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Speech and Language Disorders Associated With 7q31 Deletions Implicating *FOXP2*

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ABSTRACT

Some 7q31 deletions encompass *FOXP2,* a gene long associated with speech and language disorders. Intragenic pathogenic *FOXP2* variants cause *FOXP2*-related speech and language disorder, which has been well characterized in the literature. Conversely, the phenotype associated with 7q31 deletions is neglected. Here we characterize the phenotype of eight individuals (4 males) with 7q31 deletions (median age 4 years, 3 months, range 1–32 years). Deletion size ranged from 6.8 to 15.2 Mb. All had protracted speech and language milestones, and those with larger deletions had little to no speech. All verbal individuals had childhood apraxia of speech (5/5, 100%). Participants used augmentative and alternative communication (AAC) including key word sign (5/8, 63%), and low-tech (6/8, 75%) and high-tech (4/8, 50%) systems. Oral and written language impairment was universal. The larger the deletion size, the poorer an individual's language skills ($p = 0.03$, $p < 0.05$). Daily living, socialization, and motor skills were also impaired. Cognition ranged from average to severely impaired. Childhood feeding impairment (50%), sleep disturbance (38%), structural brain abnormalities (38%), and autism (25%) were noted. All individuals received one or more allied health therapies. Speech and language impairments emphasize the need for early, tailored speech therapy, including literacy and AAC interventions, for individuals with 7q31 deletions.

1 | Introduction

FOXP2, situated at 7q31.1, was the first gene associated with speech and language disorder in the absence of intellectual disability (Hurst et al. 1990; Lai et al. 2001). Pathogenic loss of function and missense variants in *FOXP2* cause *FOXP2*-related speech and language disorder (*FOXP2*-SLD), which is characterized by language disorder and the motor speech disorder, childhood apraxia of speech (CAS), leading to disordered planning and programming of speech motor movements (Lai et al. 2001; Morgan et al. 2023; Morison et al. 2023). More than 30 families with *FOXP2*-SLD have been reported in the literature, including a recent deep phenotyping study of 28 individuals from 17 families (Morison et al. 2023).

Cytogenic deletions at 7q31.1 can also impact *FOXP2*. These deletions are of variable size and include additional genes, resulting in a phenotype that can be considered "*FOXP2*+." Since the discovery of *FOXP2*, approximately 20 cases of 7q31 deletions including *FOXP2* have been published (Akahoshi and Yamamoto 2018; Feuk et al. 2006; Kosho et al. 2008; Lennon et al. 2007; Moreno Campos and Benítez-Burraco 2023; Nagy et al. 2021; Rice et al. 2012; Zeesman et al. 2006; Zhao et al. 2016; Žilina et al. 2012). Most are *de novo*, with only two families

reported (Nagy et al. 2021; Rice et al. 2012; Žilina et al. 2012). 7q31 deletions have been reported to cause a speech phenotype that includes CAS, phonological impairments and dysarthria, yet the speech and language phenotype in these individuals has not been well characterized (Akahoshi and Yamamoto 2018; Feuk et al. 2006; Moreno Campos and Benítez-Burraco 2023; Nagy et al. 2021; Rice et al. 2012; Zeesman et al. 2006; Žilina et al. 2012).

Beyond speech and language disorders, there is limited phenotypic data on individuals with 7q31 deletions. While some individuals with smaller 7q31 deletions have average cognition, those with larger deletions frequently have intellectual disability, with verbal intelligence quotient (verbal IQ) as a relative weakness (Klep-de Pater et al. 1979; Nagy et al. 2021; Rice et al. 2012; Žilina et al. 2012). Autism spectrum disorder (hereafter autism) and autistic features are also observed (Feuk et al. 2006; Žilina et al. 2012). Several individuals have challenging behaviors or mental health conditions (Akahoshi and Yamamoto 2018; Moreno Campos and Benítez-Burraco 2023; Žilina et al. 2012). Impairments in fine, gross, and oral motor skills and feeding difficulties, including gagging and drooling, are common yet have not been systematically reported (Akahoshi and Yamamoto 2018; Feuk et al. 2006; Lennon et al. 2007; Rice et al. 2012; Zeesman et al. 2006; Zhao et al. 2016; Žilina et al. 2012). Reports of abnormal or absent sneeze and cough reflexes and abnormal crying are also frequent (Feuk et al. 2006; Higginson et al. 1976; Rice et al. 2012; Zeesman et al. 2006). The educational and vocational outcomes are also underreported in individuals with 7q31 deletions. Most published adult cases have been inherited cases who received a 7q31 deletion genetic diagnosis after their children were diagnosed (Nagy et al. 2021; Rice et al. 2012; Žilina et al. 2012).

Here we provide the first systematic characterization of speech, language, feeding, and adaptive behavior in a cohort of individuals with 7q31 deletions implicating *FOXP2*.

2 | Methods

2.1 | Editorial Policies and Ethical Considerations

Ethics approval was obtained from the Royal Children's Hospital, Melbourne, Human Research Ethics Committee (HREC 37353A). Caregivers of participants provided written informed consent to participate in the study.

