P</i>
24	3; 4	3–5	FR	c.874C>T	p.Arg292*	De novo	Nonsense <i>P</i>
25	5; 5	3–5	FR	c.1728T>G	p.Tyr576*	Unknown	Nonsense <i>P</i>
26	24; 4	24–26	NL	c.731C>G	p.Ser244*	Unknown	Nonsense <i>P</i>
27	2; 2	0–2	CA	c.841C>T	p.Gln281*	De novo	Nonsense <i>P</i>
28	16; 4	15–17	UK	c.247_250dupAGCT	p.Phe84*	De novo	Nonsense <i>P</i>
29	5; 7	3–5	CA	c.1286C>A	p.Ser429*	De novo	Nonsense <i>P</i>
30	13; 9	12–14	DE	c.798C>G	p.Tyr266*	De novo	Nonsense <i>P</i>
31	8; 4	6–8	DE	c.1807C>T	p.Arg603*	De novo	Nonsense <i>P</i>
32	6; 0	6–8	FR	c.136C>T	p.Arg46*	De novo	Nonsense <i>P</i>
33	4; 8	3–5	UK	c.1398C>A	p.Tyr466*	Unknown	Nonsense <i>P</i>
34	11; 7	9–11	AU	c.151+1G>A	p.(?)	De novo	Splice site <i>P</i>
35	12; 5	12–14	FR	c.151+1G>T	p.(?)	De novo	Splice site <i>LP</i>
36	13; 1	12–14	FR	c.766-1G>A	p.(?)	De novo	Splice site <i>LP</i>
37	11; 4	9–11	DE	c.744C>T	p.Gly248=	De novo	Synonymous, affects splicing <i>LP</i>
38	3; 6	3–5	DK			De novo	Synonymous, affects splicing <i>LP</i>

Abbreviations: AU, Australia; BE, Belgium; CA, Canada; DE, Germany; ES, Spain; FR, France; LP, likely pathogenic as per the American College of Medical Genetics classification guidelines (Richards et al., 2015); NL, Netherlands; P, pathogenic; UK, United Kingdom; US, United States.

<sup>a</sup>Reference sequence: NM\_001356.

<sup>b</sup>Heterozygous.

psychologist) were uploaded by families to a secure portal to corroborate survey responses. Caregivers also completed feeding (Child Oral and Motor Proficiency Scale [ChOMPS]; Pados et al., 2018) and drooling (Drooling Impact Scale [DIS]; Reid et al., 2010) measures.

### 2.3 | Speech

English-speaking individuals and caregivers attended a telehealth consult with a qualified speech pathologist. Where children had sufficient speech, a minimum 5-min speech sample was taken alongside the Diagnostic Evaluation of Articulation and Phonology (DEAP) (Dodd et al., 2002). Oral motor structure and function were assessed using a systematic protocol to inform differential diagnosis of speech diagnoses (e.g., presence of impaired coordination and control of tone indicating possible dysarthria; orofacial structural deficits such as a submucous cleft palate, which may impact speech production, etc.) (Robbins & Klee, 1987). Data from the speech sample, DEAP and oral motor assessment were perceptually analyzed using rating profiles for childhood apraxia of speech (CAS) (Fedorenko et al., 2016; Mei et al., 2018) and the Mayo Clinic system for rating dysarthria (Duffy, 2020), as previously utilized in our published studies (Braden et al., 2021; Morgan et al., 2021; Morison, Meffert, et al., 2023; Morison, van Reyk, et al., 2023). During the assessment, participants were provided with breaks and extra time where required. Caregivers also completed the Intelligibility in Context Scale (McLeod et al., 2015) to determine the degree to which a participant's speech could be understood by different communication partners on a 5-point scale (1 = *never* to 5 = *always*).

### 2.4 | Language

The Vineland Adaptive Behavior Scales-Parent/Caregiver (VABS) assessed expressive, receptive and written language skills, described further below. English- and Spanish-speaking participants were assessed with the VABS-III, while French-speaking participants were administered the VABS-II (Pados et al., 2018) as there is no French third edition. Verbal individuals (>4 years old) were also assessed using the Children's Communication Checklist (CCC-2) (Bishop, 2003). Minimally verbal individuals were identified as having <40 spoken words (yet they may understand more) (Brady et al., 2021). This could be confirmed using a telehealth assessment by a qualified speech pathologist and/or the Communication Matrix (Rowland & Fried-Oken, 2010), which stratifies communication into seven levels: (1) pre-intentional behavior, (2) intentional behavior, (3) unconventional communication, (4) conventional communication, (5) concrete symbols, (6) abstract symbols (single spoken words, symbols or signs), and (7) language (combining two or more spoken words, symbols, or signs).

### 2.5 | Adaptive behavior

Socialization, daily living, and motor skills domains were also assessed using the VABS. For participants over 9 years of age, the motor skills

norms for 9-year olds were used, as no participants reached the ceiling of these norms. An overall general adaptive behavior composite (ABC) score was also obtained.

### 2.6 | Social communication

The Social Responsiveness Scale, second edition (SRS-2) (Constantino & Gruber, 2012) preschool (caregiver-rated), school age (caregiver-rated), and carer forms measured social behaviors associated with autism as defined by The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013). An overall composite score was generated for social ability as well as individual subscale scores across domains of social awareness, social cognition, social communication, social motivation, restricted interests, and repetitive behavior.

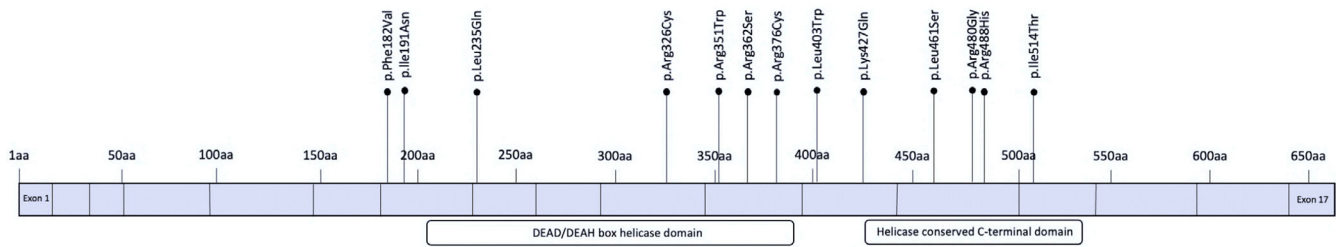
### 2.7 | Statistical analyses

Wilcoxon signed-rank tests compared individual differences between receptive and expressive language scores on the VABS-II/III to examine relative strengths in either domain. Age, VABS-II/III, CCC-2, SRS-2, and ICS data were reported using descriptive statistics. The limited sample size prohibited correlational genotype-phenotype analyses, and associations between genotype and phenotype were only descriptively explored.

