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Speech and language development and genotype–phenotype correlation in 49 individuals with KAT6A syndrome

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Abstract

Pathogenic *KAT6A* variants cause syndromic neurodevelopmental disability. "Speech delay" is reported, yet none have examined specific speech and language features of KAT6A syndrome. Here we phenotype the communication profile of individuals with pathogenic *KAT6A* variants. Medical and communication data were acquired via standardized surveys and telehealth-assessment. Forty-nine individuals (25 females; aged 1;5–31;10) were recruited, most with truncating variants (44/49). Intellectual disability/developmental delay (42/45) was common, mostly moderate/severe, alongside concerns about vision (37/48), gastrointestinal function (33/48), and sleep (31/48). One-third (10/31) had a diagnosis of autism. Seventy-three percent (36/49) were minimally-verbal, relying on nonverbal behaviors to communicate. Verbal participants (13/49) displayed complex and co-occurring speech diagnoses regarding the perception/production of speech sounds, including phonological impairment (i.e., linguistic deficits) and speech apraxia (i.e., motor planning/programming deficits), which significantly impacted intelligibility. Receptive/expressive language and adaptive functioning were also severely impaired. Truncating variants in the last two exons of *KAT6A* were associated with poorer communication, daily-living skills, and socialization outcomes. In conclusion, severe communication difficulties are present in KAT6A syndrome, typically on a background of significant intellectual disability, vision, feeding and motor deficits, and autism in some. Most are minimally-verbal, with apparent contributions from underlying motor deficits and cognitive-linguistic impairment. Alternative/augmentative communication (AAC) approaches are required for many into adult life. Tailored AAC options should be fostered early, to accommodate the best communication outcomes.

KEYWORDS
Arboleda–Tham syndrome, KAT6A syndrome, language, nonverbal communication, speech

1 | INTRODUCTION

Pathogenic variants in the lysine (K) acetyltransferase 6 A gene (*KAT6A*; also referred to as *MOZ*, *MYST3*) cause Arboleda–Tham syndrome (OMIM 616268), a syndromic form of intellectual disability (ID) also known as KAT6A syndrome. *KAT6A* belongs to the MYST family of proteins, which are involved in several core cellular functions including chromatin remodeling and gene regulation (Voss et al., 2009). The *KAT6A* protein functions in a multi-subunit complex (alongside *KAT6B*, *BRPF1/2/3*, *ING5*, and *hEAF6*) (Yang, 2015), producing a complex that acetylates lysine residues on histone H3 tails, stimulating an array of developmental functions.

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Heterozygous germline variants in *KAT6A* were first identified by exome sequencing of individuals with ID (Lee et al., 2014; Millan et al., 2016), and over 80 individuals with KAT6A syndrome have since been described in the literature. The KAT6A Foundation (https://kat6a.org) identifies more than 330 cases; however, the true prevalence is unknown. Descriptions of KAT6A syndrome have been based primarily on medical history and case notes, due to geographically-dispersed participants, and systematic and standardized assessments have not been used (Alkhateeb & Alazaizeh, 2019; Kennedy et al., 2019; Urreizti et al., 2020). Core features include mild to severe ID, motor delays, hypotonia, gastrointestinal issues, and cardiac malformations (Arboleda et al., 2015; Kennedy et al., 2019; Tham et al., 2015). Microcephaly is common and distinct facial dysmorphology may include a thin, tented upper lip, a high nose with a bulbous tip and prominent nasal bridge, bitemporal narrowing, and a short flat philtrum (Kennedy et al., 2019; Urreizti et al., 2020).

"Speech delay" is mentioned commonly in KAT6A syndrome, with researchers often describing speech as strikingly delayed or "absent" (Kennedy et al., 2019). Precisely what this means in terms of a specific speech and/or language phenotype is unclear in the absence of standardized speech and language assessments. Researchers report comprehension to be more preserved in comparison to expressive language and speech; however, all descriptions stem from medical reports or observations (Kennedy et al., 2019). To date, no studies have objectively assessed core speech or language domains, precluding prognostic counseling or development of targeted therapies. Further, recent work utilizing next-generation whole genome sequencing on a cohort of individuals ascertained for the rare speech disorder; childhood apraxia of speech (CAS), implicated a variant in *KAT6A* (Eising et al., 2019). Yet there has been no cohort study to determine whether CAS is a core feature associated with pathogenic variants in this gene.

Here we conducted the first detailed study of speech and language abilities in this population, across domains of feeding, speech, language, and adaptive behavior.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

Ethical approval was obtained through the Royal Children's Hospital, Melbourne, Human Research Ethics Committee (HREC #37353). Written informed consent was obtained from the participant or their parents or legal guardian in the case of minors or adults with ID.

2.2 | Participants

Participants were recruited via study flyers on KAT6A Foundation social media pages (website, Facebook, newsletter) and the Australian Association of Clinical Geneticists. Inclusion criteria were: (a) confirmed pathogenic or likely pathogenic variant in *KAT6A*; (b) aged 6 months or older; and (c) a speaker of English, German, Dutch, Italian, French, Portuguese, or Spanish. Exclusion criteria was the presence of any other confirmed genetic variant or syndrome likely to impact the clinical phenotype.

2.3 | Measures

Caregivers/participants completed assessments, either via online (REDCap-administered) survey or Zoom telehealth-interview. Caregivers began by completing an in-depth health and medical survey and clinical reports were obtained from local treating health professionals to confirm parent reported medical and neurodevelopmental diagnoses (i.e., ID, CAS). Participants completed a verbal or minimally-verbal protocol according to abilities.