2.2 | Participants

English-speaking caregivers self-referred their children via recruitment flyers posted to online support networks. Participants ≥6 months with 7q31 deletions were recruited. Genetic testing reports were provided to confirm a participant's genetic details (Harris et al. 2009; Harris et al. 2019). Caregivers were interviewed by a speech pathologist using video telehealth and completed online caregiver-report assessments. Cognition was assessed by the individual's treating clinician.

2.3 | Past Medical History

All caregivers completed a comprehensive medical questionnaire, previously operationalized in other monogenic disorders (Braden et al. 2021; Morgan et al. 2021; Morison et al. 2024). To verify survey responses, caregivers provided reports from treating clinicians (e.g., physiotherapists, psychologists, speech pathologists).

2.4 | Feeding

The comprehensive medical questionnaire captured information on infant feeding. Caregivers completed a standardized feeding assessment, the Child Oral and Motor Proficiency Scale (ChOMPS) (Pados et al. 2018). The ChOMPS provides standardized data for children 6 months–7 years.

2.5 | Milestones and Motor Skills

Caregivers provided information on developmental milestones and motor skills. Caregivers also completed the Vineland Adaptive Behavior Scales 3rd Edition (Vineland-3) comprehensive caregiver form, which includes a motor domain (normative mean = 100, SD = 15) (Sparrow et al. 2016). The motor domain includes fine and gross motor subdomains (normative mean = 15, SD = 3). Motor norms are only available for 9 years 11 months and younger, so the motor skills of older participants were assessed using 9 years 11-month normative data.

2.6 | Adaptive Behavior

The Vineland-3 provides standardized assessment of four domains: communication, daily living, socialization, and motor skills (normative mean = 100, SD = 15) (Sparrow et al. 2016). The daily living domain is comprised of self-care, domestic, and community skill subdomains (normative mean = 15, SD = 3). The socialization domain includes interpersonal, play and leisure, and adaptive behavior skill subdomains. An overall adaptive behavior composite (ABC) score is derived from the communication, daily living, and socialization domains (normative mean = 100, SD = 15).

2.7 | Language

The Vineland-3 communication domain (normative mean = 100, SD = 15) assessed language and is comprised of receptive, expressive, and written subdomains (normative mean = 15, SD = 3). Written language skills were only assessed for those older than 3 years of age.

Given the diversity of this cohort, several language assessments were used depending on an individual's age and verbal ability.

Caregivers of children ≥4-years-old who combined spoken words into sentences completed the standardized Children's Communication Checklist 2nd Edition (CCC-2) (Bishop 2003). The CCC-2 has normative data for children 4–16 years in 10

communication domains (normative mean = 10, SD = 3); speech, syntax, semantics, coherence (e.g., can be hard if s/he is talking about something real or make believe), inappropriate initiation, stereotyped communication (e.g., repeating back what others have just said), use of context, nonverbal communication (e.g., does not look at the person s/he is talking to), social, and interests (e.g., talks about lists of things s/he has memorized). Data of participants older than 16 years were scored using 16-year norms. The CCC-2 General Communication Composite (GCC) score assesses overall communication skills, with scores < 55 indicating communication impairment.

Caregivers of children ≤ 18-month-old completed the MacArthur Bates Words and Gestures (MCDI W&G) and the Communication and Symbolic Behavior Scales Developmental Profile (CSBS-DP) (Fenson et al. 2006; Wetherby and Prizant 2002). The MCDI W&G assesses understanding of phrases and vocabulary, and production of vocabulary and gestures. The CSBS-DP has three composite scores for social, speech, and symbolic skills (criterion cut-off for concern = ≤ 6, normative mean = 10, SD = 7). A CSBS-DP total score ≤ 81 meets the criterion cut-off for concern (normative mean = 100, SD = 15).

Caregivers of children who did not use spoken sentences to communicate (i.e., > 2 word combinations) completed the Communication Matrix (Rowland 2004). The Communication Matrix is a descriptive assessment which measures communication behaviors across four communicative functions (i) refuse, (ii) obtain, (iii) share and seek information, and (iv) for social reasons. Communication behaviors are stratified from preintentional communication when the caregiver interprets a child's behavior (level 1) through to a child combining words, signs, or symbols (language, level 7). In typical development, the skills measured on the Communication Matrix are mastered by 2 years old.

Caregivers of participants who used augmentative and alternative communication (AAC), such as speech generating devices and key word sign, were asked about their views on AAC and their child's AAC use over time.

2.8 | Speech

A speech pathologist conducted a speech assessment with verbal participants over video telehealth. Speech samples were elicited using single words from the Diagnostic Evaluation of Articulation and Phonology (DEAP) and a 5-min conversation sample (Dodd et al. 2002). CAS was assessed using operationalized features from the American Speech, Language and Hearing Association's core CAS diagnostic criteria: (Lai et al. 2001) inconsistent production of consonants and vowels, (Hurst et al. 1990) lengthened and disrupted coarticulatory transitions, and (Morgan et al. 2023) inappropriate prosody (American Speech Language and Hearing Association 2007; Mei et al. 2018). Speech subsystems respiration, phonation, articulation, resonance, and prosody were assessed for dysarthria, a neuromuscular motor speech disorder disrupting control and execution (Duffy 2020). A systematic oral motor protocol informed differential diagnosis of speech disorder types (Robbins and Klee 1987).