## 3 | RESULTS

### 3.1 | Participants

The final sample for analysis comprised 38 females (mean = 8.71 years,  $SD = 5.51$  years, range = 1.69–24.34 years) from Australia ( $n = 4$ ), Belgium ( $n = 1$ ), Canada ( $n = 3$ ), Denmark ( $n = 1$ ), France ( $n = 15$ ), Germany ( $n = 3$ ), Netherlands ( $n = 2$ ), Spain ( $n = 3$ ), United Kingdom ( $n = 3$ ), and the United States of America ( $n = 3$ ). The primary language of participants was French ( $n = 17$ ), English ( $n = 12$ ), Spanish ( $n = 3$ ), and Dutch ( $n = 1$ ). Variants were missense ( $n = 13$ ), nonsense ( $n = 12$ ), frameshift ( $n = 7$ ), splice site ( $n = 3$ ), synonymous ( $n = 2$ ), and one deletion (Table 1; Figure 1). Of the 13 participants with missense variants, 10 variants were within one of the two functional domains: the DEAD/DEAH helicase and Helicase conserved C-terminal domain (Figure 1). The remaining three missense variants were just outside these functional domains (Figure 1). Three participants had the same frameshift variant (c.1535\_1536delAT, p.His512Argfs\*5), and two had the same synonymous variant (c.744C>T, p.Gly248=). Variants in 31 participants were confirmed *de novo* and 7 were of unknown inheritance. All cases were heterozygous. The average age of genetic diagnosis was 5 years, 6 months. Genotypic and phenotypic data were submitted to Decipher (<https://decipher.sanger.ac.uk/>). Two males with hemizygous likely pathogenic *DDX3X* variants also participated (Table S2). However, their data are



**FIGURE 1** Lollipop chart showing the locations of 13 missense variants in 13 individuals with *DDX3X*-related neurodevelopmental disorder.

not included in the main analyses given the phenotypic differences caused by *DDX3X*-NDD being hemizygous in males and heterozygous in females (Snijders Blok et al., 2015).

## 3.2 | Health and development

### 3.2.1 | Medical conditions

The most common presentations (Table 2) were early feeding difficulties (75%; 24/32), followed by vision impairment (64%; 23/36). Early feeding difficulties included difficulty sucking and latching, fatigue during feeding and reflux. Despite early feeding challenges for some, 42% (10/24) of infants were breastfed, 33% (8/24) were bottle fed, and 17% (4/24) had a combination of both. Participant 26, who had a cleft palate, used a palate plate and specialized bottle to support feeding until undergoing surgery. Another participant had a percutaneous endoscopic gastrostomy tube (Participant 1). Feeding difficulties persisted over the age of 8 years in 20% (3/15) of participants. In children under 7 years, who completed the ChOMPS, all (4/4) had impaired oral motor proficiency, impacting their feeding skills (<5th percentile). Fifty-nine percent (59%; 16/27) experienced gastrointestinal symptoms, including constipation (33%; 12/36) and reflux and regurgitation (11%; 4/36). One-fifth (17%; 6/35) had a history of drooling, while almost half (43%; 15/35) were still experiencing drooling (age range 1; 8 to 24; 4 years). In those who were still drooling, the frequency and severity of drooling were quantified as 6.23/10 ( $SD = 2.05$ ) and 5.46/10 ( $SD = 1.98$ ), respectively ( $n = 13$ ) on a subjective rating of drooling severity (DIS) where 0 is no impact and 10 is a high impact. Meanwhile, 53% (19/36) had a history of ear infections, which were treated with tympanostomy tubes in situ in 47% of cases (9/19). Only 12% (4/33) had current hearing impairment, including conductive loss (1/4), mixed hearing loss (2/4), and an unspecified impairment (1/4). One participant had reported hyperacusis.

Vision impairments were common (64%; 23/36) and included hypermetropia (43%; 10/23), strabismus (30%; 7/23), myopia (17%; 4/23), astigmatism (4%; 1/23), cerebral vision impairment (CVI; 4%; 1/23) and bull's eye maculopathy (4%; 1/23). Over a third of the group (35%; 8/23) had a combination of two or more of these impairments.

With regards to neurological function, 31% (11/36) of participants had microcephaly, while 7% (2/30) had macrocephaly. One-third

(30%; 9/30) had undergone brain magnetic resonance imaging (MRI). Common MRI findings were polymicrogyria (PMG; 25%; 2/8) and hypoplasia (38%; 3/8), see Table 2. Eleven percent (4/38) of participants had an epilepsy diagnosis. Sleep difficulties (e.g., difficulty falling asleep, frequent nocturnal awakenings, early awakenings, acute sleep deprivation) were reported in 64% (16/25).

Fourteen percent (5/36) of participants reported a cardiac condition, comprising one case of each of congenital heart valve abnormality, combined atrial septal defect (ASD) and ventricular septal defect, unspecified heart malformation, an unspecified "tilted heart" condition, and ASD.

Hypoglycemia and Reynaud's disease each occurred in one participant. Birth and pregnancy complications, allergies, musculoskeletal disorders, appetite, and surgery data are reported in Table S3.

### 3.2.2 | Neurodevelopment

Developmental milestones and therapeutic supports are reported in Table 3. Most participants were delayed in achieving their gross motor skills, that is, learning to sit after 11 months old (62%; 23/37), crawl after 14 months old (65%; 22/34), and walking after 16 months old (64%; 23/36) (World Health Organization, 2006). On the VABS, participants' average gross (mean = 6.85,  $SD = 4.08$ ) and fine (mean = 5.76,  $SD = 4.64$ ) motor scores were in the low range.

Movement disorders were common (77%; 10/13), reported as chorea (10%; 1/10), ataxia (10%; 1/10), abnormal movement/tics (30%; 3/10), and stiff joints (10%; 1/10). These conditions were not reported to co-occur. Hypotonia was reported in 92% (22/24) of participants. Motor skills were supported by occupational therapy (48%; 15/31) and physiotherapy (38%; 12/32).