2.3.1 | Speech and oromotor skills

Speech was assessed for English-speaking verbal communicators, including a differential diagnosis across speech conditions. All assessments were video- and audio-recorded. Parent report, confirmed by speech pathology diagnoses, were utilized for non-English speaking families to confirm speech diagnoses.

Articulation (i.e., motor act of producing sounds) and phonological (i.e., understanding the sound contrasts in a given language) abilities were assessed with the Diagnostic Evaluation of Articulation and Phonology (DEAP, Dodd et al., 2002). Percent phonemes correct was calculated from the DEAP as a measure of speech accuracy. The presence of dysarthria was determined from an oral-motor assessment and rating a 5-min conversational speech sample using the Mayo Clinic dysarthria classification system (Braden et al., 2021; Duffy, 2013; Mei et al., 2018). CAS was diagnosed by examining connected speech, DEAP scores, and multisyllabic word production (using the Single Word Test of Polysyllables, Gozzard et al., 2006) (Fedorenko et al., 2016). Individuals met criteria for CAS if they met the three main diagnostic criteria: (1) inconsistent errors; (2) lengthened and disrupted coarticulation; and (3) inappropriate prosody (ASHA, 2021).

2.3.2 | Language, social communication, and adaptive behavior

The Vineland Adaptive Behavior Scales Parent/Caregiver Rating Form (Second and Third Edition, Sparrow et al., 2015, 2016) provided standard scores for communication, daily living skills and socialization, and an overall adaptive behavior composite for all ages. Scaled scores were calculated for the expressive and receptive language subdomains as a measure of functional language ability. The Children's Communication Checklist-2 (CCC-2) was used to assess overall communication in verbal, English-speaking participants aged 4–16 years (Bishop, 2003).

The Inventory of Potential Communicative Acts (IPCA) was used to gather information about behaviors interpreted by familiar people as purposeful and communicative (Sigafoos et al., 2000, 2006). The interview protocol has questions across 10 communicative functions: (a) social convention; (b) attention-to-self; (c) rejecting/protesting; (d) requesting an object; (e) requesting an action; (f) requesting information; (g) commenting; (h) choice making; (i) answering; and (j) imitation.

2.3.3 | Statistical analyses

Fisher's exact test was used to determine whether variant location, for those with truncating variants, had an impact on verbal ability. One-way ANOVAs compared mean scores across the Vineland subdomains.

3 | RESULTS

Forty-nine individuals (25 female) were recruited. Participants were aged between 1 year 5 months and 34 years 10 months (mean = 9 years 7 months, SD = 7 years 10 months). Most families were English-speaking (n = 36, 73%), with Spanish (n = 5, 10%), French (n = 4, 8%), Dutch (n = 3, 6%), and Norwegian/English speakers (n = 1, 2%). There were 40 truncating variants (24 frameshift; 16 nonsense), 4 splice site variants, 4 missense variants, and 1 deletion encompassing the *KAT6A* gene and several other genes. Of these variants, 20 have been reported previously.

3.1 | Medical and neurodevelopmental characteristics

Participants had a range of medical and neurodevelopmental features (Table 1, Figure 1a). Most presented with ID. In cases where participants were too young for formal cognitive testing, a diagnosis of developmental delay (DD) reported by a pediatrician was considered a comparable measure of early intellectual functioning. ID/DD was present in 93% (42/45) of individuals, with the highest proportion of individuals in the severe range (18/45, 40%). Impairments in vision were common (37/48, 77%), including vision disturbances (e.g., myopia), eye anomalies (e.g., ptosis), and cortical vision impairment. Other common health conditions included digestive problems (33/48, 69%) and chronic sleep disturbances (31/48, 65%). Movement/motor disorders were noted in roughly half of participants (23/49, 47%), ranging from mild balance issues and hypotonia to cerebral palsy and ataxia. Structural heart anomalies (22/48, 46%), renal/urogenital problems (11/48, 23%), and a history of epilepsy or seizures (11/48, 23%) were noted frequently. One third (10/31) had a diagnosis of autism, not including those who were too young to be tested or those who were not assessed for autism. One fifth (9/48) had hearing loss (HL), which was typically mild (i.e., 25–39 dBHL), bilateral, and either conductive or mixed. A range of facial dysmorphisms was seen (see Table S1 for detail).

3.2 | Feeding difficulties

Marked feeding difficulties were seen, with >90% (45/48) having feeding difficulties either historically or at the time of assessment (Figure 1b). Feeding challenges began from birth, with individuals presenting with suck-swallow incoordination, oral weakness, and frequent vomiting, often resulting in the need for nasogastric tubes. Feeding difficulty remained throughout development, and 50% (24/48) of the group had feeding issues at the time of assessment, including those in their adolescent and adult years.

3.3 | Speech features

Speech was almost always significantly impaired, with a few outliers. Structural oromotor anomalies were common (17/48, 35%), particularly micrognathia (8/48, 17%). Seventy-three percent (36/49) were nonverbal or minimally-verbal at the time of assessment (Figure 1b). Those who had no more than 30 single words or word approximations (i.e., "Mum"/"Ma-ma," "No") well past the typical age of first word development (i.e., 12 months) were considered minimally-verbal (Brignell et al., 2018). The youngest four participants, aged between 1 year 5 months and 2 years 10 months, were included in the category of minimally-verbal as they did not show signs of typical early speech development (i.e., babble).