Caregivers completed the Intelligibility in Context Scale to report whether participants were "always" (Akahoshi and Yamamoto 2018), "usually" (Morison et al. 2023) "sometimes" (Morgan et al. 2023) or "never" (Lai et al. 2001) understood by communication partners (McLeod 2015).

2.9 | Intervention and Education

Caregivers also provided information about their child's allied health therapy and education.

2.10 | Statistical Analysis

A nonparametric Spearman's rank correlation coefficient assessed whether there was a statistically significant association between deletion size, ICS, and Vineland-3 scores. Small sample size precluded additional statistical tests.

3 | Results

3.1 | Participants

Caregivers of eight participants with 7q31 deletions encompassing *FOXP2* self-referred to the study, which had been advertised via online support groups. Participants were recruited from the United States ($n = 5$), Australia ($n = 1$), Poland ($n = 1$), and Israel ($n = 1$). The median age was 4 years 3 months, ranging from 1 year to 32 years (4 males) (Table 1). All deletions were identified using chromosomal microarray, apart from participant 8, whose deletion was identified with fluorescence in situ hybridization (FISH) (Figure 1). Participant 8 received a genetic diagnosis as an adult, as genetic testing was not readily available in childhood. Age at diagnosis ranged from < 6 months to 19 years old, with a median age of 1 year, 9 months. Two deletions were confirmed *de novo*, and six had unconfirmed inheritance, although they were presumed to be *de novo*. Deletion size ranged from 6.8 to 15.2 Mb. Participant 5 also had cystic fibrosis. No participants were related.

3.2 | Co-Occurring Neurodevelopmental Conditions

Only three of eight (38%) participants had completed a cognitive assessment (Table 1). Participant 4 had a mild intellectual disability, and participant 8 had a severe intellectual disability. Participant 2 did not have an intellectual disability (performance IQ = 98). Two of eight (25%) participants had an autism diagnosis, and a further two of eight (25%) had sensory processing disorder. One-quarter of participants (2/8, 25%) had an anxiety disorder.

3.3 | Past Medical History

One-third of the cohort had a history of ear infections (3/8, 38%). Participant 7 had mild sensorineural hearing loss (25–39 dBHL). Half the cohort (4/8, 50%) had vision impairment: 2/8 (25%) with

TABLE 1 | Genotype and co-occurring conditions in this cohort.

Participant	Age assessed (range, yrs)	Sex	Deletion (GRCh37/Hg19)[a]	Deletion (Mb)	OMIM genes	Age diagnosed (yrs)	MRI	ID[c]	Co-occurring conditions
1	9–11	F	(111025533_117848384)x1	6.8[b]	21	4	NA	NA	Autism
2	3–5	M	(107462200_116279744)x1	8.8	21	1	NA	—	—
3	3–5	M	(110394939_119691362)x1	9.4	23	1	NA	NA	Autism
4	9–11	F	(110904950_120508015)x1	9.6	24	7	—	Mild	SPD, DCD
5	0–2	F	(108873698_120928615)x1	12.1	27	2	NA	NA	—
6	0–2	F	(106679365_119188264)x1	12.6	38	0.7	Asymmetrical terminal zone myelination	NA	—
7	0–2	M	(102335290_117602117)x1	15.2[b]	56	0.5	Bilateral Grade 3 intraventricular hemorrhage with hydrocephalus	NA	—
8	30–32	M	105,000,000-120,000,000[d]	15.2	46	19	Increased choline & creatine, decreased N-acetyl aspartate to creatine ratio, decreased N-acetyl aspartate to choline ratio	Severe	SPD

Abbreviations: –, feature absent; ADHD, attention deficit hyperactive disorder; autism, autism spectrum disorder; DCD, developmental coordination disorder; ID, intellectual disability; Mb, mega base; Mo, months; MRI, magnetic resonance imaging; NA, not assessed; OMIM, online Mendelian inheritance in man; SPD, sensory processing disorder, Yrs, years.

[a]All pathogenic and identified by chromosomal micro-array.

[b]Confirmed *de novo*.

[c]Full-scale intelligence quotient > 70 average cognition, 50–70 mild, 35–40 moderate, 20–35 severe, < 20 profound intellectual disability.

[d]Pathogenic, identified karyotype and fluorescence in situ hybridization.