Neurodevelopmental conditions were common (84%; 32/38). In descending order of frequency were ID (86%; 24/28 over the age of 4 years), autism (25%; 9/36), and ADHD (14%; 5/36). Forty-seven percent (18/38) had more than one neurodevelopmental condition (excluding the previously described speech and language conditions). ID was assessed according to clinician assessment and/or caregiver report and ranged from mild to severe. Twenty-four percent (6/25) of these participants were assessed using standardized intelligence quotient testing. One participant did not have an ID (Participant 12; Full-Scale Intelligence Quotient of 86), while 24% (9/38) were not assessed or were too young to be assessed. Most participants



**TABLE 2** Medical features in individuals with *DDX3X*-related neurodevelopmental disorder.

ID	Childhood feeding impairment (6 months–7 years)	Drizzling	Ear infections <sup>a</sup>	GI	Vision impairment	Sleep disturbance	Epilepsy	MRI findings
1	+	+	+	+	+	+	–	Prominent ventricular size, bilateral frontal lobes PMG, flattening of posterior globes, bilateral mesial temporal sclerosis, delayed myelination, deficiency of posterior corpus callosum, cerebellar vermis, hypoplasia.
2	+	Hx	+ <sup>a</sup>	+	–	+	–	–
3	+	+	–	–	+	–	+	–
4	+	Hx	+ <sup>a</sup>	+	+	+	–	–
5	–	–	+	–	–	+	–	–
6	–	–	–	–	–	NA	–	Hypoplasia of the cerebellum
7	–	–	+	–	–	–	–	–
8	+	+	–	–	+	–	–	–
9	–	–	–	–	+	NA	–	Brainstem hypoplasia, partial posterior lobe agenesis
10	+	+	+ <sup>a</sup>	+	+	+	–	Cerebellum abnormality indicating small cystic hemorrhage
11	+	–	–	–	+	+	–	NA
12	+	–	–	+	+	NA	–	–
13	NA	NA	NA	NA	NA	NA	–	NA
14	+	+	+ <sup>a</sup>	+	+	–	–	–
15	NA	+	+	+	+	+	–	–
16	+	+	–	+	–	+	+	PMG, pachygyria on both temporal lobes and perisylvian areas, inverted hippocampus, small hypophysis
17	+	Hx	–	+	–	NA	–	–
18	+	–	–	+	+	NA	–	–
19	–	+	+	–	+	+	–	–
20	+	+	–	–	+	+	–	Bilateral ventriculomegaly
21	+	+	+	–	+	NA	+	–
22	–	–	–	–	+	NA	–	Left frontal cortical and subcortical white matter focal signal abnormality
23	+	+	–	+	+	NA	–	–
24	+	+	–	–	–	NA	–	–
25	–	–	–	–	+	NA	–	Vascular abnormality
26	+	+	+ <sup>a</sup>	+	–	–	–	–
27	NA	+	+ <sup>a</sup>	–	–	–	–	–
28	NA	+	+ <sup>a</sup>	–	–	–	–	NA
29	NA	NA	+	+	+	+	–	–
30	+	Hx	+	–	+	+	–	NA
31	+	+	–	+	–	+	–	–
32	NA	NA	NA	NA	NA	NA	–	NA
33	+	–	+ <sup>a</sup>	–	+	+	–	NA
34	+	Hx	+	–	+	–	+	–
35	+	Hx	+	+	–	NA	–	NA
36	+	–	–	–	+	+	–	–
37	–	–	–	–	–	–	–	NA
38	+	+	+ <sup>a</sup>	–	+	+	–	–

Abbreviations: GI, gastrointestinal issues; Hx, history; MRI, magnetic resonance imaging; NA, not assessed; PMG, polymicrogyria; +, present; –, absent.

<sup>a</sup>Addressed with tympanostomy tubes in situ.

**TABLE 3** Developmental milestones and clinical supports for individuals with *DDX3X*-related neurodevelopmental disorder.

ID	Age sitting (months)	Age crawling (months)	Age walking (months)	Age independent toileting (years)	Support with personal care	Education	SP	OT	PT
1	NA	NA	NYA	NA	+	NA	NA	+	+
2	8–10	7–10	13–15	4–5	+	Mainstream PS	+	+	–
3	≥13	≥14	NYA	NYA	+	Specialized childcare	+	–	–
4	≥13	11–13	≥16	NYA	+	Specialized PS	+	+	+
5	4–7	11–13	≥16	TY	+	NA	+	NA	NA
6	11–12	≥14	≥16	2–3	NA	Specialized PS	+	–	–
7	4–7	11–13	13–15	1–2	–	Specialized PS	+	NA	NA
8	11–12	11–13	≥16	TY	+	Mainstream preschool	+	–	–
9	≥13	≥14	≥16	≥6	NA	Specialized HS	–	–	+
10	8–10	≥14	≥16	NYA	+	Mainstream childcare	+	+	+
11	NYA	NYA	NYA	NYA	+	Home schooling	+	+	+
12	8–10	≥14	≥16	≥6	NA	Mainstream HS	+	+	–
13	NA	NA	NA	NA	NA	NA	NA	NA	NA
14	8–10	>14	>16	NYA	+	Specialized PS	+	NA	NA
15	≥13	≥14	≥16	NA	+	NA	NA	–	–
16	≥13	NYA	≥16	NYA	+	Specialized preschool	–	+	+
17	11–12	≥14	≥16	≥6	NA	Specialized PS	+	–	–
18	≥13	≥14	≥16	≥6	NA	Specialized childcare	+	+	+
19	≥13	≥14	≥16	NYA	+	Specialized PS	+	+	+
20	>13	>14	>16	NYA	+	Specialized PS	+	NA	NA
21	11–12	≥14	≥16	NYA	NA	Specialized preschool	+	+	–
22	8–10	≥14	≥16	4–5	NA	Mainstream preschool	+	+	–
23	11–12	≥14	≥16	4–5	NA	Specialized PS	+	–	–
24	11–12	7–10	≥16	NYA	NA	Mainstream preschool	+	–	–
25	≥13	≥14	≥16	2–3	NA	Mainstream preschool	+	–	–
26	>13	>14	>16	NYA	+	Specialized PS	+	NA	–
27	8–10	NA	≥16	NA	+	NA	NA	+	+
28	4–7	11–13	13–15	NA	+	Specialized HS	NA	–	–
29	11–12	≥14	≥16	NA	+	Specialized childcare	NA	–	–
30	8–10	11–13	≥16	≥6	+	Specialized HS	+	–	–
31	11–12	>14	>16	4–5	+	Specialized PS	+	NA	NA
32	NA	NA	NA	NA	NA	NA	NA	–	–
33	8–10	≥14	≥16	NYA	+	Mainstream childcare	+	+	+
34	≥13	≥14	≥16	4–5	+	Specialized PS	+	+	+
35	11–12	11–13	≥16	4–5	NA	Specialized PS	+	–	–
36	≥13	11–13	≥16	NYA	+	Specialized PS	+	–	–
37	>13	>14	>16	NA	–	Specialized PS	+	–	–
38	≥13	≥14	≥16	NYA	+	Mainstream childcare	+	–	+

Abbreviations: HS, high/secondary school; NA, not assessed; NYA, not yet achieved; OT, attended occupational therapy; PS, primary/elementary school; PT, attended physiotherapy; SP, attended speech pathologist; TY, not applicable, too young; +, present; –, absent.



(92%; 23/25) required support with personal care (e.g., washing, dressing, and toileting) and 11% (3/26) had learned independent toileting skills by 4 years of age, while the remaining 2 participants did not require support (Table 3).

Behavioral problems were reported in 33% (12/36) of the cohort (Table 4). Notably, anxiety had a prevalence rate of 18% (5/28).

### 3.2.3 | Educational

Most participants attended specialized schools (69%; 22/32), while 28% (9/32) attended mainstream schools, and one child was home-schooled (Table 3).