Across the 13 verbal participants, speech profiles, and intelligibility were varied (Table 2). 10/13 verbal participants were female (77%). 11/13 had delayed speech milestones, some not achieving first words until >18 months and others not combining words until >8 years of age. Verbal participants had a range of speech disorder subtypes, and most had at least two diagnoses (Figure 1c). Phonological delay was most common (8/13, 63%), followed by phonological disorder (7/13, 54%) and CAS (7/13, 54%), but all three conditions always co-occurred with at least one other speech diagnosis. Three individuals had co-occurring CAS, dysarthria, phonological delay, and phonological disorder. All other diagnosis pairings were observed in one individual each. Diagnoses were based on past clinical reports for the five individuals who were either non-English speaking or not able to complete a telehealth speech assessment. Although only able to be calculated in a small number of cases, percent phonemes correct ranged from average to severely impaired, with 50% of those assessed in the severe range.

3.4 | Language and adaptive functioning

Most individuals were severely impaired across all adaptive functioning domains, namely daily living skills (30/37, 81%), socialization (29/37, 78%), and communication (29/37, 78%), while both receptive

TABLE 1 Medical and neurodevelopmental characteristics

ID	Sex	Age	ID	Variant (NM_006766)	Verbal	Autism	Epilepsy/ seizures	Impairment in: Motor/movement	Sleep	Behavior	Vision	GI	Cardiac	Renal/ UG	Feeding
1	F	1;5	TY	c.4664G>A p.Ser1555Asn	NV	NA	–	CP, HMD	+	–	–	+	+	–	C
2	M	1;10	TY	c.658C>T p.Arg220*	NV	NA	–	–	+	–	+	+	–	+	C
3	M	1;11	MoDD	c.4219del p.Ile1407Serfs*3	NV	NA	–	–	+	–	+	+	+	–	R
4	F	2;9	Sev	c.1951_1954delCCTC p.Pro651fs*47	NV	NA	+	CP, SP, ataxia	–	–	+	+	–	–	C
5	M	2;10	MiDD	c.5645_5646delTTins10 p.Glu1419Wfs*12	NV	NA	–	–	–	–	+	+	–	+	C
6	F	2;10	Sev	c.3070C>T p.Arg1024* (CGA>TGA)[a]	NV	NA	–	Hypotonia	+	–	+	+	+	–	C
7	M	3;0	Sev	c.3399_3400dup p.Lys1134Argfs*14	NV	+	+	Ataxia, CP, Dyskinesia, DCD	+	+	+	+	+	+	C
8	F	3;2	NA	8p11.21p11.1 deletion	MV	NA	+	Hypotonia	+	–	+	+	–	–	C
9	M	3;3	SevDD	c.3661G>T p.Glu1221*[a]	NV	NA	–	–	–	–	+	+	+	–	C
10	F	3;10	MoDD	c.1903-5_1903-2del[a]	NV	NA	–	Hypotonia, balance issues	–	–	+	+	+	–	R
11	M	4;1	SevDD	c.3286_3287insC p.Cys1096fs27[a]	MV	NA	–	–	–	–	+	–	–	–	C
12	F	4;4	Mi	c.4031_4032del p.Glu1344fs11	NV	NA	–	–	+	–	–	–	–	–	R
13	M	4;5	Sev	c.4653 T>G p.Ser1551Arg[a]	NV	NA	–	CP	+	–	+	–	–	–	C
14	M	4;7	MoDD	c.2689G>T p.Glu897*	MV	NA	–	–	–	–	–	–	–	+	R
15	F	4;9	MoDD	c.2832dupT p.Glu945*	MV	NA	–	Hypotonia	–	–	+	+	–	–	R
16	M	4;9	SevDD	c.4361dupA p.Thr1455Aspfs*9	NV	NA	–	–	–	–	+	–	+	+	C
17	F	4;11	MoDD	c.4144dup p.Thr1382Asnfs*12	V	NA	–	Ataxia	+	+	+	+	+	–	R
18	M	5;3	MiDD	c.5639C>A p.Ser1880*	V	NA	+	–	–	–	+	–	+	–	C
19	F	5;7	MiDD	c.4089_4092dup p.Asp1365Lysfs*3	V	–	–	–	+	–	+	+	–	–	R
20	M	5;11	Sev	c.4224dup p.Leu1409Ilefs*10	NV	–	–	CP, ataxia	+	–	–	+	–	–	C
21	F	5;11	Mo	c.5248_5257del10 p.Thr1750*	NV	–	–	Hypotonia	+	–	UI	–	+	–	C
22	F	5;11	Mo	c.4254_4257del p.Glu1419Wfs*12[a]	MV	+	–	–	+	–	+	+	+	–	R
23	M	6;2	NR	c.3040–5 A>G	NV	NR	NR	Ataxia	NR	NR	+	NR	NR	NR	NR
24	M	6;8	Mo	c.5617C>T p.Gln1873*	NV	–	–	–	–	+	+	–	+	–	C
25	M	6;8	Sev	c.3385C>T p.Arg1129*[a]	NV	–	–	–	+	+	+	+	+	–	R
26	F	6;10	Sev	c.3434del p.Pro1145Leufs*2[a]	NV	–	–	CP	+	–	+	+	–	–	C

TABLE 1 (Continued)