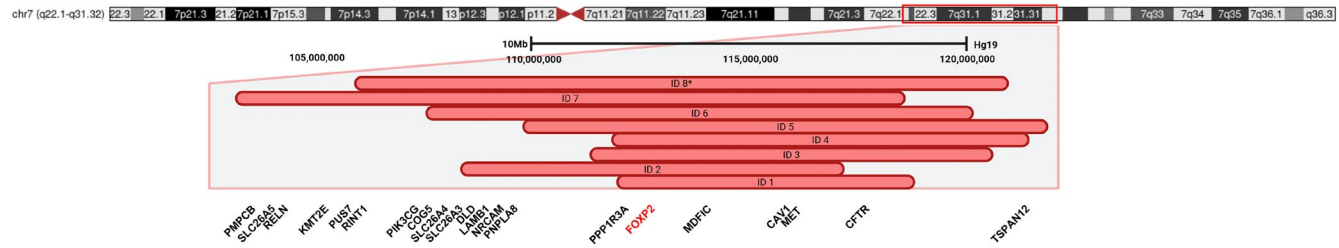

FIGURE 1 | 7q31 deletions in eight participants (GRCh37/Hg19). Participants are ordered by deletion size from 1 (smallest deletion) to 8 (largest deletion). Participant 8 mapping is by karyotype and fluorescence in situ hybridization (FISH) only. OMIM Morbid genes are shown only here.

hypermetropia, 2/8 (25%) with exotropia, 1/8 (13%) with strabismus, and 1/8 (13%) with Marcus Gunn syndrome. 1/8 (13%) of participants wore glasses.

Six of eight (75%) participants had an electroencephalogram (EEG) with no seizure activity identified. Half of participants (4/8, 50%) had undergone Magnetic Resonance Imaging (MRI), with abnormalities noted in three individuals (Table 1).

Participants with sleep disturbances (3/8, 38%) had difficulty falling asleep (2/8, 25%), and frequent and early waking (1/8, 13%).

Most participants had perinatal complications (6/8, 75%) (Table S1). In the first month of life, 3/8 (38%) infants had health problems, including jaundice (2/8, 25%), feeding impairment (2/8, 25%), and anoxia (2/8, 25%). Participant 7 (1/8, 13%) had a nasogastric tube in infancy. Two infants (2/8, 25%) had central obstructive sleep apnea. Participant 7 was hospitalized for an extended period (32 weeks) due to significant health issues, including a grade 3 intraventricular hemorrhage with post-hemorrhagic hydrocephalus controlled by a ventriculoperitoneal stent. One participant (1/8, 13%) had a high-pitched cry in infancy.

Of the six participants who were old enough, 4/6 (66%) had dental problems including frequent dental caries (2/6, 33%) and prolonged retention of a deciduous tooth (1/6, 16%). Participant 2 had both eczema and asthma (1/8, 13%). Participant 8 had kyphosis and localized pain in their right hand, with no known cause.

Participant 5 who had cystic fibrosis had gastroesophageal reflux in the first 2 years of life. Participant 6 also had gastroesophageal reflux in the first year of life. Half of the cohort (4/8, 50%) drooled more than peers, with 3/8 (38%) still drooling at the time of assessment despite being aged 1–32 years.

3.4 | Feeding

The 4/8 (50%) participants with the largest 7q31 deletions had feeding impairments < 7 years old. For participant 8, feeding impairment persisted into adulthood.

Half of participants (4/8, 50%) completed the ChOMPS and all had "high concerns" (< 5th percentile) across the domains of "complex movement patterns" (e.g., licks food off lip), and "fundamental oral motor skills" (e.g., sticks tongue out). Oral motor coordination (e.g., eats food without gagging; 1/4, 25% "high concern") and basic movement patterns were relative strengths (e.g., pulls to stand; 2/4, 50% "high concern"). Overall, all participants had total ChOMPS scores of "high concern."

3.5 | Milestones and Motor Skills

Only participant 1, who had the smallest deletion, said their first words by 12 months (Table 2). Of those who had acquired first words (5/8, 63%), this occurred after 18 months for three individuals. The 3/8 (28%) participants with the largest deletions (> 12.5 Mb) had still not said their first words (aged 14 months, 18 months, and 32 years). Only the 2/8 (25%) participants with the smallest deletions (< 9 Mb) could combine words into short sentences, albeit with delayed onset at 4–5 years of age.

Motor milestones were also delayed (Table 3). Most participants could sit without support before one year old (5/8, 63%) and crawl before 13 months old (4/8, 50%). Of the six participants walking, five learned to do so after 16 months of age. Participant 7 with a 15.2 Mb deletion (1/8, 13%) could not sit unsupported, crawl, or walk at 18 months old. 3/8 (38%) participants (deletions < 10 Mb) learned to ride a bike. All participants apart from participant 4 (7/8, 88%) required assistance with personal care activities. Hypotonia was common (6/8, 75%) and ubiquitous for those individuals with deletions > 9 Mb.

Six participants completed the Vineland-3, and 2/6 (33%) participants had average motor skills on the Vineland-3 (Table 3). Yet, as a group, motor skills were moderately low on average (median = 76, range 57–96), with impairments in both fine (median = 9, range 5–15) and gross motor skills (median = 11, range 5–16).

3.6 | Adaptive Behavior

On the Vineland-3, participants had low average daily living skills ($n = 6$, median = 73, range 21–83), including self-care (median = 9, range 2–11), domestic skills (median $n = 6$, range 1–12), and community activities (median = 6, range 1–11). Individuals also had difficulties with socialization (median = 75, range 20–98), across interpersonal (median = 11, range 1–14), play and leisure (median = 10, range 1–16), and adapting skills (median = 9, range 4–14) subdomains (Figure 2a). Only participant 1 had an average socialization domain score.