## 3.3 | Speech

Speech developmental trajectories were markedly prolonged for most of the group; when compared to typical speech milestones of first words at ~12 months and first sentences at 2–3 years (Table 4). Only three participants said their first words by 12 months of age. An additional six participants said their first words between 12 and 15 months, and 16 participants said their first words when they were older than 15 months of age. Eleven participants, aged between 2 and 24 years, had not yet said their first words. Development of spoken sentences was also delayed, with only 4 of the 15 individuals with spoken language began combining words before 3 years of age. Speech milestone data was not available for the two participants.

At the time of testing, 94% (29/31) of participants had attended speech pathology services. Speech intelligibility was impaired (ICS). On average, participants were “usually” to “always” understood by their caregivers (mean = 3.83;  $SD = 0.87$ ) but were “barely” understood by strangers (mean = 1.93;  $SD = 0.94$ ). Only 20% (6/30) of participants were “always” understood by their caregivers (aged between 3 and 15 years old; ICS).

Sixty-six percent (22/33) of participants over the age of 2 years were minimally verbal. A qualified speech pathologist assessed the six verbal, English-speaking participants over telehealth (Participants 2, 7, 14, 28, 30, 34). Of these six verbal, English-speaking participants, 83% (5/6) had CAS, and one had dysarthria (Participant 14). CAS always co-occurred with one or more other speech disorders: articulation disorder (Participants 7, 28, 30 with an interdental lisp and 14 with an /r/ distortion) and/or phonological disorder (Participants 2, 14, 30) and/or phonological delay (Participant 2). To verify local clinical reports, caregivers provided home videos of participants who were non-English speaking and/or minimally verbal. Where these participants' caregivers spoke English and were agreeable to a telehealth appointment, a qualified speech pathologist held a video telehealth appointment with families where parents spoke English. This included one verbal child who spoke both Dutch and German (not English) (Participant 37). Furthermore, telehealth appointments were also held with two minimally verbal participants (Participants 10 and 27) and their families. A further two verbal participants (Participants 9 and 36) were reported to have a speech pathologist

diagnosis of CAS by their caregivers but were not assessed directly via telehealth as their families spoke a language other than English.

## 3.4 | Language

Thirty-four participants completed the VABS (two participants did not complete the measure; and VABS was not accessible for one German-speaking and one Dutch-speaking participant). Most participants (82.35%; 28/34) scored in the Low range in the communication domain, indicating severe communication impairment (mean = 44.85;  $SD = 21.45$ , normative mean = 100, normative  $SD = 15$ ; Figure 2). Likewise, scores on all communication subdomains indicated severe language impairment (low scores being 1–9; population mean = 10, normative  $SD = 3$ ) (Figure 2). Wilcoxon signed-rank tests revealed a significant difference between receptive (mean = 6.03,  $SD = 4.63$ ) and expressive (mean = 5.12,  $SD = 4.39$ ) language skills ( $p = 0.05$ ). Participants performed similarly on the written communication subdomain also, scoring within the low range (1–9) (mean = 5.65,  $SD = 3.78$ ). Participant 5 was the only individual to score within the adequate range (>85) for their overall communication skills. Descriptive exploration of genotype and phenotypes revealed no clear association between variant type and language or cognitive skills.

Seven participants completed the CCC-2 (normative mean = 10,  $SD = 3$ ) (Figure 3a) as the remainder of the cohort were too young (3%; 1/29), non-English speaking (52%; 15/29), were minimally verbal (38%; 11/29), or did not complete the assessment (7%; 2/29). Speech was the most impaired domain (mean = 0.14,  $SD = 0.38$ ,  $-3 SD$ ). All other domains, except stereotyped communication and interests, fell within three standard deviations below the normative mean. Stereotyped communication and interests were 2 standard deviations below the normative mean.

The Communication Matrix was completed for 21 minimally verbal participants, a tool to understand the communication status of anyone functioning at the early stages of communication or using forms of communication other than speaking or writing (Figure 4). Nineteen percent (4/21) obtained the highest communication level of language (Level 7, combining words/symbols). Percent of skills mastered across communication functions and levels of communication ranged from 7.5% to 83.75%. All participants could use intentional presymbolic communication (behavior that is intentional, but not intentionally communicative, e.g., smiling when happy), for refusing, obtaining (requesting, making choices) and social communication (e.g., greeting and farewelling) functions. Over half the cohort used abstract symbols (e.g., signs, single words) to communicate refusal, obtaining, social, and information (e.g., asking and answering questions) functions. For those using abstract symbols; making choices and requesting new objects was challenging. No participant was able to use language to offer and share. Of the four participants at Level 7 (combining signs, symbols, or spoken words), most had challenges with social and information communication functions.

Augmentative and alternative communication (AAC) forms (e.g., sign language, gesture, speech-generating devices, picture

**TABLE 4** Speech and language phenotype, and neurodevelopmental conditions in individuals with DDX3X-related neurodevelopmental disorder.