ID	Sex	Age	ID	Variant (NM_006766)	Verbal	Autism	Epilepsy/ seizures	Impairment in: Motor/movement	Sleep	Behavior	Vision	GI	Cardiac	Renal/ UG	Feeding
27	M	6;11	Sev	c.3631_3632delGT p.Val1211*	NV	−	+	−	+	+	+	+	+	+	R
28	M	7;6	Mo	c.1285dupG p.Glu429Glyfs*7	MV	+	−	−	+	+	+	−	−	−	R
29	F	8;3	SevDD	c.3385 C>T p.Arg1129*[a]	MV	−	−	Abnormal tightness in right hip	+	+	+	+	+	−	C
30	F	9;9	Mo	c.1639_1640del p.Met547Glufs*3[a]	V	−	+	−	−	−	+	−	−	−	−
31	F	10;0	Sev	c.4228_4232delAAAGA p.Lys1410Gfs*7[a]	V	−	−	−	+	+	+	+	−	−	R
32	M	10;6	Mo	c.3182 T>A p.Leu1061*	MV	+	−	−	+	−	−	+	−	+	R
33	M	10;6	−	c.3182 T>G p.Leu1061*[a]	NV	+	−	−	+	+	−	+	−	+	C
34	M	10;8	MiDD	c.2437-1G>A: IVS14-1G>A	V	+	−	CP (spastic diplegia)	+	−	+	+	+	−	R
35	M	10;8	NA	c.5212G>A p.Asp1738Asn	V	+	+	−	+	+	−	+	−	−	C
36	F	10;8	Mo	c.3070C>T p.Arg1024*[a]	NV	−	−	−	−	−	+	+	−	−	−
37	F	10;9	Sev	c.3349_3350insCA p.Asp1117fs*7	MV	−	−	CP	+	−	+	−	+	+	R
38	F	11;1	−	c.4025delA p.Lys1342Argfs*11[a]	V	−	−	−	+	−	+	+	+	−	R
39	M	12;4	Sev	c.3640A>T p.Lys1214*	NV	−	−	−	−	−	+	+	+	−	C
40	F	12;6	Mo	c.1308_1309insCGCAA p.Tyr437Argfs*43[a]	V	−	−	Abnormal tics/ movements	−	−	+	+	−	−	−
41	F	13;2	Mo	c.3070C>T p.Arg1024*[a]	MV	−	−	Hypotonia	+	−	+	−	−	−	R
42	F	17;2	Mo	c.3230delA p.Asn1077Metfs*46[a]	V	+	−	CP	+	−	−	+	−	−	R
43	F	17;9	Mo	c.5505_5508del p.Asn1836fs*15[a]	V	−	+	−	−	−	+	−	+	−	R
44	F	18;7	Sev	c.3596delG p.Gly1199Aspfs*95	NV	−	+	CP, spasticity, ataxia	+	+	−	+	+	−	C
45	M	19;6	Mo	c.4256_4260dupAGCTG p.Asp1421Serfs*13	NV	−	−	−	−	−	−	+	−	−	R
46	M	28;8	Sev	c.3338C>G p.Ser1113*	NV	+	+	Hyperekplexia, DCD	+	−	+	+	−	−	C
47	F	30;4	Mi	c.1748G>A p.Gly583Glu	V	−	−	−	+	−	−	−	−	+	C
48	F	31;10	Mi	c.1136C>G p.Ser379*[a]	V	−	−	Hypotonia, JDM	−	−	+	+	+	+	C
49	M	33;11	Sev	c.3040-1_3040delGA[a]	NV	+	+	CP	+	−	+	−	−	−	R

Note: ID23 and ID42 have a diagnosis of CP alongside a history of birth anoxia.

Abbreviations: +, present; −, none/absent; C, current; CP, cerebral palsy; DD, developmental delay; GI, gastrointestinal; HMD, hyperkinetic movement disorder; JDM, juvenile dermatomyositis; Mi, mild; Mo, moderate; MV, minimally-verbal; NA, not assessed; NR, not reported; NV, nonverbal; R, resolved; Sev, severe; SP, spastic paraplegia; TY, too young; UG, urogenital; UI, under investigation; V, verbal.

[a]Previously reported variant.