The ABC score reflected subdomain and domain scores, and ranged considerably (median = 70, range 20–81). Deletion size correlated with ABC score ($p = 0.03$, $p < 0.05$, Figure 2a).

TABLE 2 | Speech and language features in this cohort.

Participant	Age first words (mo)	Age first sentences (yrs)	Verbal or minimally verbal*	Communication standard score[a]	Receptive scaled score[b]	Expressive scaled score[b]	Written scaled score[b]	CAS	AAC
1	< 12	4–5	V	76	8	11	13	+[c]	+
2	15–18	4–5	V	80	13	11	11	+[c]	+
3	≥ 18	NYA	V	67	6	8	12	+	+
4	≥ 18	NYA	MV	NA	NA	NA	NA	+	+
5	≥ 18	NYA	MV	NA	NA	NA	NA	+	+
6	NYA	NYA	MV	55	2	2	NA	NA	+
7	NYA	NYA	MV	44	6	2	NA	NA	+
8	NYA	NYA	MV	20	1	1	1	NA	+

Abbreviations: –, not present, +, feature present, AAC, augmentative and alternative communication, CAS, childhood apraxia of speech, Mo = months, MV, minimally verbal were not combining words to create spoken sentences at time of assessment, NA, not assessed, NYA = not yet achieved, V, verbal individuals were combining words to create spoken sentences at time of assessment (> 2 words combined), Yrs, years.
[a]Vineland-3 normative mean = 100, SD = 15.
[b]Vineland-3 normative mean = 15, SD = 3, Written not assessed for participants > 3-years-old.
[c]Directly assessed as part of this study other cases are based on treating clinician report.

TABLE 3 | Motor milestones and skills, therapy and education.

Participant	Age assessed (range, yrs)	Age crawling (mo)	Age walking (mo)	Motor skills standard score[a]	Gross motor scaled score[b]	Fine motor scaled score [b]	SP	OT	PT	Current activity
1	9–11	11–13	≥ 16	96	16	13	+	+	+	Mainstream school
2	3–5	7–10	≥ 16	83	15	10	+	+	+	Specialized pre-school
3	3–5	11–13	≥ 16	73	11	9	+	+	+	Specialized pre-school
4	9–11	≥ 14	≥ 16	NA	NA	NA	+	NA	NA	Mainstream school
5	0–2	≥ 14	13–15	NA	NA	NA	+	+	+	Too young for school
6	0–2	11–13	NYA	87	10	15	+	+	+	Mainstream pre-school
7	0–2	NYA	NYA	57	5	6	+	+	+	Too young for school
8	30–32	≥ 14	≥ 16	57	8	5	+	+	+	Adult disability day program

Abbreviations: –, absent;+, present; Mo, months; NYA, not yet achieved; OT, previous or present occupational therapy; PT, previous or present physiotherapy; SP, previous or present speech therapy.
[a]Vineland-3 normative mean = 100, SD = 15.
[b]Vineland-3 normative mean = 15, SD = 3.

3.7 | Language

The Vineland-3 communication domain ($n = 6$) was the lowest domain on average (median = 61, range 20–80, Figure 2a,b and Table 2). Participants with smaller deletions had stronger language than those with larger deletions ($p = 0.03$, $p < 0.05$, Figure 2a). As a group, the cohort showed receptive (median = 6, range 1–13) and expressive language impairments (median = 5, range 1–11). Expressive language skills had a stronger association with deletion size ($p = 0.04$, $p < 0.05$) than receptive