ID	Milestones		Language skills <sup>a</sup>				Speech			Neurodevelopment—other		
	Age first words (months)	Age first sentences (years)	Verbal or minimally verbal	Receptive	Expressive	Written	CAS	Dysarthria	Autism	Cog impair	Other	
1	≥18	NYA	MV <sup>b</sup>	Low	Low	Low	NA	NA	— <sup>c</sup>	Mod <sup>c</sup>	BP	
2	≥18	NYA	V <sup>d</sup>	Mod Low	Low	Low	+	—	— <sup>c</sup>	Mild	—	
3	NYA	NYA	MV <sup>b</sup>	Low	Low	Low	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Sev <sup>c</sup>	BP	
4	<12	NYA	MV <sup>b</sup>	Low	Low	Low	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Mod <sup>c</sup>	SPD	
5	12–15	NYA	NA	Adequate	Mod Low	Adequate	— <sup>c</sup>	— <sup>c</sup>	+	NA	—	
6	12–15	≥8	V <sup>e</sup>	Low	Low	Low	— <sup>c</sup>	— <sup>c</sup>	+	Mod	DCD	
7	12–15	6–7	V <sup>d</sup>	Mod Low	Low	Low	+	—	— <sup>c</sup>	Mild	—	
8	15–18	NYA	NA	Low	Mod Low	NA	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	NA	—	
9	≥18	≥8	V <sup>e</sup>	Low	Low	Low	+	— <sup>c</sup>	— <sup>c</sup>	Sev <sup>c</sup>	DCD, BP	
10	NYA	NYA	MV <sup>d</sup>	Low	Low	Low	MV	MV	— <sup>c</sup>	NA	—	
11	NYA	NYA	MV <sup>b</sup>	Low	Low	NA	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Sev <sup>c</sup>	—	
12	≥18	2–3	MV <sup>b</sup>	Mod Low	Mod Low	Mod Low	— <sup>c</sup>	— <sup>c</sup>	+	—	ADHD	
13	NA	NA	NA	Low	Mod Low	Low	NA	NA	NA	NA	NA	
14	12–15	6–7	V <sup>d</sup>	Low	Low	Low	+	+	— <sup>c</sup>	Mod <sup>c</sup>	—	
15	≥18	NYA	MV <sup>b</sup>	Low	Low	Low	NA	NA	+	Mod <sup>c</sup>	BP	
16	≥18	NYA	MV <sup>b</sup>	Low	Low	Low	NA	NA	— <sup>c</sup>	NA	—	
17	NYA	NYA	MV <sup>b</sup>	Low	Low	Low	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Mod	—	
18	NYA	NYA	MV <sup>b</sup>	Low	Low	Low	—	— <sup>c</sup>	— <sup>c</sup>	Mod <sup>c</sup>	ADHD, DCD	
19	NYA	NYA	MV <sup>b</sup>	Low	Low	Low	— <sup>c</sup>	— <sup>c</sup>	+	Sev <sup>c</sup>	SPD	
20	NYA	NYA	NA	NA	NA	NA	+	— <sup>c</sup>	+	Mod <sup>c</sup>	SPD, BP	
21	NYA	NYA	MV <sup>b</sup>	Low	Low	Low	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Sev <sup>c</sup>	BP	
22	12–15	2–3	MV <sup>b</sup>	Low	Adequate	Mod Low	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Mod <sup>c</sup>	—	
23	≥18	4–5	V <sup>e</sup>	Low	Low	Low	— <sup>c</sup>	— <sup>c</sup>	+	Mod <sup>c</sup>	ADHD	
24	NYA	NYA	MV <sup>b</sup>	Adequate	Low	Adequate	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Mod <sup>c</sup>	—	
25	≥18	NYA	MV <sup>b</sup>	Low	Low	Low	+	— <sup>c</sup>	— <sup>c</sup>	NA	DCD	
26	NYA	NYA	MV <sup>b</sup>	NA	NA	NA	—	+	— <sup>c</sup>	Sev <sup>c</sup>	ADHD, DCD, SPD, BP	
27	<12	NYA	MV <sup>b,d</sup>	Mod Low	Low	NA	MV	MV	— <sup>c</sup>	Mild <sup>c</sup>	BP	
28	≥18	6–7	V <sup>d</sup>	Low	Low	Low	+	—	+	NA	—	
29	15–18	2–3	MV <sup>b</sup>	Low	Mod Low	Low	NA	NA	— <sup>c</sup>	NA	BP	
30	15–18	≥8	V <sup>d</sup>	Low	Low	Low	+	—	— <sup>c</sup>	Sev <sup>c</sup>	DCD, BP	
31	≥18	4–5	NA	NA	NA	NA	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Mod	ADHD, Cerebral Palsy, DCD, SPD, BP	
32	NA	NA	MV <sup>b</sup>	NA	NA	NA	NA	NA	NA	NA	NA	

(Continues)

TABLE 4 (Continued)

ID	Milestones		Language skills <sup>a</sup>				Speech			Neurodevelopment—other		
	Age first words (months)	Age first sentences (years)	Verbal or minimally verbal	Receptive	Expressive	Written	CAS	Dysarthria	Autism	Cog impair	Other	
33	NYA	NYA	MV <sup>b</sup>	Low	Low	Low	MV	MV	+ <sup>c</sup>	Sev <sup>c</sup>	SPD	
34	12–15	4–5	V <sup>d</sup>	Mod Low	Mod Low	Low	—	—	— <sup>c</sup>	Mod <sup>c</sup>	—	
35	≥18	4–5	MV <sup>b</sup>	Low	Low	Low	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Mod <sup>c</sup>	—	
36	≥18	≥8	V <sup>e</sup>	Low	Low	Low	+ <sup>c</sup>	+ <sup>c</sup>	— <sup>c</sup>	Sev <sup>c</sup>	BP	
37	15–18	4–5	V <sup>d</sup>	Mod Low	Mod Low	Low	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Mod	—	
38	<12	NYA	MV <sup>b</sup>	Low	Low	Low	— <sup>c</sup>	— <sup>c</sup>	— <sup>c</sup>	Sev <sup>c</sup>	—	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP, behavioral problems (e.g., anxiety, aggression/self-injury); CAS, childhood apraxia of speech; Cog impair, intellectual disability; DCD, developmental coordination disorder; Mod, moderate; MV, minimally verbal (<40 spoken words, identified using telehealth assessment and/or using the caregiver-completed Communication Matrix (Brignell et al., 2018)); NA, not assessed; NYA, not yet achieved; Sev, severe; SPD, sensory processing disorder; V, verbal (>40 spoken words (Brignell et al., 2018)); +, present; —, absent.

<sup>a</sup>Language skills range as scored by the Vineland Adaptive Behavior Scales Second/Third Edition [low (1–9; 2nd percentile and below), moderately low (10–12; 3rd–16th percentile), adequate (13–17; 18th–82nd percentile), moderately high (18–20; 84th–97th percentile), high (21–24; 98th percentile and above)]. Cog impair, level of cognitive impairment: no cognitive impairment (IQ ≥ 85), mild, mild intellectual disability (55–70 IQ); Mod, moderate (40–55); Sev, severe (25–40).

<sup>b</sup>Determined by caregiver Communication Matrix responses.

<sup>c</sup>Caregiver report.

<sup>d</sup>Assessed via telehealth.

<sup>e</sup>Corroborated by achievement of speaking in sentences.

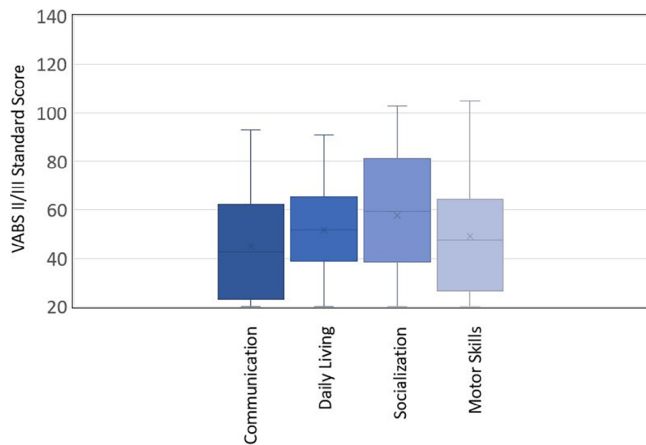
exchange systems) were used by participants who were minimally verbal or had severely impaired speech intelligibility (Figures 5 and S1). For those who provided data on frequency use and type of AAC use ( $n = 30$ ), this differed from birth to 2 years, 3–5 years ( $n = 26$ ), 6–10 years ( $n = 17$ ), 10–15 years ( $n = 12$ ) to adolescence and adulthood (>16 years,  $n = 6$ ). Several participants used signs or gestures (unaided AAC) in their first 2 years of life (73%; 21/30). Sign and gesture remained an important communication tool throughout early childhood (73%; 19/26), early (64%, 11/17), and later (50%; 6/12) school years, through to late adolescence and beyond (50%; 3/6). Some participants used single signs and gestures, whilst others combined signs to create sentences. Aided AAC (i.e., literal aids to support communication) was infrequently used in the first 2 years of life (10%; 3/26). Aided AAC systems ranged from dedicated AAC applications on a tablet to Picture Exchange Communication Systems (Bondy & Frost, 1998) and Pragmatic Organization and Dynamic Display books (Porter & Cafiero, 2009). However, use of aided AAC markedly increased when children entered school (6–10 years, 41%; 7/17). Like sign and gesture, aided AAC remained important for many participants into late adolescence (50%; 3/6). Concurrent use of sign/gesture and aided AAC was common. When participants were 3–5 years old, 100% (6/6) of individuals who used aided AAC also used signs/gestures. Across ages, aided AAC was frequently used in conjunction with sign and/or speech. Only one participant used solely aided AAC to communicate at >16 years old.