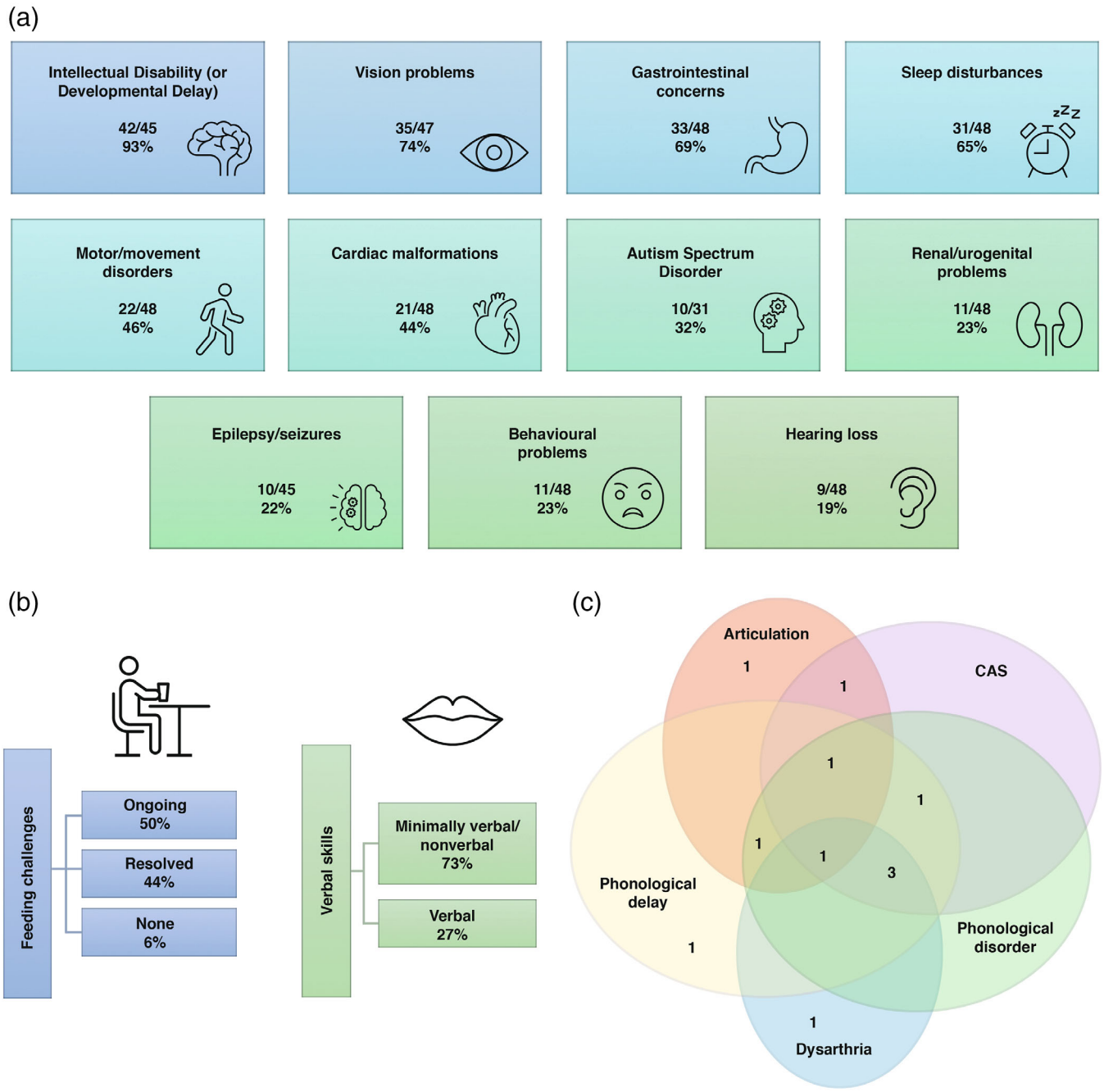

FIGURE 1 (a) Medical and neurodevelopmental co-morbidities. (b) Feeding and communication. (c) Number of individuals with co-occurring speech diagnoses

and expressive language were severely impaired (27/37, 73% and 30/37, 81%, respectively). Mean standard scores across all domains were significantly impacted: specifically, communication (mean = 47.6, SD 22.6), daily living skills (mean = 55.5, SD 18.5), socialization (mean = 57.5, SD = 21.4), and motor skills (mean = 58.4, SD 23.7), as well as the overall adaptive behavior composite (mean = 55.6, SD = 17.8). Receptive (mean = 6.1, SD = 4.5) and expressive (mean = 4.3, SD = 4.9) language scores were also significantly impacted (see Table S2). Mean communication domain scores were not statistically different to socialization ($p = 0.065$) or daily living skills domain mean scores ($p = 0.122$). Receptive and expressive mean scores were not statistically different from each other ($p = 0.121$).

The IPCA was completed for $n = 29$ English-speaking participants (Table 3). Due to time constraints, eight caregivers did not complete the IPCA by study cut-off. Individuals used a range of symbolic and nonsymbolic forms to communicate. Symbolic communication included: (i) speech/words; (ii) alternative and augmentative

TABLE 2 Breakdown of verbal participants' speech features

Participant	17	18	19	30	31	34	35	38	40	42	43	47	48
Sex, age	F, 4;11	M, 5;3	F, 5;7	F, 9;9	F, 10;0	M, 10;8	M, 10;8	F, 11;1	F, 12;6	F, 17;2	F, 18;0	F, 30;0	F, 31;10
Language	French	English	English	Dutch	English	English	English	English	English	English	English	Norwegian	English
Speech milestones													
First words	>18 m	>18 m	>18 m	15–18 m	12–15 m	>18 m	>18 m	<12 m	>18 m	12–15 m	15–18 m	12–15 m	>18 m
Sentences	4–5 y	4–5 y	4–5 y	2–3 y	6–7 y	6–7 y	6–7 y	2–3 y	4–5 y	>8 y	4–5 y	2–3 y	>8 y
Phonological processes													
Delayed	NA	+	+	NA	+	+	+	NA	NA	+	–	NA	+
Atypical	NA	+	+	NA	+	+	–	NA	NA	+	–	NA	+
%Phonemes correct[a] (percentile, severity)	NA	67.1 (1, severe)	91.9 (9, mild)	NA	71 (1, severe)	50 (1, severe)	96.8 (37, average)	NA	NA	79.5 (1, severe)	99.1 (50, average)	NA	98.6 (50, average)
Speech diagnoses	Artic dis, phon delay/dis[b]	CAS, phon delay/dis	CAS, artic dis, phon delay/dis	Artic dis[b]	CAS, artic dis, dysarthria, phon delay/dis	CAS, dysarthria, phon delay/dis	Phon delay	Overall comm[n] delay[b]	CAS, artic dis.	CAS, dysarthria, phon delay/dis	Dysarthria	None	CAS, dysarthria, phon delay/dis

Abbreviations: +, present; –, absent; artic, articulation; CAS, Childhood Apraxia of Speech; comm[n], communication; dis, disorder; F, female; m, months; M, male; NA, not available; phon, phonological; y, years.

[a]Individuals who were older than the normative sample, had raw scores compared to the oldest scoring range (>6;11), as all individuals beyond this would be expected to achieved a high accuracy of phoneme production.