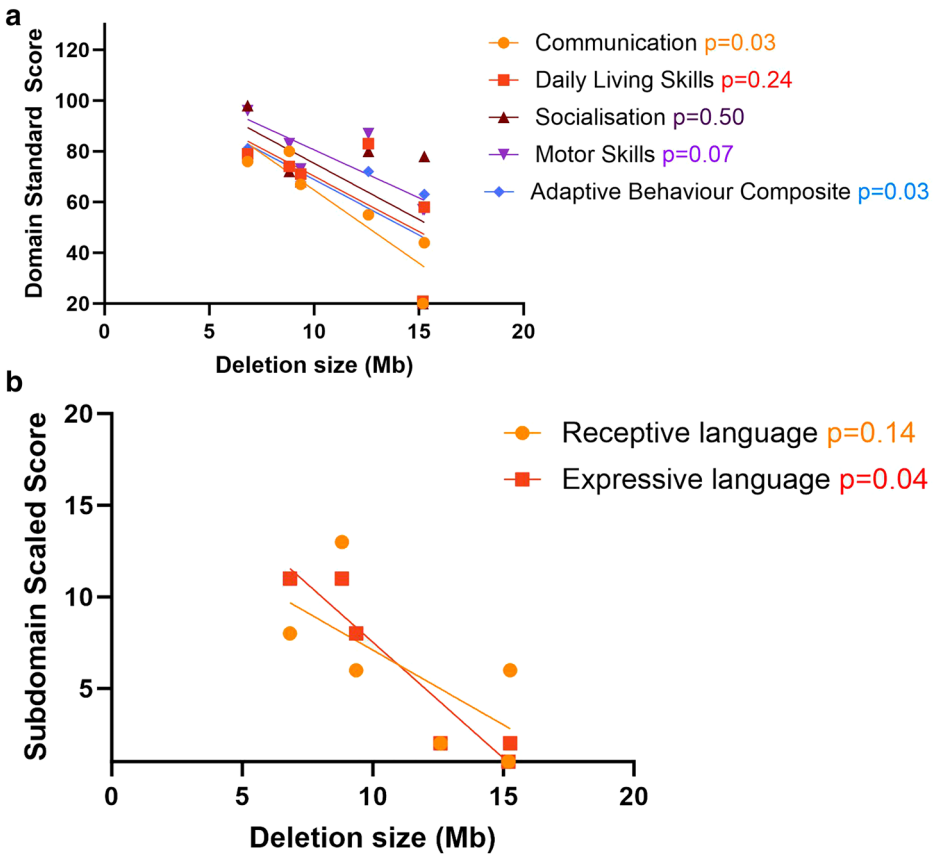

FIGURE 2 | (a) 7q31 deletion size and Vineland Adaptive Behavior Scale Third Edition Standard Scores in six participants. Normative mean = 100, SD = 15. Mb = Mega base. (b) 7q31 deletion size and Receptive and Expressive Language Subdomains Scaled Scores from the Vineland Adaptive Behavior Scales Third Edition in six participants. Normative mean = 15, SD = 3. Mb = Mega base.

language skills ($p = 0.14$, $p > 0.05$, Figure 2b). For participants over 3 years old ($n = 4$) literacy skills (median = 12, range 1–13) ranged from average to severely impaired.

Two participants (participants 1 and 2) with higher verbal abilities completed the CCC-2. Participants' highest subdomain was initiation (scaled scores ≥ 7), and speech was the lowest subdomain (scaled scores = 2 and 3). Overall, communication skills were severely impaired (GCC scores Participant 1 = 32 and Participant 2 = 51).

Participants 6 and 7 completed the MCDI W&G and CSBS-DP. On the MCDI W&G, both participants scored below the 5th percentile for gestures, vocabulary comprehension (receptive language) and production (expressive language) skills. Both participants also had CSBS-DP speech, social, and symbolic scores that met the criterion cut-off for concern. Total CSBS-DP scores were also below the criterion cut-off for concern (scores = 71 and 67, respectively).

Participants 3, 4, 6–8 completed the Communication Matrix ($n = 5$, Figure 3). On average, these participants communicated at Level 4, using intentional, pre-symbolic behaviors such as vocal intonations and pointing. On average, communicating to request was a relative strength, with 4/5 (80%) participants requesting using concrete symbols (Level 5, objects or symbols that physically resemble what they represent). On average, participants had mastered approximately half of the skills on the Communication Matrix (percent of total skills mastered: average = 46%, SD = 23%). Level 6 (abstract symbols, single signs or words) was the highest level of communication behavior for all participants (Figure 3).

Participant 5 was unavailable for language assessment.

Participants had used low-tech (6/8, 75%, e.g., communication books) and high-tech AAC (4/8, 50%, e.g., speech generating devices). 5/8 (63%) participants had used key word sign ranging from single signs to 2–3 signs combined to create a sentence.

Seven caregivers reported their opinions on AAC and their child's therapy. 3/7 (43%) said that AAC was the most helpful communication intervention. When asked if their children would communicate more effectively if they increased their use of AAC, 5/7 (71%) agreed, 2/7 (29%) were neutral, and 1/7 (14%) disagreed. 2/7 (29%) caregivers held the misconception that AAC would inhibit their child's speech.

3.8 | Speech

At the time of the study, 5/8 (63%) participants used verbal speech as their main means of communication, and all these participants had CAS (Table 2).