### 3.5 | Adaptive behavior

On the VABS, participants usually fell within the low range in all domains (Figure 2, normative mean = 100,  $SD = 15$ ). Standard scores on the ABC were within the low range (mean = 47.21,  $SD = 18.95$ ). Daily living skills ranged from low to moderately low (mean = 51.56,  $SD = 20.59$ ), as did socialization skills (mean = 57.67,  $SD = 24.91$ ).

### 3.6 | Social communication

Nine caregivers completed the SRS-2 (Figure 3b). SRS-2 data was not obtained from 41% (15/37) of participants due to the assessment being unavailable in the appropriate language, while 8% (3/37) of participants were too young to be assessed (<2 years), 27% (10/37) did not complete the tool and one declined, citing they felt the survey was not relevant for their child who is minimally verbal and whose behaviors are difficult for them to interpret.  $T$  scores demonstrated severe difficulties across social communication domains, indicating a high likelihood of autism in all participants (8/8) assessed. Interestingly, only two of the participants (Participant 19 and Participant 33) who had an SRS-2 completed also had a confirmed autism diagnosis, while the remaining 7 of 35 with a confirmed autism diagnosis did not complete the SRS-2. Taken together, 16 of 36 (44%) participants had a high likelihood of autism and/or a confirmed autism diagnosis. Restricted and repetitive behaviors were also substantially present



**FIGURE 2** The Vineland Adaptive Behavior Scales domain scores of participants ( $n = 34$ ). The Vineland Adaptive Behavior Scales Second and Third Edition (Normative Mean = 100,  $SD = 15$ ) scores  $<70$  are low/severe, 71–85 moderately low/moderate,  $>85$  average/within normal limits (minimum score = 20, maximum score = 140). Domain scores for participants were: communication (mean = 44.85;  $SD = 21.45$ ), daily living (mean = 51.56,  $SD = 20.59$ ), socialization (57.67,  $SD = 24.91$ ), motor skills (mean = 49.18,  $SD = 22.67$ ). Median = center line, mean =  $\times$ .

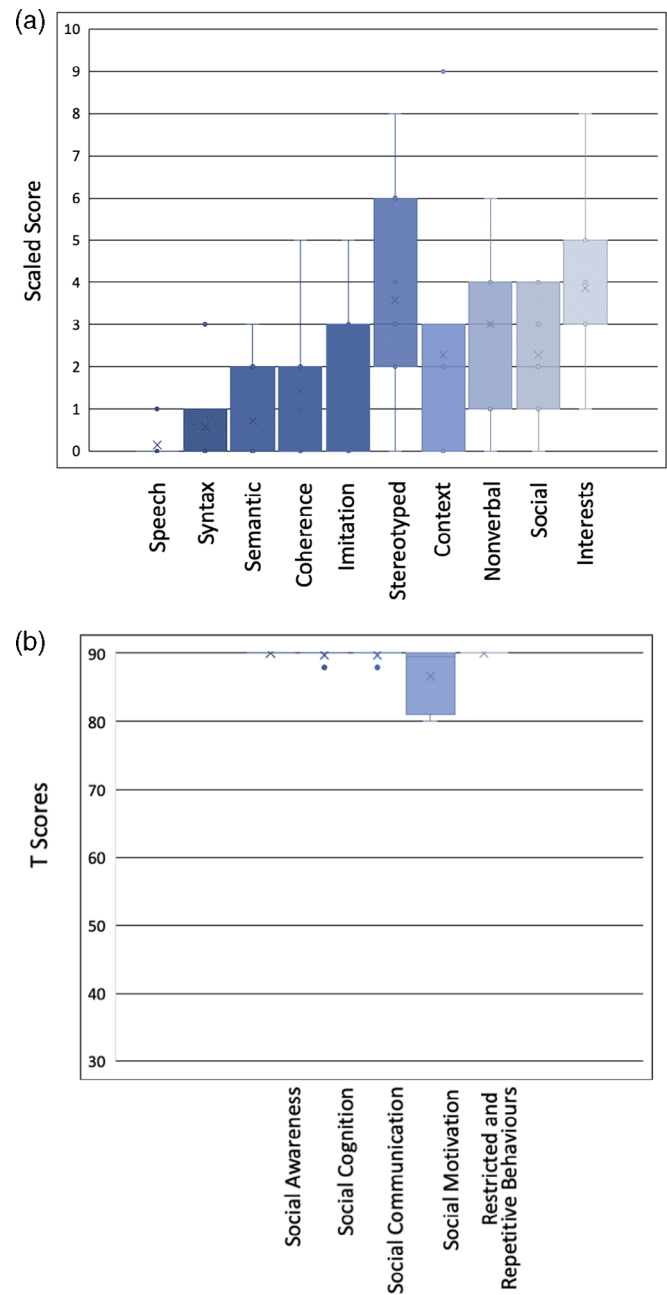
(Figure 3b; mean = 89.00,  $SD = 2.83$ ; normative mean = 60,  $SD = 10$ , range 34–90). Social motivation was a relative strength of the cohort (Figure 3b; mean = 84.75,  $SD = 5.87$ ; normative mean = 60,  $SD = 10$ , range 34–90).

## 4 | DISCUSSION

Here, we systematically characterized speech and language abilities in individuals with *DDX3X*-NDD. We have also expanded the neurodevelopmental phenotype, providing details of co-occurring neurodevelopmental conditions and reporting on educational settings and therapeutic supports.