[b]Clinical diagnosis.

communication (AAC); including sign language, communication devices, and eye point; (iii) symbolic gestures, such as pointing; and (iv) facial expressions. Nonsymbolic communication included: (i) prelinguistic vocalizations, such as babble; (ii) nonlinguistic vocalizations, such as crying and laughing; and (iii) nonverbal behaviors including body movements, face/eye movements, breathing changes, challenging behaviors (e.g., aggression, self-injury), and stereotypical behaviors (e.g., hand flapping). A number of AAC devices were used by participants including Proloquo2go ($n = 3$), LAMP Words For Life ($n = 2$), Snap Core First ($n = 1$), Clicker Communicator ($n = 1$), Liberator Accent 800 NuVoice ($n = 1$), PECS (Picture Exchange Communication System) ($n = 1$), Satillo Touch Chat ($n = 1$), and switches ($n = 1$). Seven non-English speaking participants, who were unable to complete the IPCA also reported the use of AAC devices/techniques currently or historically, including PECS ($n = 1$), Proloquo2go ($n = 1$), Makaton ($n = 2$), Pragmatic Organization Dynamic Display Book ($n = 1$), GoTalk4+ ($n = 1$), Tobii Eye Tracker 4C ($n = 1$), Grid 3 ($n = 1$), Look to Learn software ($n = 1$), and computer pictograms ($n = 3$). One family also described using "concrete objects" to represent an activity/request (i.e., spoon indicates food, cup indicates drink, and shoe indicates going out).

3.5 | Associations between type/location of variants and phenotypic features

Those participants with protein truncating variants were divided into early- and late-truncating variants to determine associations with phenotype. Late-truncating variants were those in the last two exons (exons 16 and 17), while early-truncating variants occurred in exons 1–15. This early versus late delineation was based on previous work (Kennedy et al., 2019). Increased severity of ID was more common in those with late-truncating variants compared to early truncating variants (Figure 2a).

Using Fisher's exact test, we found no association between verbal ability and variant location. However, adaptive behavior scores were statistically stronger for those with early truncating variants across the domains of communication ($p = 0.04$), daily living skills ($p = 0.01$), socialization ($p = 0.02$), and overall adaptive behavior ($p = 0.01$) (Figure 2b). Receptive language scores were statistically better for those with early truncating variants ($p = 0.002$). No statistical difference was found in expressive language scores according to variant location ($p = 0.24$).

Four individuals presented with missense variants. Regarding ID, one had mild ID, one severe ID, one had not been assessed, and one was too young to be assessed. In addition, two of these individuals were verbal and two were minimally-verbal. Across adaptive behavior scores, two of the individuals with missense variants were not assessed due to speaking a language other than English, while the other two each had subtest scores ranging from moderately low to low. Overall, considering the spread of data and small sample of missense variants, conclusions could not be drawn regarding whether these variants stratified on measures.

TABLE 3 Percentage of symbolic and nonsymbolic behaviors used to express communicative functions

	Symbolic communication						Nonsymbolic communication			
	Speech/ words	AAC: Sign language	AAC: Comm[n] device	AAC: Eye point	Symbolic gesture	Facial expression	(Pre) linguistic vocal[n]	Nonlinguistic vocal[n]	Nonverbal behaviors	DNC
Social convention										
Greets others	31%	21%	3%	0%	14%	45%	62%	34%	55%	0%
Farewells others	38%	34%	3%	0%	21%	7%	38%	14%	41%	7%
Responds to name	24%	3%	0%	0%	3%	38%	28%	14%	59%	3%
Attention to self										
Gets attention	45%	21%	10%	0%	17%	10%	66%	45%	69%	0%
Seeks comfort	21%	14%	0%	0%	38%	3%	38%	28%	69%	0%
Shows off	21%	10%	7%	0%	0%	17%	24%	34%	59%	21%
Reject/protest										
Responds if routine is disrupted	14%	10%	0%	0%	0%	0%	21%	34%	59%	31%
Responds when they do not like something	31%	10%	3%	0%	7%	0%	24%	62%	76%	0%
Request object										
Requests object	41%	31%	24%	7%	38%	7%	45%	34%	55%	0%
Requests food	34%	34%	21%	7%	28%	0%	41%	28%	31%	10%
Requests more	31%	45%	21%	10%	14%	7%	31%	17%	28%	3%
Request action										
Requests help dressing	31%	21%	10%	0%	14%	0%	31%	14%	24%	31%
Requests the toilet	31%	24%	7%	0%	24%	0%	28%	7%	14%	38%
Requests someone to come/be near	34%	14%	3%	0%	21%	3%	34%	14%	55%	7%
Request information										
Asks for clarification	21%	14%	0%	0%	0%	0%	14%	3%	17%	48%
Asks for information	21%	0%	3%	0%	10%	0%	14%	3%	10%	48%
Comment										
Expresses happiness	28%	10%	14%	0%	7%	41%	59%	59%	76%	0%
"sadness/anxiety"	17%	10%	7%	0%	3%	7%	34%	15	76%	0%
"pain/sickness"	28%	3%	3%	0%	17%	0%	28%	14	45%	3%
"anger/frustration"	15%	7%	3%	0%	0%	0%	21%	72%	69%	7%
"when tired"	24%	17%	3%	0%	14%	0%	14%	17%	52%	3%
Choice making										
Chooses between objects	28%	10%	24%	10%	48%	0%	10%	3%	21%	0%
Chooses what to do	28%	21%	31%	14%	38%	0%	17%	3%	41%	0%
Answering										
Answers others communication attempts	28%	7%	0%	0%	10%	24%	45%	24%	72%	0%
Answers yes	41%	7%	10%	0%	24%	10%	31%	10%	14%	7%
Answers no	38%	21%	3%	0%	24%	0%	28%	24%	24%	10%
Imitation										
Attempts to imitate speech	38%	3%	0%	0%	0%	0%	41%	3%	17%	31%

Note: Darker shading indicates behaviors exhibited by many (>40%); Lighter shading indicates behaviors exhibited by some (20%–39%). Represents data available for $n = 29$ who completed the IPCA.