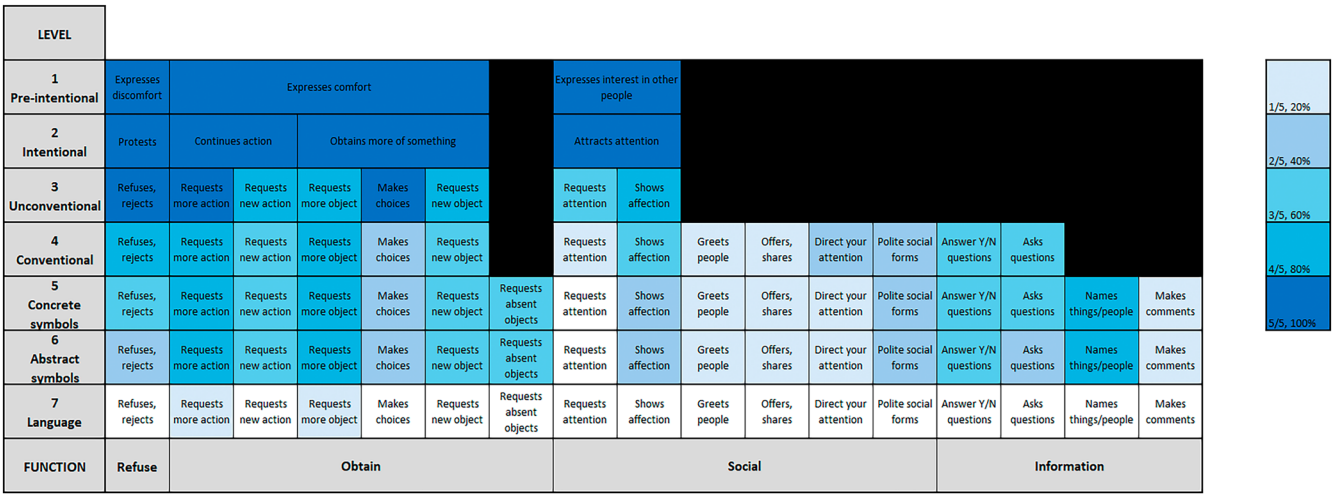

FIGURE 3 | Communication matrix scores in five participants with 7q31 deletions. Level 7 Language = combination of two or more spoken words, signs, or symbols. Y = yes, *N* = no.

On the ICS, participants ($n = 7$) were "usually" (score = 4) to "never" (score = 1) understood on average. No participants were "always" (score = 5) understood by all conversation partners. Caregivers understood their children the best (median = 4, range 1–5), while participants' friends rarely understood them (mean = 2, range 1–4). Deletion size was significantly correlated with how well participants were understood by friends, acquaintances, teachers and strangers ($p < 0.05$) but did not correlate with how well they were understood by their family members.

3.9 | Intervention and Education

All participants had received speech (8/8, 100%), occupational therapy (7/7, 100%), and physiotherapy (7/7, 100%). One participant did not report on occupational therapy or physiotherapy (Table S2).

Three of eight (38%) participants were old enough for school; two participants attended mainstream and one attended a specialist setting. After school, the sole adult, participant 8, attended a disability day services program.

Four of eight (50%) caregivers reported that their child had lost previously learnt skills for a period of ≥3 months, for instance losing the ability to babble. Caregivers did not report whether their child regained skills, or if there were potential triggers or patterns of skill loss.

4 | Discussion

Speech and language impairments are ubiquitous in individuals with 7q31 deletions, and there are similarities between the speech and language phenotypes associated with 7q31 deletions and *FOXP2*-SLD, such as a high incidence of CAS. Yet, speech, language, and cognitive ability are markedly more impaired in individuals with 7q31 deletions compared with individuals with *FOXP2*-SLD (Morison et al. 2023).

While most individuals with *FOXP2*-SLD have delayed speech and language milestones, most learn to speak, and cognition is relatively intact (Morgan et al. 2023; Rice et al. 2012). In contrast, our data show that individuals with 7q31 deletions that include *FOXP2* may have little or no speech well into adulthood. For example, participant 8 had no spoken words in their 30s; however, they did communicate using key word sign. No individuals with 7q31 deletions in this cohort were always understood by all communication partners.

Our cohort mirrored published cases, including feeding impairment, hypotonia, and gross motor impairment (Lennon et al. 2007; Nagy et al. 2021; Rice et al. 2012; Zeesman et al. 2006; Žilina et al. 2012). Similarly, individuals with smaller deletions may learn to talk, albeit with significant motor speech and language impairment, but those with larger deletions are unlikely to learn to speak (Feuk et al. 2006; Rice et al. 2012; Žilina et al. 2012). Deletion size correlated with communication and adaptive behavior scores, though small numbers and differing ages precluded robust analysis of this association. There were also individuals with smaller deletions (e.g., Participants 1 and 2) who had relatively strong language and cognitive skills compared to the rest of the cohort. Participant 2 with an 8 Mb deletion also had average cognitive ability, which has been previously reported in an individual with a similar deletion size (Zeesman et al. 2006).

Like previous studies, there was unexplained phenotypic heterogeneity in our cohort. Even individuals in the same family with the same genotype can differ. For instance, Nagy et al. (2021) described three sisters and a mother, one of whom had average cognition and attended mainstream school, while another had a moderate to severe intellectual disability and attended a specialist school (Nagy et al. 2021). Few case series of unrelated individuals have impeded our knowledge of genotype–phenotype correlations associated with 7q31 deletions. Future studies with larger cohorts could elucidate the association between deletion size, adaptive behavior, and communication outcomes. Additionally, as cognition included verbal IQ here, future research should delineate between verbal and non-verbal cognitive abilities.

One study has systematically compared the phenotype of individuals with *FOXP2*-SLD (the KE family) and a family with a translocation involving *FOXP2* (the TB family) between two families (Tomblin et al. 2009). However, there has been no comparison of individuals with large 7q31 deletions, as in this cohort, and individuals with *FOXP2*-SLD. Consistent with previous reports, we found here that individuals with 7q31 deletions are more likely to have co-occurring neurodevelopmental conditions, such as autism and intellectual disability, compared to those with *FOXP2*-SLD (Morgan et al. 2023; Morison et al. 2023). Half of caregivers reported that their child had lost skills that they had previously been capable of, reflecting a similar incidence of parent-reported regression in autistic children (Brignell et al. 2017). Only one-quarter of our cohort had an autism diagnosis. Yet, as the international average age of autism diagnosis is 5 years of age (van't Hof et al. 2021), many individuals in our cohort may yet to be diagnosed. There is also complexity in diagnosing autism in the presence of intellectual disability (Thurm et al. 2019). Future research should further characterize the reported skill loss in individuals with 7q31 deletions, including age, patterns of skill loss, and whether there are any triggers for the skill loss.