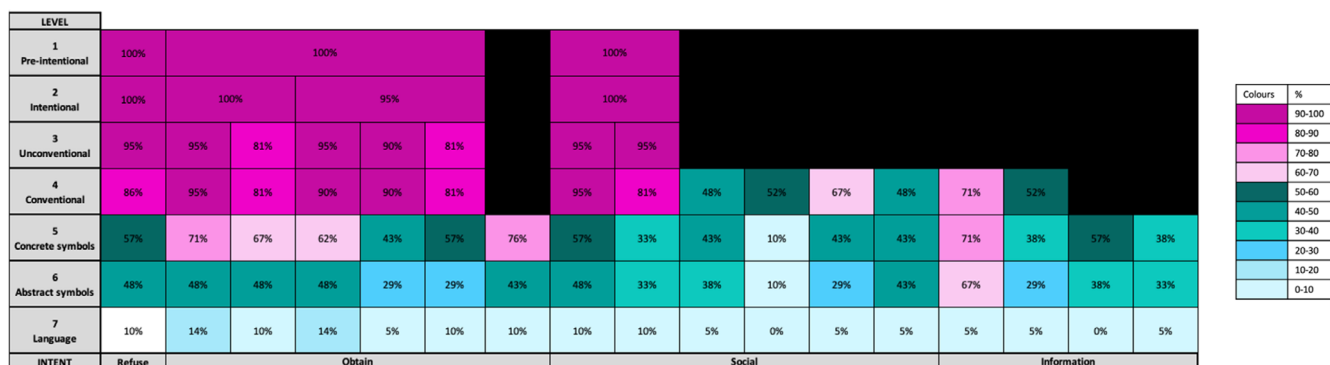
### 4.1 | Speech and language

Our systematic characterization of speech and language in *DDX3X*-NDD found that speech disorder was pervasive across the group. Sixty-six percent (22/33) of participants over the age of 2 years were minimally verbal. This is largely consistent with previous reports of 52% of females over 5 years being reported as minimally verbal (Lennox et al., 2020). Whilst recent genotype–phenotype correlational data in a cohort of 14 individuals suggested that missense variants or in-frame deletions are associated with poorer speech and language outcomes in *DDX3X*-NDD than protein-truncating variants (Tang et al., 2021), there was no clear clinical nor genotype–phenotype data evident to explain the range of cognitive, speech, and language profiles in this larger cohort. This group was characterized by a range of pathogenic/likely pathogenic variant types, at least one other

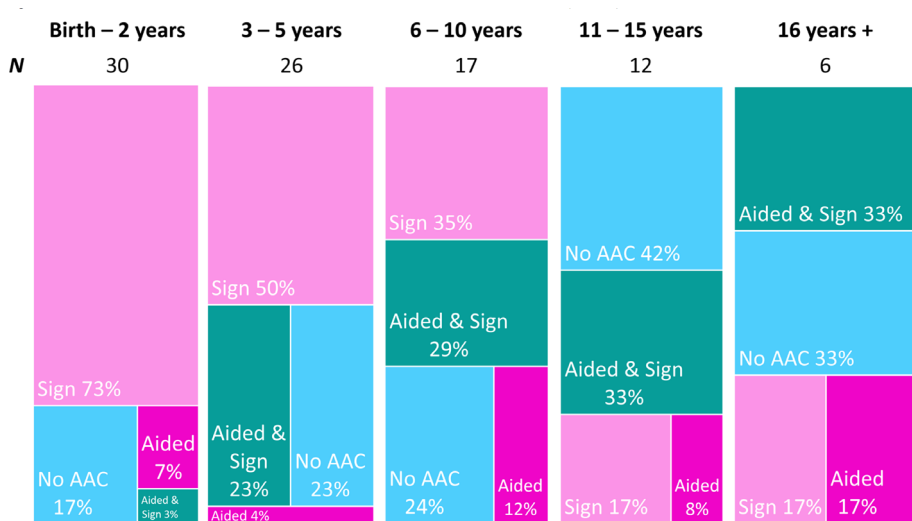


**FIGURE 3** (a) Communication skills in children who completed the Children's Communication Checklist–Second Edition (CCC-2,  $n = 7$ ). Normative mean = 10;  $SD = 3$ . Outlier =  $\bullet$ , median = center line, mean =  $\times$ . (b) Social behavior domains on the Social Responsiveness Scale–Second Edition (SRS-2,  $T$  scores;  $n = 8$ ). Higher  $T$  scores indicate higher levels of autistic traits (normative mean = 60,  $SD = 10$ , range 34–90).  $T \leq 59$ : social behavior within normal limits,  $T = 60$ –65: mild difficulty,  $T = 66$ –75: moderate difficulty,  $T \geq 76$  severe difficulty, where the maximum  $T$  score is  $\geq 90$ . Social awareness (mean = 89.50,  $SD = 0.93$ ), social cognition (mean = 89.25,  $SD = 1.49$ ), social communication (mean = 89.25,  $SD = 1.49$ ), social motivation (mean = 84.75,  $SD = 5.87$ ), restricted interests and repetitive behavior (mean = 89.00,  $SD = 2.83$ ). Outliers =  $\bullet$ , median = center line, mean =  $\times$ .

neurodevelopmental condition (e.g., autism, ADHD, developmental coordination disorder, and behavioral problems), a moderate to severe



**FIGURE 4** Communication Matrix results of minimally verbal participants with *DDX3X*-NDD ( $n = 21$ ). The Communication Matrix represents four reasons to communicate (refuse things, obtain things, engage in social interaction and to provide or seek information) across seven levels of communication ranging from pre-intentional (behavior not under an individual's control) to language (combining symbols). Percentage participants who have achieved skill is shown.



**FIGURE 5** Percent of communication modalities used from birth to adolescence ( $n = 30$ ). Sign includes natural gestures (e.g., shaking head, pointing), single signs such as Makaton or Key Word Sign (e.g., signing 'more') and sign language. Aided refers to aided augmentative and alternative communication (AAC) and includes high-tech/electronic AAC (e.g., speech generating devices) and low-tech/nonelectronic AAC (e.g., Picture Exchange Communication System).

level of ID, and even included the oldest participants in the sample, those aged 22 and 24 years. Verbal individuals also had impaired speech intelligibility and a high prevalence of the prototypic severe speech disorder; CAS. Similar to the minimally verbal group, verbal participants had a range of pathogenic variant types, one or more neurodevelopmental conditions, and a moderate to severe level of ID. Due to the prevalence of motor speech disorders in assessed, English-speaking individuals, it is likely that motor speech disorders were also present in individuals who spoke a language other than English and were not directly assessed for speech here. In other genetic conditions causative for CAS, speech disorder profiles have been found to be similar across different languages (Morison, Meffert, et al., 2023). Future research is required to investigate the speech profile of individuals with *DDX3X*-NDD across language backgrounds.