Abbreviations: AAC, alternative and augmentative communication; comm[n], communication; DNC, does not communicate this; vocal[n], vocalization.

4 | DISCUSSION

Here we provide a large and comprehensive study of feeding, speech, language, and adaptive functioning in individuals with *KAT6A* variants, utilizing a range of standardized measures. While marked communication impairment is a core feature of KAT6A syndrome, these speech and language deficits occurred alongside ID, vision disturbances, cardiac and digestive issues, and persistent feeding difficulties.

Most individuals with *KAT6A* variants in our study presented with complex medical and neurodevelopmental needs, and largely relied on nonverbal means of communication, even into adulthood. Almost all presented with severe and equivalent difficulties across the adaptive behavior domains of communication, daily living skills, socialization, and motor skills. While the prevalence of minimally-verbal communication is in line with past reports (Arboleda et al., 2015; Kennedy et al., 2019), adaptive communication, daily living skills, socialization,

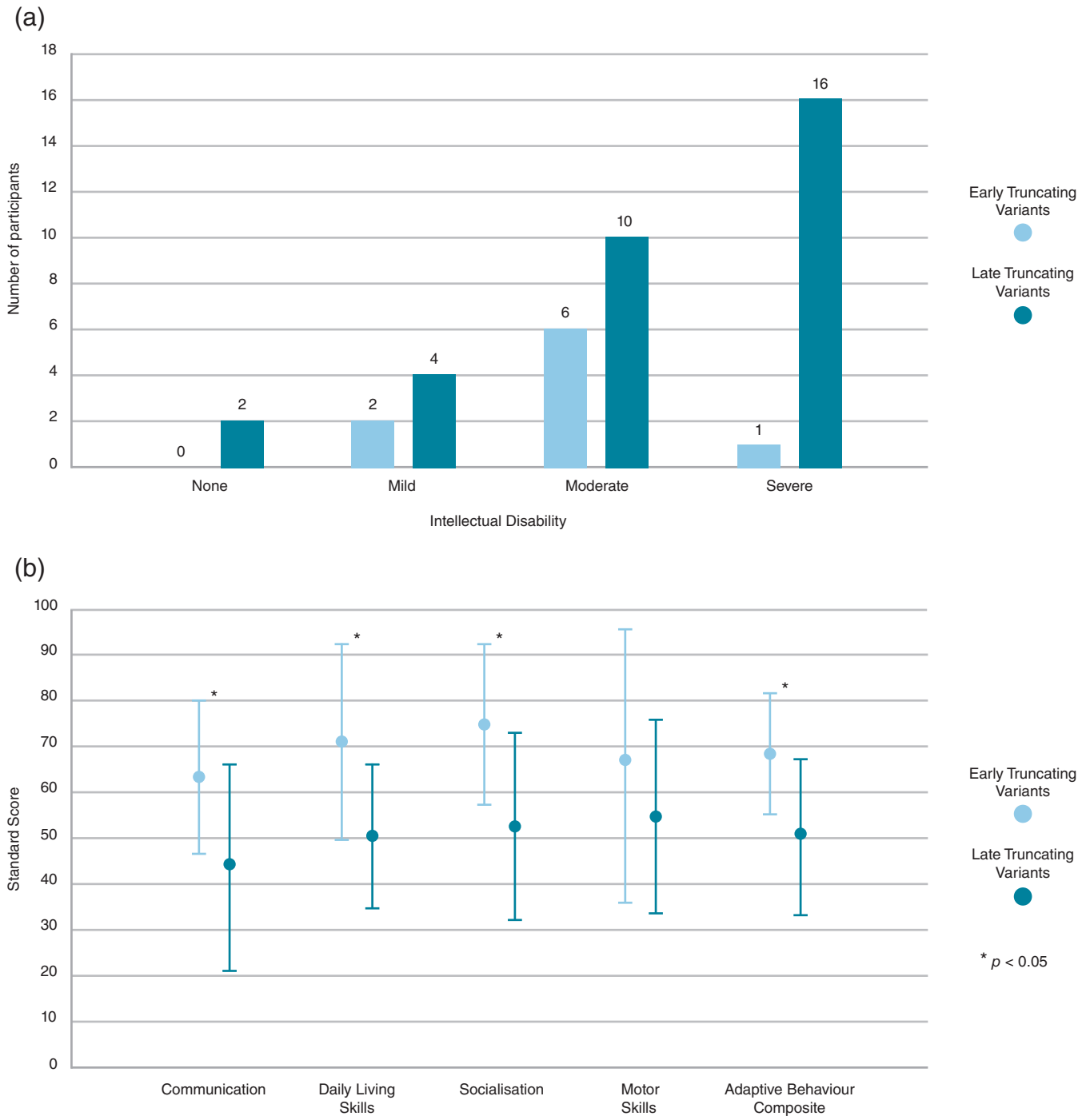

FIGURE 2 (a) Distribution of intellectual disability according to early- versus late-truncating variants. (b) Adaptive behavior domain mean standard scores according to early- versus late-truncating variant

and motor development were also severely impaired, highlighting the global, rather than specific linguistic, impacts of *KAT6A*. A recent study that analyzed sleep and adaptive behavior using alternative measures mirrored these observations of global impairment, strengthening our conclusions here (Smith & Harris, 2021).