The greater severity of speech impairment and developmental disability in patients with 7q31 deletions, compared to those with *FOXP2* variants, is likely explained by the loss of additional genes in deletion patients. In our cohort, all the 7q31 deletions were relatively large, with sizes ranging from 6.8 to 15.2 Mb, and involving between 21 and 56 genes (Perez et al. 2025). However, the identity of the genes contributing to the more severe phenotype in 7q31 deletion patients remains unclear. Although multiple genes in this region are predicted to be haploinsufficient, only one, *KMT2E*, is known to cause a neurodevelopmental disorder when deleted, and this gene was only deleted in Participant 7. Loss-of-function variants in *KMT2E* cause O'Donnell-Luria-Rodan syndrome, characterized by global developmental delay, speech delay, variably delayed intellectual development, and subtle dysmorphic features (O'Donnell-Luria et al. 2019). One notable autosomal recessive gene at 7q31 is *CFTR*, which was deleted in seven of our eight participants. Individuals with 7q31 deletions are therefore at increased risk of cystic fibrosis, and this was the case with Participant 5, who was a compound heterozygote with a *CFTR* single nucleotide variant on one allele and her 7q31 deletion affecting the other *CFTR* allele (Farrell et al. 2024).

Our findings also have implications for speech therapy in individuals with 7q31 deletions. Like other monogenic conditions causative for CAS, individuals with 7q31 deletions would likely benefit from AAC due to the high incidence of motor speech disorder, protracted speech milestones, and the fact that some individuals were not speaking well beyond the age of expected first spoken sentences (2–3 years old) (Forbes et al. 2024; St John et al. 2022). Additionally, many caregivers emphasized AAC as critical in their child's speech and language therapy. However, many caregivers believed the misconception that AAC hinders speech development (Romski and Sevcik 2005). Consequently, clinicians should provide accurate AAC education and early AAC access to all children with 7q31 deletions and their families (Jensen et al. 2023; Smith et al. 2016).

For individuals who use speech to communicate, tailored CAS interventions are also indicated due to the high incidence of CAS in individuals with 7q31 deletions (Morgan et al. 2018). Speech therapy should not be limited to AAC and CAS interventions for individuals with 7q31 deletions and their families. Universal oral and written language impairments in assessed individuals emphasize the need for language-focused interventions to support comprehension and expression. Children with CAS, language disorder, and intellectual disability are at high risk of literacy impairment (Hildebrand et al. 2020; Kaspi et al. 2023; Lervåg et al. 2018; Nilsson et al. 2025), necessitating early and systematic phonics instruction (Chou et al. 2024). Literacy skills are also important in the context of AAC, allowing individuals who use AAC to communicate a broader range of vocabulary than symbols alone allow (Light and McNaughton 2014). Future longitudinal studies could investigate speech and language trajectories over time, including AAC use.

Speech therapy may also focus on feeding, as children with 7q31 deletions are likely to have infant and childhood feeding impairment. In child and adulthood, complex movements such as licking the food off the lips and fundamental oral skills, like protruding the tongue, were often challenging.

In conclusion, we have systematically defined the speech, language, and medical phenotype of a cohort of individuals with 7q31 deletions encompassing *FOXP2*. Though this cohort was small, it is the largest cohort of individuals with 7q31 deletions, allowing for the identification of similarities and differences between individuals with 7q31 deletions and *FOXP2*-SLD. Speech and language milestones are protracted, with pervasive speech and language disorders. Individuals with large deletions may not develop speech, and all individuals who speak have the motor speech disorder, CAS. Moreover, co-occurring neurodevelopmental conditions of autism and intellectual disability are more common in individuals with 7q31 deletions than in those with *FOXP2*-SLD (Morison et al. 2023). Childhood feeding impairment is also prevalent. Comprehensive and systematic phenotyping allows clinicians and families to make informed decisions. Our results emphasize the necessity of early, tailored speech and language therapy, including literacy, AAC, and feeding interventions for individuals with 7q31 deletions.

Author Contributions

Conceptualization: A.T.M. Data curation: L.D.M., R.B., D.J.A., A.T.M. Formal analysis: L.D.M., D.J.A., A.T.M. Funding acquisition: A.T.M. Investigation: L.D.M., R.B., A.T.M. Methodology: L.D.M., A.T.M. Project administration: L.D.M., A.T.M. Resources: A.T.M. Software: A.T.M. Supervision: A.T.M. Writing – original draft: L.D.M., A.T.M. Visualization: L.D.M. Writing – review and editing: L.D.M., R.B., D.J.A., A.T.M. Correspondence: A.T.M. Guarantor: A.T.M.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1.** Supporting Information.