Further to speech disorders, language (i.e., the ability to understand and use words and sentences/grammar, as distinct from speech production) was also typically characterized by severe receptive, expressive, and written language impairments. With this said, receptive language was a statistically significant strength when compared

to expressive language ability. In other genetic conditions causative for severe speech disorder, receptive and expressive language skills are often commensurate. Examples from past studies include over two thirds of participants with *SETBP1* haploinsufficiency with equivalent impairments in receptive and expressive speech (Morgan et al., 2021). Similarly, *KAT6A* syndrome and *DYRK1A* syndrome showed no significant differences between expressive and receptive language abilities (Morison et al., 2022; St John et al., 2022). In contrast, a recent *CDK13*-related disorder cohort also reported a relative strength in receptive language skills (Morison, van Reyk, et al., 2023). Encouragingly, a strength in receptive language is considered to be one predictor of success with AAC use (Brady et al., 2013; Ganz et al., 2023). Stereotyped communication (i.e., words or phrases used repeatedly) was common. All participants could use intentional presymbolic communication, skills that occur between 3 and 8 months in typically developing infants (World Health Organization, 2006). Several participants displayed abstract communication skills typically seen in toddlers (12–24 months) (World Health Organization, 2006). Abstract communication skills were challenging for some communication functions, such as making choices



or requesting new objects. Few participants combined words/symbols to communicate, particularly to engage in social interaction or to provide or seek information.

Whilst AAC use differed between participants from early childhood to adolescence, it is evident that AAC is needed for many individuals with *DDX3X*-NDD. Sign was used frequently in the early years and remained an important mode of communication as participants grew older. By adolescence, however, sign was not used in isolation. Many participants used two or more AAC methods (e.g., sign language and communication aids, sign language and speech). Sign alone did not appear to meet the communication needs of adolescents who required AAC, and was only used to supplement aided AAC. Sign language and aided AAC were also important tools to augment unclear speech, caused by the high incidence of CAS in this population (Binger, 2007; Oommen & McCarthy, 2014). Consequently, AAC should be introduced early for individuals with *DDX3X*-NDD, and the use of sign and aided AAC should be dynamic to meet an individual's needs. The average age at genetic diagnosis in this cohort (5 years 6 months) was older than when individuals begin combining words in typical development (2–3 years old). Consequently, it is important to note that AAC should be implemented for individuals with such significantly delayed verbal speech, even in the absence of a genetic diagnosis. Most minimally verbal individuals could use abstract symbols (e.g., sign) to communicate, indicating an ability of individuals with *DDX3X*-NDD to use abstract symbols. However, only a quarter of individuals combined abstract symbols to communicate, and even these individuals had difficulty communicating for social and information reasons. Individuals who use AAC often experience a dichotomy between the communication system they are exposed to (speech) and the communication system they use (AAC) (Smith & Grove, 2003). AAC intervention should provide an AAC-rich learning environment, and support the development of language to meet a range of communication functions, so that individuals with *DDX3X*-NDD can reach their full communicative potential with AAC.

## 4.2 | Neurodevelopment

The neurodevelopmental profile of this cohort was largely characterized by ID, and secondarily by autism, and ADHD, consistent with previous reports of a high prevalence of these conditions in *DDX3X*-NDD (Levy et al., 2023). The majority of the cohort were reported to have a neurodevelopmental condition, while almost half had more than one neurodevelopmental condition (excluding speech and language conditions). Most prominent was ID, whereby scores ranged from mild to severe in participants who were formally assessed. This rate and range of ID is largely consistent with the reported rate of 97% in a recent summary of *DDX3X*-NDD findings (Levy et al., 2023). Autism was reported in one quarter of participants, while ADHD was reported in 14% (5/36). This is consistent with previously reported rates of 27% with autism; however, slightly below the expected rate of 22% for ADHD (Levy et al., 2023).

Consistent with previous findings in a summary paper (Levy et al., 2023), the majority of participants were delayed in achieving their motor milestones, independently toileting, and were impacted across all domains of adaptive functioning, particularly in the communication domain. Meanwhile, anxiety had a higher prevalence rate of 18% (5/28) compared to previous studies, which reported 7% of participants experiencing generalized anxiety disorder (Levy et al., 2023). Anxiety is also likely underrecognized in this population, given the high prevalence of neurodevelopmental conditions, which often co-occurs at a rate of up to 73% with ID (Edwards et al., 2022), an average of 40% with autism (van Steensel et al., 2011) and 25% with ADHD (D'Agati et al., 2019). Moreover, individuals with *DDX3X*-NDD may use informal communication behaviors (e.g., crying) to communicate anxiety in the absence of formal communication skills (e.g., speech, AAC), which may not be readily identified as anxiety by communication partners.

## 4.3 | Educational

We are the first to report on education in a cohort of participants with *DDX3X*-NDD, finding that two thirds of participants attended specialist schools, while one-third attended mainstream school. Previous case reports of three males with *DDX3X* variants who had moderate to severe ID attended specialist schools (Nicola et al., 2019). Further examination of educational support needs for school-aged children is warranted to inform recommendations for access to tailored supports (e.g., modified lessons, specialist staff and/or equipment/technology).

## 4.4 | Implications

Our findings also highlight the importance of seeking speech pathology services to facilitate the use of AAC during early childhood, followed by targeted speech and language therapy (such as evidence-based CAS therapy) when verbal communication skills develop. Conducting robust trials of AAC and CAS-specific therapies in individuals with *DDX3X*-NDD is an important direction for future research. Our work also identified that individuals with *DDX3X*-NDD would benefit from comprehensive neuropsychological evaluations to identify cognitive strengths and support needs, alongside potential co-occurring conditions such as autism, ADHD, and anxiety. In addition, occupational and physiotherapy interventions may be beneficial as fine and gross motor deficits were observed consistently. Given our study was limited by its cross-sectional nature, longitudinal designs in future research would be beneficial to assess speech and language development overtime.

## 5 | CONCLUSIONS

In conclusion, we characterized speech and language in *DDX3X*-NDD and identified high rates of minimally verbal individuals and CAS as common features. Until now, an evaluation of speech and language phenotypes has not been undertaken in *DDX3X*-NDD. Moreover,



social motivation was identified as a relative strength in *DDX3X-NDD*, showing the desire to communicate even in the face of severely impaired speech and language abilities. The critical need for AAC in this group, even for adults in their 20s, emphasizes the need for early, tailored, and comprehensive AAC interventions to optimize communication and quality of life outcomes.

## AUTHOR CONTRIBUTIONS

**Elana J. Forbes:** Data curation, formal analysis, investigation, visualization, writing—original draft, review and editing. **Lottie D. Morison:** Data curation, formal analysis, investigation, visualization, writing—original draft, review and editing. **Fatma Lelik:** Formal analysis, writing—review and editing. **Tegan Howell:** Data curation, investigation, writing—review and editing. **Simone Debono:** Data curation, investigation, writing—review and editing. **Himanshu Goel:** Resources, writing—review and editing. **Pauline Burger:** Resources, writing—review and editing. **Jean-Louis Mandel:** Resources, writing—review and editing. **David Geneviève:** Resources, writing—review and editing. **David J. Amor:** Methodology, resources, writing—review and editing. **Angela T. Morgan:** Conceptualization, methodology, funding acquisition, writing—original draft, review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## 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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## SUPPORTING INFORMATION

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

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