Across the cohort, almost 90% presented with some form of feeding difficulty in their lifetime, including weak and uncoordinated suck/swallow reflexes as infants, vomiting, an inability to ingest food orally, and the need for nasogastric feeding tubes and gastrostomy throughout infancy, but also through to childhood and beyond for some. Half had feeding difficulties at the time of participating, some well into their adolescent and adult years. This is unsurprising considering the severity of motor and coordination issues observed and the links to feeding and swallowing development (Adams-Chapman et al., 2013; McFarland & Tremblay, 2006).

When examining the subset of verbal participants, we did not see a trend for early or typical speech and language milestones being predictive of better speech outcomes later. While some achieved developmentally appropriate speech milestones, others who went on to develop verbal speech were, in contrast, still strikingly delayed, indicating a need for close monitoring in the early years and persistence with speech pathology intervention. Structural anomalies with the ability to impact oromotor function such as micrognathia have the capacity to impact speech clarity and precision. Yet the most significant contributions to decreased intelligibility were cognitive or neurological, with origins in linguistic (e.g., phonological delay), motor execution (e.g., dysarthria), or motor planning and programming deficits (i.e., CAS). For the two individuals who achieved age-appropriate speech milestones, there were no similarities in their type or location of KAT6A variant (i.e., c.3230delA p.Asn1077Metfs*46 and c.1748G>A p.Gly583Glu).

Descriptively and anecdotally, past studies reported relative strengths in receptive communication compared to expression (Kennedy et al., 2019; Millan et al., 2016); however, this was not reflected in our standardized scores. Here receptive communication was affected across the group, and almost always in-line with expressive communication. This trend has been seen across other rare genetic syndromes, where significant expressive communication deficits tend to imply that receptive language is more intact to observers (Braden et al., 2021; Morgan et al., 2021). Considering how many individuals relied on nonverbal (and nonsymbolic) behaviors to express their wants and needs, it is understandable that standardized assessments and scores would reflect poorly.

Whether due to an underlying motor praxis or more complex association between language and ID, those with KAT6A syndrome relied most often on nonverbal behaviors to communicate. Across the group, children were always able to greet others, get attention, seek comfort, indicate dislike, make requests/choices, express basic emotions (i.e., happy/sad), and answer communication attempts by caregivers. However, they were less likely to have any discernible means to ask for clarification/information, request help with dressing or toileting, or respond when their routine was disrupted. Caregivers in this group needed to be highly attune to their child's individual behaviors to understand communicative intention, as individuals often used nonsymbolic behaviors like nuanced body movement or subtle eye-gaze to communicate specific needs. For those with truncating variants in *KAT6A*, most individuals who are nonverbal or minimally verbal have an associated ID; however, there were a few outliers who did not present with ID or DDs. A nonverbal presentation does not necessarily indicate ID, as the inability to produce verbal speech may arise from a motor praxis issue, rather than a cognitive one, as noted in participant 33.

Considering the number of individuals who could not use verbal communication, it would be appropriate to suggest a variety of formal AAC to facilitate interactions with other individuals, beyond immediate caregivers. Formal AAC was utilized by some, but across limited communicative functions. For example, AAC was rarely used to seek comfort, request help, ask for information, express feelings, or answer questions. Although formal communication means such as sign language or picture devices would be ideal for many, this was sometimes complicated by the child's motor ability, access to devices, and appropriate clinicians to facilitate successful use.

We were unable to identify a genotype–phenotype trend in the location of the *KAT6A* variant corresponding to the binary measure of verbal versus nonverbal, as others have done with some medical and neurodevelopmental features (Kennedy et al., 2019). Our sample size may have been too small to detect a trend, with so few verbal cases. Our data did, however, show a significant trend in severity of adaptive behavior with variant location, whereby late-truncating variants appeared to result in poorer adaptive behavior outcomes across the group. This was also the case for late-truncating variants impacting severity of ID, mirroring trends observed by others (Kennedy et al., 2019).

5 | CONCLUSION

Severe communication disorder is common in those with pathogenic *KAT6A* variants, yet these deficits occur alongside a background of ID, motor, feeding, and daily living skill impairments. Individuals with *KAT6A* variants in this cohort displayed a spectrum of linguistic abilities. While some appear to have verbal potential impeded by complex motor speech diagnoses, others display a more global cognitive impairment associated with significantly impaired receptive and expressive language ability. Very few individuals with KAT6A syndrome in our cohort developed clear and intelligible speech.

Further research is required to systematically examine predictors of good versus poor communication outcomes. Intensive speech therapy was common across the entire group regardless of verbal ability, with a range of therapeutic approaches being applied often including an emphasis on both building verbal speech as well as fostering alternative communication methods. Strikingly, most relied on alternative means of communication into adolescence and adulthood (e.g., body movements and sign language). Although alternative communication is often successful in the home and with familiar caregivers, many individuals with KAT6A syndrome lack more universal communication approaches, such as communication/speech generating devices, which could enhance communication with a wider number of communication partners and ultimately improve quality of life. Those diagnosed with KAT6A syndrome are likely to benefit from early identification and implementation of more formal and widely applicable AAC systems to optimize communication outcomes.

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CONFLICT OF INTEREST

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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